EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ASSESSMENT REPORT
FOR
Brinavess

International Nonproprietary Name:

vernakalant

Procedure No. EMEA/H/C/001215

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 30 July 2009 an application for Marketing Authorisation to the European Medicines Agency for Brinavess, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the Agency/CHMP on 20 September 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication: conversion of atrial fibrillation to sinus rhythm.

1.1.1. Information on paediatric requirements

Pursuant to Article 7, of Regulation (EC) No 1901/2006 the application included an Agency Decision EMEA-000226-PIP01-08 for the following condition: atrial fibrillation on the granting of a product-specific waiver for all subsets of the paediatric population and in the above mentioned condition on the grounds that the disease for which the specific medicinal product is intended occurs only in adult population.

1.1.1.1. Scientific advice :

The applicant received Scientific Advice from the CHMP on 20 September 2007. The Scientific Advice pertained to clinical aspects of the dossier.

1.1.2. Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Karl Broich**

- The application was received by the Agency on 30 July 2009.
- The procedure started on 19 August 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2009 .
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2009 .

- During the meeting on 17 December 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 December 2009 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 April 2010 .
- During the CHMP meeting on 22 April 2010, the CHMP agreed on a list of Outstanding Issues to be addressed in writing by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 May 2010.
- The Rapporteurs circulated the Joint Assessment Report on the response to the CHMP List of Outstanding Issues on 7 June 2010.
- During the meeting on 24 June 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Brinavess. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2010.

2. Scientific discussion

2.1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by un-coordinated atrial activation with consequent deterioration of atrial mechanical function. AF is the most common sustained arrhythmia encountered in the adult population. It is estimated that 4.5 million people in the European Union (EU) have paroxysmal or persistent AF [Fuster et al, 2006]. The overall prevalence in a recent prospective study of a large, elderly European population was 5.5%, rising from 0.7% in those aged 55-59 years to 17.8% in those aged 85 years and above [Heeringa et al, 2006]. Atrial arrhythmias are also common in patients subsequent to cardiac surgery, with overall incidences reported in large scale studies ranging from 23% to 35% [Mariscalco and Engstrom, 2007; Maisel et al, 2001; Mathew et al, 2004]. AF can cause discomfort and is associated with a number of symptoms, such as palpitations, chest pain, dyspnoea, fatigue and light-headedness. AF can also lead to stroke, congestive heart failure, and an overall increased risk in morbidity and mortality. Conversion of AF to sinus rhythm (SR) may be accomplished with either electrical or pharmacological methods. There are a number of benefits associated with acute conversion of AF to sinus rhythm. Conversion to sinus rhythm regularises ventricular rate, improves cardiac function, cardiac output, and exercise capacity, improves symptoms, and improves haemodynamics. In addition, rapid conversion of AF may prevent or reverse the development of atrial electrical and structural remodelling associated with AF, which are difficult to reverse as the duration of AF increases. Consequently, limiting atrial remodelling may prevent development of refractory AF and ultimately reduce disease progression. An important benefit of pharmacological conversion specifically is to provide an alternative to electrical cardioversion and its associated risks, including risks associated with sedation and anaesthesia. Other adverse events associated with electric cardioversion 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. The available agents for pharmacologic cardioversion include: class Ic agents in particular flecainide and propafenone and class III in particular amiodarone, and ibutilide. The use of most of these agents is associated with rapid conversion of AF, except for amiodarone. The commonly reported adverse events with their use are the development of arrhythmia (atrial flutter [AFL] with flecainide and torsades de pointes with ibutilide). All of these agents except for amiodarone are contraindicated in patients with abnormal ventricular function. The development of an agent with a rapid onset of action, associated with a less

arrhythmogenic potential that can be used in patients with structural heart disease is a potential advantage.
Vernakalant hydrochloride (VH) injection is a novel intravenously administered anti-arrhythmic drug that acts preferentially in the atria designed to rapidly convert AF to sinus rhythm. Vernakalant has a unique potassium and sodium channel blocking profile that is enhanced under the conditions of AF and results in preferentially atrial selective actions. VH injection has a short pharmacokinetic half-life which results in a rapid onset and offset of action. The proposed therapeutic indication for VH 20 mg/ml was: rapid conversion of recent onset atrial fibrillation (≤ 7days duration) to sinus rhythm. The approved indication is: 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.

VH should be administered by intravenous infusion, by qualified medical personnel in a monitored clinical setting appropriate for cardioversion. The recommended initial infusion is 3 mg/kg to be infused over a 10 minute period. If conversion to sinus rhythm 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. If conversion to sinus rhythm occurs during either the initial or second infusion, that infusion should be continued to completion.

Merck Sharp & Dohme (Europe), Inc. filed a full stand alone application in accordance with Regulation 726/2004 Article 3(2)(a) and Directive 2001/83/EC Article 8(3) for the registration of the new active substance vernakalant hydrochloride concentrate for solution for infusion, 20 mg/ml.

2.2. Quality aspects

2.2.1. Introduction

Brinavess is a sterile, isotonic, buffered concentrate for solution for infusion which is presented as 10 ml and 25 ml single dose vials containing 20 mg/ml of vernakalant hydrochloride corresponding to 200 mg and 500 mg of vernakalant hydrochloride per vial, as active substance. Prior to intravenous infusion into the patient, vernakalant concentrate is diluted with either of the recommended diluents (0.9% Sodium Chloride Injection, Lactated Ringers Injection, or 5% Dextrose Injection).
Excipients are citric acid, sodium chloride, water for injection and sodium hydroxide (for pH-adjustment).
The primary container consists in a single use Type I glass vials with a chlorobutyl rubber stopper and an aluminium overseal.

2.2.2. Active substance

Vernakalant hydrochloride which has the chemical name (3R)-1-[(1R,2R)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl]pyrrolidin-3-ol hydrochloride is a white to beige powder and entirely synthetic enantiomerically pure new chemical entity. It is highly soluble in water. In the buffered formulation, the molecule is expected to exist almost exclusively in its ionic and presumably more water-soluble form.
There are eight potential stereoisomers (having identical molecular composition and varying only in configuration at the chiral centers). The trans isomers are known to be biologically/pharmacologically active, while the biological/pharmacological properties of the cis isomers are unknown. The levels of all the isomers of vernakalant hydrochloride are controlled in the final drug substance specification.
There is no evidence of polymorphism occurring in vernakalant hydrochloride, although three hydrate forms were found (Form A, B, and C). It should be noted that the drug substance is highly soluble in water and is fully solubilized during the drug product manufacturing process. The morphology of the solid drug substance, therefore, has no impact on the physical characteristics of vernakalant concentrate, which is an aqueous solution. Vernakalant hydrochloride produced by the proposed commercial manufacturing process is Form A.

2.2.2.1. Manufacture

The synthesis involves six process steps starting from commercially available starting materials.

Adequate In-Process Controls are applied during the synthesis of vernakalant drug substance. Control methods for intermediate products, starting materials and reagents, have been presented.

Batch analysis data of six consecutive batches from the manufacturer are presented and confirm consistency and uniformity of the manufacturing process.

2.2.2.2. Specification

The active substance specifications include tests for appearance, identification (HPLC, IR and titration), colour of solution, pH, water determination, residual solvents (GC), residue of ignition, palladium content, assay (HPLC), related substance (HPLC, indirect chiral CE, chiral CE), bacterial endotoxins, microbiological examination tests (TAMC, TYMC, and tests for specified microorganisms (Pathogens))
Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.3. Stability

Stability studies under long term and accelerated conditions were conducted on three batches manufactured by the proposed commercial manufacturing process as well as two batches manufactured by the previous process. Samples were stored in the proposed commercial packaging for 48 months (one batch 60 months) at 25ºC/60%RH and up to 9 months of storage at 40ºC/75%RH and under stress conditions. Test parameters are appearance, clarity and colour of solution, pH, specific rotation, water determination, HPLC assay, HPLC related substances, indirect chiral CE non-chromophoric impurities, direct chiral CE isomeric impurities, particle size, bacterial endotoxins, and microbial limit tests.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

The results justify the proposed retest period.

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

The development of the manufacturing process was guided by the physico-chemical properties of the active substance (dissociation constant, solubility profile, solution pH, particle size, and polymorphism).

The manufacturing process development was focused on the critical steps of the process. Compatibility studies were performed in order to determine the compatibility of Brivaness with different diluents for IV infusion and bags and infusion sets.

The formulation used during clinical studies is the same that the used for marketing.

The excipients used in the manufacture of vernakalant concentrate are citric acid monohydrate, sodium chloride, sodium hydroxide, and water for injections. All formulation excipients comply with Ph Eur specifications.

Brivaness is packaged in a clear, hydrolytic Class I vial in accordance with Ph. Eur. 3.2.1. closed by chlorobutyl rubber with FluroTec Plus® barrier film (fluoro-resin film [ETFE]) laminated on the product contact side of the stopper. The stopper is sealed with aluminum overseal with a plastic flip-off cap).

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

The containers/closures used are compliant with European Pharmacopoeia requirements. The suitability of the container-closure is based on stability studies where no interactions between the product and the container-closure system were detected.

2.2.3.2. Adventitious agents

Not applicable

2.2.3.3. Manufacture of the product

The manufacturing methods utilized are conventional manufacturing processes commonly used to produce parenterals and involve the following steps: 1) solution compounding including pH adjustment, 2) filtration, 3) sterilization of stoppers and overseals, 4) washing and depyrogenation of vials, 5) filling and capping, 6) terminal sterilization, and 7) inspection and packaging.

Validation studies have been carried out in several batches and are satisfactory**.** The in process controls are adequate for this pharmaceutical form.

2.2.3.4. Product specification

The drug product specifications include appropriate tests for appearance, identification, assay (HPLC, 95-105%), degradation products (HPLC), pH, osmolality (Ph Eur), particulate contamination (Ph Eur), extractable volume (Ph Eur), sterility (Ph Eur), and bacterial endotoxins (Ph Eur).

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are justified by toxicology studies.

2.2.3.5. Stability of the product

Stability data for 3 primary stability batches and 3 site-specific stability batches are provided. Two of the three primary stability batches as well as all three of the site-specific stability batches used drug substance originating from the proposed RC route. Samples for the site-specific stability batches were stored for up to 12 months of storage at 30ºC/65%RH and up to 6 months of storage at 40ºC/75%RH and samples for the primary stability batches were stored for up to 36 months of storage at 25ºC/60%RH and up to 6 months of storage at 40ºC/75%RH. The applicant stated that batches of the 500 mg commercial presentation will be manufactured and placed on stability using the same protocol as used for the 200 mg site specific stability batches (i.e., stored at 30°C/65% RH and at 40°C/75% RH at inverted position).

Samples were tested for the same parameters as for release with exception of identification.
As a conclusion from the stability studies, the results indicate satisfactory stability and support the shelf life and conditions of use as stated in the SPC.
In accordance with EU GMP guidelines 2 , any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe

2.3. Non-clinical aspects

2.3.1. Introduction

Vernakalant is a multi-ion channel blocker blocking potassium channels that control atrial action potential repolarisation (the transient outward potassium current (I_{to}), the ultrarapid delayed rectifier potassium current (I_{Kur}), the acetylcholine activated potassium current (I_{KACh}), the ATP-sensitive potassium current (K_{ATP}) and the rapid delayed rectifier potassium current (I_{Kr}) which is encoded by hERG), combined with voltage- and frequency-dependent blockade of cardiac sodium channels. These actions result in prolonged atrial refractoriness and rate-dependent slowing of atrial conduction and limited effects on ventricular electrophysiology.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics in vitro
Vernakalant blocked early-activating potassium channels (Ito, IKur and IKr) and the acetylcholine activated potassium channel (IKACh) that predominantly affect atrial repolarisation, combined with concentration-, voltage- and frequency-dependent blockade of sodium channels. The atrial specific currents, IKur and IKACh, were blocked with IC50 values which are in the therapeutic concentration range for humans (5-15 µM). Vernakalant did not inhibit IKs and IK1, which are important in ventricular repolarisation. Neither did it block calcium channels. Similar results were seen following exposure to the diastereomers of vernakalant. Although hERG channels were blocked by vernakalant, the potency of vernakalant was 30- to 100-fold less than that of the other anti-arrhythmic agents, quinidine or propafenone. At clinically relevant concentrations, vernakalant would not be expected to have side-effects related to pharmacological actions on other receptors systems. Vernakalant or its diastereomeric mixture RSD1225 had negligible to minor effects in isolated guinea pig or rabbit atrial or ventricular tissues. In rabbit whole-ventricle Purkinje fibres, vernakalant did not significantly alter the APD at clinically relevant concentrations. Vernakalant, at relatively high concentrations (30 µM), was effective in attenuating dofetilide-induced action potential prolongation and in terminating dofetilide-induced EADs in rabbit Purkinje fibres. Increases in APD90 observed following exposure to higher concentrations of vernakalant were minimal in comparison to Class III antiarrhythmic drugs, such as dofetilide. These results suggest a lower proarrhythmic potential for vernakalant than observed with dofetilide.

Primary pharmacodynamics in vivo
The primary effects of vernakalant in vivo were prolonged atrial refractoriness and rate-dependent slowing of atrial conduction. Vernakalant had less effect on the ventricular refractory period. This preferential effect on the atrial tissue lowers the risk of proarrhythmia compared to drugs that predominantly block sodium channels (e.g., Class IC, flecainide), or pure blockers of predominantly ventricular potassium channels (i.e. Class III, IKr blockers). The rate-dependent block of sodium channels at high activation rates during atrial arrhythmia further biases the action of vernakalant toward atrial tissue rather than toward the normally polarised ventricle beating at lower rates. Based on the mechanism of action, an effect of verkanalant on QT prolongation might be expected. It is surprising that in dogs, despite occasional findings in the 14-day repeated-dose toxicity study (LAB study 2000-622), no effect has been observed in the studies on primary pharmacodynamics. Although vernakalant blocked the hERG channel in vitro, it did produce no or little QT prolongation and early after depolarisations (EAD), the trigger for torsade de pointes (TdP) in rabbit Purkinje fibers and it did not induce TdP in a sensitive rabbit proarrhythmia model. In contrast, vernakalant attenuated proarrhythmic effects induced by dofetilide in rabbit Purkinje fibers and terminated clofilium-induced

Torsade de Pointes (TdP) in the rabbit proarrhythmia model. These effects are most likely due to blocking the late sodium inward current, which shortens the AP and is sufficient to offset its action on IKr, in combination with not blocking IKs. These actions are in contrast to those observed following exposure to agents such as ibutilide, which significantly prolong the QT interval and induce TdP at therapeutic plasma levels in various nonclinical models. Vernakalant converted AF in various animal AF-models, exerted a protective effect in porcine and rat ischaemia-induced arrhythmia, and did not exhibit ventricular proarrhythmic activity. In dogs, vernakalant converted AF with an ED_{50} of approximately 1 mg/kg, which is within the therapeutic range for humans. A conversion rate of 100% was observed at 4 mg/kg. Although decreases in blood pressure (BP) and heart rate (HR) were observed at elevated exposures to vernakalant in anaesthetised rats, guinea pigs, pigs and dogs, the potential for cardiovascular depression appears to be low based on experiments in conscious dogs and anaesthetised nonhuman primates. Similar effects were observed following exposure to the diastereomers of vernakalant. The ion channel activity of the metabolites RSD1385 and RSD1390 was less or equivalent to that of vernakalant. However, while electrophysiologically active on ion channels, neither metabolite is likely to have clinically relevant effects at the low plasma levels seen during clinical studies with vernakalant

2.3.2.2. Secondary pharmacodynamic studies

Non-clinical studies have been conducted to investigate potential mechanisms underlying hypotensive events associated with vernakalant injection. A dose-dependent left ventricular negative inotropic effect was seen with intravenous vernakalant in a haemodynamic study in anaesthetised dogs at high plasma concentrations (a ≥3-fold margin above the Cmax observed at therapeutic doses). Little or no vasodilatory effects were observed at these high concentrations. These data 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. Subjects with underlying left ventricular dysfunction or CHF (who have a higher incidence of hypotensive events after treatment with vernakalant) appear to be more sensitive to vernakalant, although it should be noted that vernakalant was not reported to induce or worsen heart failure in clinical trials. Three of the 4 most common side effects seen in humans were dysgeusia, sneezing and cough. The mechanism for these events was investigated and a direct effect of vernakalant on histamine release (i.e. mast cell activation) is unlikely. High single and repeat doses in animals resulted in toxicities predominantly, but not exclusively, related to neurological changes (excess salivation; tremor; emesis and tremor, convulsion, uncoordinated gait, decreased activity, dyspnoea and mortality at higher doses). In non-clinical models, vernakalant appears to have a significantly reduced potential for both ischaemia- and repolarisation-related pro-arrhythmia, compared to currently available Class I and III antiarrhythmic drugs, respectively. The effects of vernakalant on BP and QT-interval were investigated using PK/PD Modelling based on data from the intravenous phase III studies and is described in Safety section.

2.3.2.3. Safety pharmacology programme

Safety pharmacology studies were performed to examine the potential effects of vernakalant on cardiovascular, renal, respiratory, central, peripheral and autonomic nervous systems and gastrointestinal tract. Exposures achieved in these studies were at least equivalent to those achieved in man. In these studies, no significant vernakalant-related effects were seen on the central nervous, cardiovascular, or respiratory systems at clinically relevant dosages. Convulsions were only observed following infusion with supratherapeutic doses (64 µmol/kg/min; total cumulative dose in three rats: 425 to 550 µmol/kg) of vernakalant.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacodynamic interactions were observed between vernakalant and the ß blocker propranolol, the calcium channel blocker, verapamil or the anticoagulant warfarin.

2.3.3. Pharmacokinetics

Analysis
The methods of analysis have been sufficiently validated for vernakalant and its metabolites: RSD1385, and RSD1390 in plasma from rat, dog and rabbit. RSD1385 and RSD1390 were determined in rat plasma on the day of collection. These metabolites were thus analysed within a period in which the stability of the metabolites is within acceptable levels. The levels of RSD1385 (up to 41 ng/ml) and RSD1390 (below the limit of detection of 30 ng/ml) can be considered as true values and are not this low due to degradation of the metabolites before analysis. Accuracy and precision of RSD1231 was good. The stability of RSD1231 has been demonstrated.

Absorption
Most studies were performed with iv administration, which is the recommended administration route for the present application. Plasma concentrations of vernakalant declined rapidly after administration. For the tested doses, AUC of vernakalant increased in about a linear fashion with dose. For all animal species Cmax and AUC-values were observed that were higher than the Cmax and AUC in humans at the anticipated dose. Note that the administration of vernakalant in mouse, rat and monkey is infusion over a short period of time (20 sec to 2 min). In dog, the infusion is performed during 10 min. In humans, infusion during 10 or 20 minutes is recommended. As vernakalant rapidly distributes to tissues, the plasma profile during and directly after infusion is likely to be affected by the duration of the infusion. This should be considered when interpreting the PK data. When the same dose is administered during a longer period of infusion, the plasma concentration will probably be lower than when a shorter infusion time is used.

Distribution
Vernakalant is distributed rapidly and extensively to tissues. After a single iv dose, radioactivity in the tissues declines rapidly within 24 hours. At later time points (72 and 168 h postdose) radioactivity could only be determined in the gastrointestinal tract tissue and contents, liver (not in bile), kidney+urine and in Long Evans rats in the eye (at relatively high levels) and skin. The latter suggests binding of drug-derived radioactivity to melanin. Protein binding was low for vernakalant (25-50%). Blood:plasma concentration ratios were generally less than one, indicating that vernakalant does not specifically bind to erythrocytes.

Metabolism
RSD1231, a diastereomer of vernakalant, appears to be formed in man, especially in poor metabolizers. However, RSD1231 was not found in animal plasma, except occasionally in mouse plasma at low concentrations. Therefore, the toxicity of RSD1231 cannot be assessed in animal studies in which vernakalant is administered. The AUCs of metabolites RSD1385 and RSD1390 were low in the animal species tested, accounting for <2% for both metabolites in pregnant rabbit, and respectively <7% and <1% in dog. Cytochrome P450 2D6 appears to be the major isoenzyme able to transform vernakalant into RSD1385. As the enzymes involved in the transformation to RSD1390 and RSD1231 are unknown, potential interactions cannot be assessed. It should be recognised that these metabolites play a more prominent role in humans, especially poor metabolizers, than in animals. However, as the current application is for single use only, the potential for interactions with other drugs is not very large. For these reasons, further elucidation of the mechanism of metabolism for RSD1390 and RSD1231 is not required. However, this may change if the drug will be used in a chronic manner.

Excretion
Excretion was only assessed in rat and not in other animal species. Following intravenous administration of ^{14}C-vernakalant in the rat, most of the radioactivity was excreted in the faeces (60-69%). Nearly all radioactivity was excreted within the first 24 h postdose. Mostly phase II conjugates of vernakalant were found in the bile. Hence, it can be assumed that phase II conjugation reactions play a major role in the elimination of vernakalant. No studies were conducted on the excretion of vernakalant into breast milk. This is described in the SmPC. This can be understood as atrial fibrillation is a condition that occurs predominantly in elderly (> 55 years).

Pharmacokinetic drug interactions
Vernakalant and its diastereomer RSD1231 are substrates of P-glycoprotein. However, a major impact of interactions via P-glycoprotein is not anticipated as the drug is administered intravenously, thus circumventing interactions with other drugs via P-glycoprotein during first pass. On the other hand, a large fraction of vernakalant and its metabolites are excreted via the bile and may thus be reabsorbed.

An interaction via this pathway cannot be excluded. In vitro, drug-drug interaction studies were performed with vernakalant. For propafenone and fluoxetine, known as inhibitors of CYP2D6, an interaction is likely. Hence, the in vitro study suggests that interactions with drugs that are inhibitors or inducers of CYP2D6 cannot be ruled out. However, it is unlikely that clinically relevant interactions occur with these drugs in clinical practice. The CYP2D6 is involved in the metabolism of vernakalant to RSD1385. However, the mechanism by which vernakalant is transformed to RSD1390 and RSD1231 is unknown.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

The acute toxicity of vernakalant was investigated by a single intravenous administration in the rats, rabbits and dogs. The maximum tolerated dose in rats was higher than that in dogs, but lower than that in rabbits. Acute adverse effects included neurological effects in rats (uncoordinated gait, tremors, decreased activity), rabbits (ataxia, head shaking, splayed posturing, reduced proprioception, coarse tremor, decreased locomotor activity) and dogs (tremors, salivation, convulsions and disorientation). These signs appear to be related to the pharmacological activity (ion channel blockade). These effects disappeared after 15-20 minutes after administration. No effects on body weight, food consumption or clinical laboratory parameters were identified. In plasma, the concentration of vernakalant rapidly declined within 24 hours after infusion. At NOAEL doses, the plasma concentration in rats (7.5 µg/ml) and 10 mg/kg in rabbits (3.4 µg/ml) were in the same range as that at the proposed clinical dose in human (5.5 µg/ml). As vernakalant rapidly distributes to tissues, the plasma profile during and directly after infusion is likely to be affected by the duration of the infusion. It should be noted that the administration of vernakalant in rats and rabbits is infusion over a short period of time (2-5 min). In dog, the infusion is performed during 10 min. In humans, infusion during 10 or 20 minutes is anticipated. This should be considered when interpreting the toxicological data. Based on these considerations, no effects are expected in human.

2.3.4.2. Repeat dose toxicity (with toxicokinetics)

Repeated dose toxicity studies for 7, 14 and 28 days were performed in rats by a 2-minute intravenous infusion and in dogs by 10-minute intravenous infusion once daily. The results showed no relevant macroscopic or histopathology findings. In both species, the overt symptoms were essentially the same as those observed in the single-dose toxicity studies. Despite the fact that in these studies vernakalant was daily administrated, these symptoms consequently disappeared within 20 minutes (rats) or 60 minutes (dogs) after dosing. There were also no findings that these symptoms became worse upon duration of treatment. In rats, the NOAEL for overt symptoms was 10 mg/kg/day in the 14–day study and 20 mg/kg/day in the 7- and 28-day studies. In dogs, these NOAEL are 10 mg/kg/day and 5 mg/kg/day, respectively. These NOAEL values are in the same range as those observed in the single dose toxicity studies. In the 14-day study in dogs, two animals showed occasionally a prolongation of the QRS complex and/or some ST changes. Based on the mechanism of action of vernakalant, a similar effect might be expected. Further, in the 14- and 28-day studies in dogs, minimal to moderate hemorrhages and minimal to mild subcutaneous inflammation were noted at the site of injection. In view of the fact that vernakalant is intended for single dose administration, these findings are not a concern for human.

2.3.4.3. Genotoxicity

Vernakalant does not exhibit genotoxic potential, since it was not genotoxic in the bacterial reverse mutation assay (Ames test) and in in-vitro and in-vivo assays on chromosome aberrations.

2.3.4.4. Carcinogenicity

Long-term carcinogenicity studies were not performed. This was accepted since vernakalant is intended for single administration.

2.3.4.5. Reproduction Toxicity

Segment I studies were conducted in rats, segment II studies in rats and rabbits, whereas segment III studies were performed in the rats. In these studies, vernakalant was dosed via a slow intravenous injection/infusion, ~2 min in rats, and ~5 min in rabbits once daily. In the Segment I rat study, there

was no effect on male and female fertility. There was no effect on mating, oestrous cyclicity, sperm parameters, or other fertility indices, pregnancy, and litter parameters. The litter averages for corpora lutea, implantations, viable and nonviable embryos and percentage of nonviable embryos per litter were not significantly different among the four dose groups. In the Segment II studies, specific malformations (short/absent tails, vertebral malformations, short/absent digits) were seen in single instances in rats and rabbits which had also been described for another Class III antiarrhythmic drug (almokalant) and therefore might have been classified as treatment related. In response to Day 120 LoQ, the applicant submitted two further embryofetal development studies in rats and rabbits, respectively, with oral administration of vernakalant two times a day. In these studies short/absent tails, vertebral malformations, and short/absent digits were not observed although the exposure levels were higher than those obtained in the intravenous studies and thus these specific malformations do not appear to be treatment related. However, based on the results of the oral embryofetal development studies where other malformations (misshapen/absent/fused skull bones including cleft palates, bent radius, bent/misshapen scapula, constricted trachea, absent thyroid, undescendent testes) were observed in almost all rat fetuses from the high dose group and an increased embryofetal lethality, increased number of fetuses with fused and/or additional sternebrae was seen in rabbits at the highest doses tested, it has to be concluded that vernakalant has a teratogenic potential. As the exposure in the intravenous embryofetal development studies was not sufficient when compared to the human exposure teratogenic effects cannot be excluded for humans even after a single dose of intravenous vernakalant. For safety reasons the results of the embryofetal development studies performed with oral vernakalant are included into sections 4.6 and 5.3 of the SPC. The placentas appeared normal. No conclusions can be drawn on the potential of vernakalant to traverse the placenta, as no studies have been performed. In the Segment III study in rats, the maternal NOAEL was 20 mg/kg/day, whilst that for reproduction in the dams and viability, growth and development in the offspring was 40 mg/kg/day. No studies have been conducted on the excretion of vernakalant into breast milk.

2.3.4.6. Local Tolerance

The potential for injection site toxicity was examined in a 14-day repeated-dose IV dog study. No test article-related toxicity was observed. In the 28-day IV toxicity study in the dog, the microscopic finding of minimal to moderate "haemorrhage" correlated with the macroscopic observation "discolouration, red" at the injection site in all vernakalant dose groups. Minimal to mild subacute inflammation was also seen at the injection site of some vernakalant-treated dogs.

2.3.4.7. Other toxicity studies

Hemolytic potential
VH at a concentration of 20 mg/ml and dilutions of this stock solution in sodium chloride did not cause hemolysis of rat erythrocytes. According to section 6.6 of the SPC, VH should be diluted to 4 mg/ml before use. This means that at the concentration to be used clinically, no hemolytic activity is expected in human.
Metabolites
In humans and preclinical species, circulating metabolites of vernakalant include the major metabolite, RSD1385, a 4-O-demethylated metabolite, and RSD1390 the minor 3-O-demethylated analogue. AUC values of metabolites RSD1385 and RSD1390 were low in the animal species tested. The third metabolite RSD1231, a diastereoisomer of vernakalant, was not found in animals, but was found in human at low levels, most commonly after repeat oral dosing and/or in poor metabolisers. The potential repeated dose toxicity and mutagenicity and clastogenicity of this metabolite have therefore been examined. The results of these studies showed no concerns.
Phototoxicity
The phototoxic potential has not assessed. This is approved by the CHMP, since vernakalant does not to absorb light in the wavelength range 290 – 700 nm.
Impurities
The proposed limits of isomeric impurities in the drug substance are NMT 0.2% for RSD1230 and RSD1234 and NMT 0.3% for RSD1231. These limits are qualified by the presence of sufficient excess of these impurities in the batches of the drug substance in the toxicology studies.
Four genotoxic impurities have been identified in vernakalant. TCA and TCI-DMPE are genotoxic impurities as part of the manufacturing process. Cyclohexene oxide and trichloroacetonitrile are two further genotoxic impurities. These four impurities are genotoxic by mutagenic activity. For the presence of genotoxic impurities in the drug substance, the applicant has calculated a limit of 343 ppm. This limit is based on the fact that vernakalant is recommended for a single dose only.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA was submitted based on the EMEA/CHMP/SWP/4447/00 guideline (CHMP, 2006) together with a study in which the log K_{ow} of the active ingredient was determined. The log K_{ow} of vernakalant is < 4.5, hence the substance is considered to be not bioaccumalative. Based on this screening criterion, VH is considered not to be PBT (persistent, bioaccumalative, toxic). Using this Fpen and the dose of 453 mg/patient/day, PEC surface water = 9.5 ng/L, which is below the trigger value it was considered that a further assessment is not deemed necessary. A low environmental exposure of the product is expected in this special case because it is a medicinal product used in case of emergency and only in a monitored clinical setting.

2.3.6. Conclusion on the non-clinical aspects

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, and genotoxicity. With respect to reproduction no effects on pregnancy, embryofoetal development, parturition or postnatal development were observed after intravenous administration of vernakalant at exposure levels (AUC) similar or below the human exposure levels (AUC) achieved after a single intravenous dose of vernakalant. In embryofetal 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 intravenous 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 embryofetal lethality, increased number of foetuses with fused and/or additional sternebrae were seen in rabbits at the highest doses tested.

2.4. Clinical aspects

2.4.1. Introduction

Vernakalant hydrochloride is an entirely synthetic new chemical entity with a potassium and sodium channel blocking profile that is enhanced under the conditions of AF and results in predominantly atrial selective actions and a reduced potential for ventricular proarrhythmia.
The proposed dosing regimen is an initial infusion of 3 mg/kg over 10 minutes. If conversion to sinus rhythm 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. The maximum proposed dose for marketing is 5.0 mg/kg.
Most drugs currently in use for treatment of AF are indiscriminate, targeting channels in both atrial and ventricular tissue and are therefore associated with life-threatening ventricular arrhythmias. VH is an intravenous antiarrhythmic agent for the rapid conversion of symptomatic recent onset AF (≤ 7 days duration) to sinus rhythm in haemodynamically stable patients.
It is the first of a new generation of AF converting agents that show preferential effects for atrial tissue and limited actions on ventricular tissue. Vernakalant has been designed to minimise the proarrhythmic risk associated with previous generations of antiarrhythmic agents.
Vernakalant exerts its anti-arrhythmic activity in the atria by concentration dependent blockade of early activating potassium channels and the acetylcholine activated potassium channel combined with concentration-, voltage- and frequency dependent blockade of sodium channels.
The net result is prolonged atrial refractoriness and rate-dependently slowed atrial conduction.
The clinical development programme for VH injection consists of 12 clinical studies (six are submitted under the clinical pharmacology section and six to support efficacy/safety). In addition, a Phase 3 active comparator study versus amiodarone was submitted together with the responses to the D120 LoQs.
Scientific Advice from the EMEA was given during the following procedure: EMEA/H/SA/938/1/2007/SME/II. Scientific advice was also sought from different EU regulatory authorities: NL, UK, SE, FR.

2.4.2. GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Number (Acronym)	Study and Population	Design	Exposure	
			Placebo	Vernakalant Injection
Clinical Pharmacology/Pharmacodynamic Studies				
1235-1-04-12-01	Phase 1 in HV	Single rising dose	6	23
04-0-195	Mass balance in HV	Radiolabel study	0	8
1235-SMH1[a]	Phase 2 in patients undergoing electrophysiological evaluation	Electrophysiology study	0	19
6517-CL-0011	Phase 1 in HV	Single dose, 4-way crossover, dose proportionality	13	12
VERO-106-REN	PK and safety in subjects with normal renal function and mild, moderate and severe renal impairment	Open-label, Two-way crossover, Single dose	0	24
VERO-107-HEP	PK and safety in subjects with normal hepatic function and mild, moderate and severe hepatic impairment	Open-label, Two-way crossover, Single dose	0	24
		Total Clinical Pharmacology:	**19**	**110**
Efficacy/Safety Studies				
1235-0703 (ACT I) Pivotal	Phase 3 in AF patients	Double-blind, placebo-controlled	115	221
04-7-010 (ACT III) Pivotal	Phase 3 in AF or AFL patients	Double-blind, placebo-controlled	131 (AF: N=121)	134 (AF: N=118)
1235-0104 (ACT II) Pivotal	Phase 3 in post-cardiac surgery AF or AFL patients	Double-blind, placebo-controlled	54 (AF: N=50)	107 (AF: N=100)
05-7-012 (ACT IV)	Phase 3 in AF patients	Open-label safety study	0	236
1235-1001 (CRAFT)	Phase 2 in AF patients	Double-blind, placebo-controlled	20	36
1235-0703B (Scene 2)	Phase 2/3 in AFL patients	Double-blind, placebo-controlled	15	39
		Total Phase 2/3 Efficacy/Safety Studies:	**335**	**773**
		TOTAL ALL STUDIES:	**354**	**883**

2.4.3. Pharmacokinetics

2.4.3.1. Absorption

In patients, average peak plasma concentrations of vernakalant were 3.9 µg/ml following a single 10 minute infusion of 3 mg/kg VH, and 4.3 µg/ml following a second infusion of 2 mg/kg with a 15 minute interval between doses.

2.4.3.2. Distribution

Vernakalant is extensively and rapidly distributed in the body, with a volume of distribution of approximately 2 l/kg. It's rapid distribution leads to a decrease in serum concentration by > 40% from peak within 5 minutes after the end of infusion. A dose proportional increase in $AUC_{0\text{-}90min}$ was observed in patients who received both the 3 mg/kg and 2 mg/kg infusions compared to those that only received a single 3 mg/kg infusion. The mean Vss (123.13 L for extensive metabolisers, 112.66 L for poor metabolisers) was approximately 30 times the total blood volume (approximately 5.2 L for an average 70 kg human) and approximately 3 times the total body water (approximately 42 L for an average 70 kg human). Vernakalant is distributed into saliva. Vernakalant is not extensively bound to plasma proteins. The free fraction of vernakalant was 53-63% in human serum.

2.4.3.3. Elimination

Vernakalant is mainly eliminated by CYP2D6 mediated O-demethylation in CYP2D6 extensive metabolisers (EM). Glucuronidation and renal excretion are the main mechanisms of elimination in CYP2D6 poor metabolisers (PM). The mean elimination half life of vernakalant in patients was approximately 3 hours in CYP2D6 EM and approximately 5.5 hours in PM. Vernakalant is extensively metabolised, primarily by CYP2D6. RSD1385 is the major plasma metabolite, occurring primarily in the glucuronidated form, and RSD1390, is scarcely present or undetectable. Metabolism of vernakalant is slower and less extensive in CYP2D6 PM, who have higher concentrations of unchanged vernakalant systemically, and have a higher proportion of vernakalant excreted unchanged in the urine. Direct glucuronidation of vernakalant is more important in these subjects. RSD1231, a diastereomer of vernakalant, and its glucuronide, RSD1231G, are also observed primarily in PM, but at relatively low levels. Finally, hydroxylation of vernakalant, which is followed by excretion in the faeces, was also detected in PM. According to the applicant no other CYP isozymes are involved in the metabolism of vernakalant. The enzymes involved in the in vivo metabolism of vernakalant into metabolite RSD1390 is unknown. The metabolic pathway leading to the formation of RSD1231 in CYP2D6 PM is not well understood. RSD1231 is a diastereomer of vernakalant resulting from the chiral inversion of vernakalant's pyrrolidinyl hydroxyl group. With respect to the clinical importance, in a short term iv application the issue of a possible metabolic pathway does not require further investigations.

Consequences for genetic polymorphism. Differences in vernakalant metabolism have been observed in CYP2D6 PM compared to EM following a dose of vernakalant injection. Metabolism is slower and less extensive in PMs. PMs have higher concentrations of unchanged vernakalant systemically, and higher proportions of vernakalant excreted unchanged in the urine. However, in both EM, representing the majority of individuals and PMs of CYP2D6 vernakalant is rapidly and widely distributed, which reduces the potential difference in acute exposure between EMs and PMs. Peak concentrations of vernakalant are comparable in EMs versus PMs after single- or double-infusions (approximately 8% higher for PM's). Furthermore, PM's were found to have a 50% lower vernakalant clearance, which resulted in an acute exposure ($AUC_{0\text{-}90\ min}$) of vernakalant for PM's approximately 15% higher than Ems. The difference in total AUC might be higher but is not of clinical relevance. Therefore, dose adjustment based on metaboliser status is not necessary. Vernakalant showed linear pharmacokinetic properties in the dose range of 0.1 mg/kg to 5 mg/kg following a 10-minute intravenous infusion.

2.4.3.4. Dose proportionality and time dependencies

VH showed linear pharmacokinetic properties in the dose range of 0.1 mg/kg to 5 mg/kg following a 10-minute intravenous infusion. Time dependency was not studied. This was considered by the CHMP acceptable as VH is not intended to be used chronically.

2.4.3.5. Special populations

Acute exposure is not significantly influenced by gender, history of congestive heart failure, renal impairment, or concomitant administration of beta blockers and other medications, including warfarin, metoprolol, furosemide and digoxin. In patients with hepatic impairment, exposures were elevated by 9 to 25%. No dose adjustment of VH is required for these conditions, nor on the basis of age, serum creatinine or CYP2D6 metaboliser status.

2.4.3.6. Pharmacokinetic interaction studies

Vernakalant is a substrate for P-glycoprotein and is a substrate and moderate inhibitor of CYP2D6. Albeit no inhibition of P-Gp was observed in vitro from patients receiving e.g. immunosuppressant agents as cyclosporine are of relevance. According to the applicant, at present, there is no indication of a PK interaction with cyclosporine. As vernakalant is less than 50% bound to serum proteins, binding related drug interactions are not expected. Only drug-drug interactions for the vernakalant oral formulation were presented by the applicant. However, relevance of these oral formulation drug-drug interaction studies is limited due to the lack of first pass metabolism on iv administration and the minimal effect of CYP2D6 expression and concomitant use of CYP2D6 inhibitors on Cmax and AUC0-90min with acute iv administration. While the terminal elimination phase may be slowed by CYP2D6 inhibitors, rapid and extensive distribution is the main determinant of Cmax with iv dosing. A population PK study of the interaction of CYP2D6 inhibitors, beta-blockers, and the four most commonly used concomitant medications (warfarin, metoprolol, furosemide and digoxin) with vernakalant did not suggest that dose adjustment was required for vernakalant. Especially as vernakalant injection is indicated for rapid intravenous therapy (duration of 30 minutes) and is dosed to a known, well-defined pharmacologic action (conversion of arrhythmia) or to a maximum of two 10-minute infusions. However, the clinically most relevant interaction to be excluded is a possible interaction with vitamin K antagonists. The Pop-PK study does not sufficiently address this issue. The applicant commented on the lack of a formal interaction study between vernakalant and Vitamin K antagonists. It is stated that based on theoretical considerations on the known metabolic pathways and excretion of warfarin and other vitamin. K antagonists, as well as on preclinical studies no interactions with vernakalant are expected. The points raised by the applicant were considered by the CHMP valid especially for the short term i.v. use.

2.4.4. Pharmacodynamics

2.4.4.1. Mechanism of action

Vernakalant is an anti-arrhythmic medicine that acts preferentially in the atria by prolonging atrial refractoriness and by rate-dependently slowing impulse conduction. These anti-fibrillatory actions on refractoriness and conduction are thought to suppress reentry, and are potentiated in the atria during AF. The preferential effects of vernakalant on the atria are postulated to result from its block of currents that are expressed in the atria (e.g., the ultra-rapid delayed rectifier potassium current; and the acetylcholine-activated potassium current), but not in the ventricles, as well as the unique electrophysiologic condition of the fibrillating atria. Because of its relatively atrial selective actions, vernakalant does not readily fit in the Vaughan Williams anti-arrhythmic drug classification, which is based on ventricular activity (for further discussion on clinical effect of vernakalant on ventricular conduction, please see below under Thorough analysis of QT data).

2.4.4.2. Primary and Secondary pharmacology

The pharmacodynamic program for vernakalant is quite limited, especially as it represents a new class of anti-arrhythmics. In the single PD study (1235-SMH1), two dose levels of vernakalant were infused iv (a total of 2.5 mg/kg or 5 mg/kg). The results showed that vernakalant prolonged atrial effective refractory period (AERP) in a dose-dependent manner, which was not associated with an increase in ventricular effective refractory period VERP. A significant increase in PR-interval was observed with the higher dose but this was not accompanied by bradycardia. However, the clinical significance of this finding could better be identified in the pivotal studies. No significant changes were detected in the ECG recordings, but the numbers are too limited precluding robust conclusions. No further clinical studies were conducted to investigate other pharmacodynamic properties of vernakalant. The applicant mainly refers to animal data and PK/PD modelling. The animal data in addition to experience from clinical trials show that vernakalant can lead to hypotension in susceptible patients. According to non-clinical data, this hypotension could probably be mediated through a negative inotropic effect. However,

clinical data investigating this mechanism is lacking. A population pharmacokinetic-pharmacodynamic analysis of vernakalant injection in patients with AF or AFL was conducted to describe exposure-response relationship for QT interval and systolic blood pressure (SBP) using data collected in ACT I, ACT II, ACT III, ACT IV, and SCENE 2 trials. The main results are discussed in the Safety section. Similarly, the cause of dysgeusia, sneezing and cough was not further investigated clinically.

2.4.5. Clinical efficacy

Table E1: Clinical Studies for Vernakalant Injection

Study Number (Acronym)	Phase	Population/ Disease Duration	Vernakalant Dose[a]	Design	Number of Patients by Treatment		
					Pbo	Vkt	Total
PIVOTAL							
ACT I	III	AF > 3 hours to ≤ 45 days	3.0 mg/kg, + 2.0 mg/kg if required [c]	Randomised, Double-blind, Placebo-controlled	115	221	336
ACT III	III	AF or AFL[b] > 3 hours to ≤ 45 days	3.0 mg/kg, + 2.0 mg/kg if required [c]	Randomised, Double-blind, Placebo-controlled	131	134	265
ACT II	III	AF or AFL post-cardiac surgery[b] > 3 hours to ≤ 72 hours	3.0 mg/kg, + 2.0 mg/kg if required [c]	Randomised, Double-blind, Placebo-controlled	54	107	161
Supportive							
CRAFT *Dose finding study*	IIa	AF > 3 hours to ≤ 72 hours	0.5 + 1.0 mg/kg or 2.0 mg/kg, + 3.0 mg/kg if required [c]	Randomised, Double-blind, Placebo-controlled	20	36	56
ACT IV *Safety study*	III	AF > 3 hours to ≤ 45 days	3.0 mg/kg, + 2.0 mg/kg if required [c]	Open-label	0	236	236
Scene 2 *Patients with AFL*	II/III	AFL > 3 hours to ≤ 45 days	3.0 mg/kg, + 2.0 mg/kg if required [c]	Randomised, Double-blind, Placebo-controlled	15	39	54
VERI-305-AMIO (AVRO)[d] *Comparative study*	III	AF >3hours to ≤48 hours	3.0 mg/kg, + 2.0 mg/kg if required [c]	Randomised, Double-blind, Active-controlled	120[e]	120	240

a Patients assigned to the control group received placebo (saline). b Studies included small numbers of patients with AFL. After these studies were initiated, results from a phase 2/3 study showed Vernakalant to be ineffective for conversion of atrial flutter at the doses studied. The indication for this application is conversion of atrial fibrillation to sinus rhythm. c The second dose of Vernakalant injection or placebo was administered if the patient was in AF or AFL at the end of the observation period following the first dose. d This study is currently ongoing. e Amiodarone, and not placebo, is the comparator in the AVRO study.

2.4.5.1. Dose response study

The currently proposed dose is 3.0 mg/kg followed by 2.0 mg/kg if required. Animal studies and phase I studies showed that single doses up to 4-5 mg/kg were tolerated but accompanied with mild neurosensory side effects and transient ECG changes. Therefore, the choice of investigating doses less than 4 mg/kg seems reasonable.

CRAFT (1235-1001)

Methods
CRAFT was a proof-of-concept phase IIa prospective, randomised, double-blind, placebo-controlled, dose-ranging, multicentered study to investigate the tolerance and efficacy of vernakalant. Patients with new or recurrent AF at baseline for a period of > 3 hours but < 72 hours were recruited. Patients were randomized to one of three arms: 2 dose regimens of vernakalant or placebo. The lower dose group received 0.5 mg/kg IV over 10 minutes followed by a 30-minute observation period, and if no conversion to sinus rhythm or termination of AF was seen, a dose of 1 mg/kg was given over 10 minutes. The higher dose group received 2 mg/kg over 10 minutes and if conversion or termination of AF did not occur within a 30-minute observation period, a second dose of 3 mg/kg was administered.
The primary efficacy endpoint was termination of AF during infusion or the 30-minute post-infusion period following either dose. Secondary endpoints included the number of patients in sinus rhythm at 30 minutes, 1 hour, and 24 hours after the end of the first infusion, and the time to conversion of AF to sinus rhythm. In this study, the term "termination" of AF was defined as the absence of AF and the term "conversion" of AF was defined as the presence of sinus rhythm.

Results
Patient disposition This study included 65 patients at 15 clinical sites in Canada and the United States. Of these, 56 received study medication and completed the study. The majority of patients were white (53/56, 94.6%) and male (34/56, 60.7%). Mean age was 60.9 years (min, 24 years; max, 88 years). Treatment groups were comparable in demographics, other baseline characteristics, vital signs and prior medications. Prior to dosing, duration of AF in the treatment groups was 24.7 hours (mean) and 19.5 hours (median) for vernakalant 2.0+3.0 mg/kg, 23.6 hours (mean) and 11.5 hours (median) for vernakalant 0.5+1.0 mg/kg, and 17.8 hours (mean) and 13.3 hours (median) for placebo.
Efficacy Results: A dose response between the treatments can be observed, with termination of AF occurring in 5.3% of placebo patients, 11.1% of patients receiving 0.5+1.0 mg/kg vernakalant injection, and 61.1% of patients receiving 2.0+3.0 mg/kg vernakalant injection. AF termination was significantly greater with the high dose (2.0+3.0 mg/kg) compared to the low dose (0.5+1.0 mg/kg) vernakalant groups and compared to placebo. Only the higher dose regimen resulted in significant termination of AF compared to placebo (a total conversion rate 61.1% compared to 5.3% for placebo, p=0.0003, at 30 minutes). At 24 hours, the rate of conversion in the high dose vernakalant group (excluding electric cardioversions) was only numerically higher than that of placebo: 78.6% versus 50% respectively. The median time to conversion was significantly reduced from 162 min in the placebo group to 14 minutes using vernakalant. The results of CRAFT study support that vernakalant (2 mg/kg IV infusion + 3 mg/kg IV infusion if necessary) is more effective than placebo in converting AF to SR within the first hour. At 24 hours, no significant advantage over placebo is seen.

Choice of dose
Doses of 2 mg/kg and 3 mg/kg resulted in termination of AF in 44.4% and 36.4% of the patients respectively in CRAFT. In the pivotal trials, the applicant investigated administering the higher dose first aiming for better results with the first dose. The rationale was accepted by the CHMP and is supported with PK data that showed that average peak plasma concentrations of vernakalant were 3.9 µg/ml following the 3 mg/kg vernakalant, increasing further to 4.3 µg/ml following a second infusion of 2 mg/kg within 15 minutes interval.

2.4.5.2. Main studies

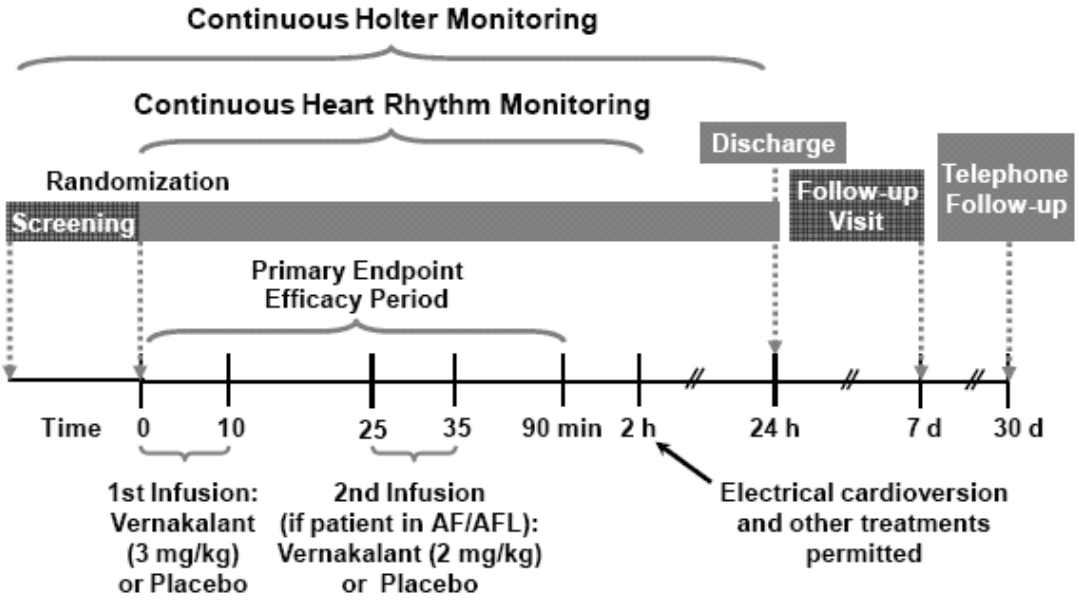
There were three pivotal studies submitted. ACT I and ACT III have almost identical design and address patients with paroxysmal AF, while ACT II recruited patients with AF after cardiac surgery. ACT I and ACT III are therefore presented together.

ACT I/III:

2.4.5.2.1. Methods

These were randomised, double-blind, placebo-controlled, multicentre, efficacy and safety studies in patients with AF/AFL. The results of the supportive study Scene-2 showed that vernakalant was not effective in patients with AFL and accordingly the objectives of ACT III were re-focused on AF patients only by an amendment. This approach was considered by the CHMP as acceptable. The current report focuses on the results pertaining to the claimed indication i.e. short term AF (3 hrs to 7 days). Patients were administered vernakalant 3 mg/kg as a 10-minute infusion or placebo. The infusion was followed

by a 15-minute observation period after which a second 10-minute infusion of vernakalant 2.0 mg/kg or placebo was administered if the patient was in AF or AFL at the end of the observation period. The design of the clinical studies was comparable and is depicted in figure below.



2.4.5.2.1.1. Study Participants

Patients 18 years of age or older with a diagnosis of AF ranging in duration from > 3 hours to ≤ 45 days were recruited. Patients were stratified on the basis of AF duration of either 3 hours to 7 days or 8 days to 45 days. In the ACT I study, a total of 360 patients were planned to be enrolled of which 240 were to have AF duration 3 hours to 7 days and 120 were to have AF duration 8 days to 45 days. In the ACT III study, a total of 280 patients were planned to be enrolled, of which 200 were to have AF or AFL duration 3 hours to 7 days and 80 were to have AF or AFL duration 8 days to 45 days. Within each of these strata, patients were randomly assigned to receive vernakalant injection or placebo (2:1 randomisation in ACT I and 1:1 randomisation in ACT III).

Main Inclusion Criteria

The study population in the pivotal phase III studies consisted of adults (≥ 18 years) who were haemodynamically stable with a current arrhythmia episode of >3 hours and ≤ 45 days. Identification of the baseline rhythm, initial therapy, and post-treatment care was according to standard clinical procedures and the investigator's judgment. Patients with pacemakers were included in the studies, as they were patients with a history of a variety of cardiac conditions, including ischaemic heart disease, hypertensive heart disease, stable congestive heart failure and myocardial infarction (if the infarction occurred more than 30 days prior to dosing). Serum potassium was corrected if < 3.5 mEq/L. Patients on background cardiac rate control drugs such as beta-adrenergic blocking agents, calcium antagonists, or digoxin were allowed in the study. Patients were also allowed concurrent oral antiarrhythmic medication.

Main Exclusion Criteria

Patients were excluded if they had unstable New York Heart Association (NYHA) Class IV congestive heart failure (CHF), or heart failure requiring intravenous inotrope therapy. Patients with prolonged QT syndromes, myocardial infarction or cardiac surgery within the past 30 days, or acute coronary syndrome were also excluded. Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis or significant valvular stenosis were excluded from the later stages of the ACT III study by a protocol amendment. Adequate warnings are implemented in the SPC to indicate these excluded subgroups. Patients who develop AF after cardiac surgery were included in the ACT II study.

2.4.5.2.1.2. Treatments

Patients were to receive a 10-minute infusion of vernakalant injection (3.0 mg/kg) or placebo. The infusion was followed by a 15-minute observation period after which a second 10-minute infusion of vernakalant 2.0 mg/kg or placebo was administered if the patient was in AF or AFL at the end of the observation period. For patients who weighed > 113 kg, the dose was to be based on a weight of 113 kg. The infusion was to be discontinued if the uncorrected QT interval increased to >0.550 seconds or by >25%; HR decreased between 40 and 50 bpm with symptoms or to <40 bpm; SBP increased to >190 mm Hg or decreased to <85 mm Hg; new bundle-branch block developed or QRS increased ≥50%; or polymorphic ventricular tachycardia, a sinus pause of ≥5 seconds, or intolerable side effects occurred. Study completion was defined as participation in the study through the last protocol-defined assessment (telephone follow-up at 30 days post-dose). The study blind was maintained until database lock unless un-blinding was required for safety reasons.

2.4.5.2.1.3. Objectives

The primary objective was to demonstrate the effectiveness of vernakalant injection 3.0 mg/kg, followed by 2.0 mg/kg if required, in the conversion of AF (and AFL in ACT III) to sinus rhythm for a minimum duration of 1 minute, within 90 minutes of first exposure to study drug (time 0 = start of first infusion). The secondary objective was to assess the safety of vernakalant injection in this patient population.

2.4.5.2.1.4. Outcomes/endpoints

The primary efficacy endpoint for both pivotal trials was the proportion of patients with AF of > 3 hours to ≤ 7 days duration who converted to sinus rhythm for a minimum duration of 1 minute within 90 minutes of first exposure to study drug. Although patients with durations of AF till 45 days were recruited, the primary endpoint focused on patients with paroxysmal AF (≤7 days). Pharmacological cardioversion is considered more effective in this subgroup. In the CHMP SA given to the applicant, the chosen primary endpoint was considered appropriate and in line with clinical requirements for rapid pharmacological response, however, the clinical relevance of the conversion to SR of 1 minute duration was questioned. A clinically relevant conversion to SR was considered to be at least of 24-48 hours duration. The time limit of 1.5 hours and the fact that electric cardioversion and other therapies were allowed after 2 hours limit the possibility to observe the spontaneous cardioversion rate. Analyses of maintenance of sinus rhythm for longer periods are currently submitted. The CHMP scientific advice also proposed further analysis for the duration of AF e.g. less than 48 hours and AF of unknown duration, which will be discussed below. A Clinical Events Committee (CEC) composed of four cardiologists was employed to confirm efficacy endpoints. CEC members were blinded to treatment assignment.

2.4.5.2.1.5. Sample size

In ACT I and ACT III, the study plan called for 360 and 280 patients to be stratified at enrolment based on duration of AF (and AFL in ACT III) respectively. Stratification was to result in 240 and 200 patients with short-duration AF and 120 and 80 patients with long-duration AF respectively.

2.4.5.2.1.6. Randomisation

Patients within each cohort were then randomly assigned to treatment in a 2:1 (vernakalant:placebo) ratio in ACT I and a 1:1 in ACT III.

2.4.5.2.1.7. Blinding (masking)

The study blind was maintained until data base lock except for study ACT II which had an interim safety analysis (an additional interim safety analysis was added to ACT II in support of a requirement by the FDA; ACT II is further discussed below).

2.4.5.2.1.8. Statistical methods

The primary efficacy analysis for the ACT I/ACT III pooled pivotal data was conducted using the full analysis set defined as all randomised patients with AF who received any amount of study drug (vernakalant injection or placebo). The same population was used for primary efficacy analysis in the individual studies and had been defined *a priori* in the respective analysis plans. The statistical methods were considered by the CHMP acceptable.

2.4.5.2.2. Results

Patient disposition
Patient disposition in ACT I and ACT III is presented by treatment in table E4.

Table E4: Patient Disposition in ACT I and ACT III.

	ACT I				ACT III			
	Number (%) of Patients				Number (%) of Patients			
Disposition Parameter	Placebo (N = 119)		Vernakalant (N = 237)		Placebo (N = 121)		Vernakalant (N = 119)	
Randomised	119	(100)	237	(100)	121	(100)	119	(100)
Short duration AF cohort (>3h to ≤7 days)	79	(66.4)	158	(66.7)	84	(69.4)	86	(72.3)
Long duration AF cohort (8 days to ≤45 days)	40	(33.6)	79	(33.3)	37	(30.6)	33	(27.7)
Study Drug Received								
Any amount	115	(96.6)	221	(93.2)	121	(100)	118	(99.2)
Completed first dose	115	(96.6)	215	(90.7)	120	(99.2)	114	(95.8)
Any amount of second dose	114	(95.8)	150	(63.3)				
Completed second dose	113	(95.0)	148	(62.4)	118	(97.5)	77	(64.7)
Study Completion Status								
Completed study[a]	114	(95.8)	216	(91.1)	119	(98.3)	117	(98.3)

Of the patients randomized in ACT I, twenty one patients (8.9%) in the vernakalant group versus 5 patients (4.2%) in the placebo group, withdrew from the study. Almost half of these patients withdrew due to spontaneous conversion to SR. This emphasizes the importance of knowing the spontaneous conversion rate in this population. Most importantly, 3 patients died (rupture aortic aneurysm, pulmonary edema and pneumonia and respiratory arrest). The causes of death were considered not related to vernakalant. Two cases of myocardial infarction also led to withdrawal. The list of withdrawals is more limited in ACT III: (only 2 patients in either group). The patient's withdrawal in the vernakalant group due to ventricular fibrillation ended in death related to study drug.

2.4.5.2.2.1. Baseline data

No significant differences were observed between treatments in the overall population or short-duration cohort for the baseline demographic parameters (age, sex). Still, the representation of females (29.4%) and to a lesser extent older patients ≥ 75 years (19%) appears quite limited. In the pooled analysis, treatment groups were balanced with respect to baseline use of rate and rhythm control medications and patients with implanted rate control devices. However, some significant differences in the background use of antiarrhythmic drugs (AAD) was observed within the individual studies, in particular: in ACT III, the use of Class I AAD was significantly more in the vernakalant group (18.6% vs. 7.1% for placebo p= 0.026) and the use of digoxin was significantly more in the placebo group (15.5% vs. 5.8% for vernakalant p=0.041). The use of sotalol in ACT I was also higher (14.3%) than ACT III (6.3%). Such discrepancies in individual studies are probably corrected when examining the primary efficacy population. Most of the recruited patients presented with AF-related symptoms (89.5% and 79.4% in ACT I and ACT III respectively). The reported symptoms included palpitation, rapid heart rate and fatigue. Groups were generally balanced in their background medical history. It can be observed that the recruited patients were not a high risk group, with hypertension recorded in only 42%, ischemic heart disease in (10-20%), myocardial infarction in 6-10%. CHF was present in around 15-19% (Table E3).

Table E3: Summary of Baseline Medical History in ACT I and ACT III.

Condition	ACT I (N = 336)		ACT III [a] (N = 239)	
Hypertension	144	(42.9)	102	(42.7)
Structural Heart Disease	117	(34.8)	81	(33.9)
Congestive heart failure	50	(14.9)	45	(18.8)
Ischaemic heart disease	68	(20.2)	26	(10.9)
Valvular heart disease	34	(10.1)	29	(12.1)
Myocardial infarction[c]	33	(9.8)	14	(5.9)

Only in ACT III detailed information regarding CHF was presented. The results show that the recruited patients were mainly of NYHA I/II classes. This is worrisome especially because of the reported hypotension. No robust conclusions can be made on the administration of vernakalant in patients with NYHA III.

2.4.5.2.2.2. Outcomes and estimation

After the first dose, 39.8% (92/231) of vernakalant-treated patients in the short duration AF cohort converted to sinus rhythm (compared to 1.3% [2/159] of placebo patients); 57% of the primary AF population received a second dose (n=132/231). In the short duration AF cohort who did not convert to sinus rhythm and thus received a second dose, 20% (n=26/132) converted to sinus rhythm subsequent to initiation of the second infusion (compared to 2.6% [4/156] of placebo patients that received a second dose). The additive effect of the second dose, if any, cannot be independently established. In total, the administration of vernakalant resulted in a conversion rate of 51.1% compared to 3.8% in the placebo group. This means a total percent difference of 47.3% (95% CI: 40.2-54.4) between the vernakalant and placebo groups. Efficacy results were significant in the pooled analysis as well as in the individual studies (table E4).

Table E4: Conversion of Atrial Fibrillation to Sinus Rhythm by Cohort and for the Overall Population - ACT I/III Pooled Pivotal Data

Cohort Study/Data	Placebo n/N	Placebo (%)	Vernakalant n/N	Vernakalant (%)	% Difference [a] (95% CI)	P-Value	Odds Ratio (95% CI) [b]
Short Duration (AF > 3hr, ≤ 7 d)							
ACT I (N = 220)	3/75	(4.0)	74/145	(51.0)	47.0 (37.8, 56.3)	<0.0001 [c]	
ACT III (N = 170)	3/84	(3.6)	44/86	(51.2)	47.6 (36.3, 58.9)	<0.0001 [c]	
Pooled (N = 390)	6/159	(3.8)	118/231	(51.1)	47.3 (40.2, 54.4)	<0.0001 [c]	26.7 (11.2, 63.7)
Overall Population (AF > 3hr, ≤ 45 d)							
ACT I (N = 336)	3/115	(2.6)	78/221	(35.3)	32.7 (25.7, 39.6)	<0.0001 [c]	
ACT III (N = 239)	4/121	(3.3)	47/118	(39.8)	36.5 (27.1, 45.9)	<0.0001 [c]	
Pooled (N = 575)	7/236	(3.0)	125/339	(36.9)	33.9 (28.3, 39.5)	<0.0001 [c]	18.0 (8.2, 39.6)
Long Duration (AF ≥ 8d, ≤ 45 d)							
ACT I [d] (N = 116)	0/40		4/76	(5.3)	5.3 (0.2, 10.3)	0.30 [e]	
ACT III [d] (N = 69)	1/37	(2.7)	3/32	(9.4)	6.7 (-4.7, 18.0)	0.33 [e]	
Pooled [d] (N = 185)	1/77	(1.3)	7/108	(6.5)	5.2 (-0.1, 10.5)	0.142 [e]	5.3 (0.6, 43.7)

The results are comparable to those reported with other AAD e.g flecainide or ibutilide. No significant results were shown for vernakalant in the long duration AF subgroup. This is in line with previous data showing that both electric and pharmacological cardioversion are less effective in long standing AF and supports the limitation in the indication to the duration of AF to 7 days. Patients with an AF duration of < 48 hours are considered of particular clinical importance, as no anti-coagulation is needed in this subgroup before pharmacological conversion, if no other indication co-exists. It is re-assuring to know that the results in this subgroup were also consistent with the short term cohort (61.2% in vernakalant versus 4.9% in placebo group). Patients with unknown AF duration, a group that could also be encountered in real practice were not included in the clinical program. The time frame of the primary endpoint i.e. 90 minutes is too short to prove a clinically relevant maintenance of SR. The current data show that SR was effectively maintained beyond 90 minutes, 97.2% and 93% at 24 hours/discharge and 7 days respectively and for patients not on concomitant AAD: 100% and 98.2% respectively (table E5). It is not clear why patients not on concomitant AAD would have better efficacy in maintenance of SR and whether the results are statistically significant compared to the reported values in the placebo group (83.3%)(the numbers of placebo patients who spontaneously converted to SR are too few to allow reasonable comparison; n= 6 patients in each placebo subgroup). The applicant states that details on timing of AAD use were not collected during the ACT I and ACT III studies and that this different use may reflect differences in co-morbidities as well. However, no claims are made on the maintenance of SR.

Table E5: Life-Table Estimate of the Maintenance of Sinus Rhythm for Patients Who Converted to Sinus Rhythm Within 90 Minutes of First Exposure to Study Drug - ACT I/ACT III Pooled Pivotal Data

Time Point[a]	Short-Duration Cohort (AF > 3hr, ≤ 7 d)				All Patients (AF > 3hr, ≤ 45 d)			
	Placebo		Vernakalant		Placebo		Vernakalant	
	SR %	SE %	SR %	SE %	SR %	SE %	SR %	SE %
All Patients (N)	(N=6)		(N=118)		(N=7)		(N=125)	
2 Hours	83.3	15.2145	98.2	1.2350	85.7	13.2260	98.3	1.1686
4 Hours	83.3	15.2145	98.2	1.2350	85.7	13.2260	98.3	1.1686
8 Hours	83.3	15.2145	98.2	1.2350	85.7	13.2260	98.3	1.1686
24 Hours/Discharge	83.3	15.2145	97.2	1.5872	85.7	13.2260	97.4	1.5061
7 Days	83.3	15.2145	93.0	2.5734	85.7	13.2260	92.3	2.6202
Patients Not Receiving Concomitant Antiarrhythmics (N)	(N=6)		(N=72)		(N=7)		(N=74)	
2 Hours	83.3	15.2145	100.0	0.0	85.7	13.2260	100.0	0.0
4 Hours	83.3	15.2145	100.0	0.0	85.7	13.2260	100.0	0.0
8 Hours	83.3	15.2145	100.0	0.0	85.7	13.2260	100.0	0.0
24 Hours/Discharge	83.3	15.2145	100.0	0.0	85.7	13.2260	100.0	0.0
7 Days	83.3	15.2145	98.2	1.7389	85.7	13.2260	96.6	2.3959

Further analysis showed that approximately 30% of placebo patients had spontaneous conversion by hour 24 (excluding pharmacological/electrical cardioversions), still showing an advantage for vernakalant (97%). Another issue is the data regarding patients who did not convert to SR within 1.5 hours but subsequently converted within 24 hours. According to the applicant, patients recruited in the ACT I/ACT III program are patients in which the decision to cardiovert was considered necessary. In patients who failed to convert to SR within 24 hours, cardioversion was attempted in 70%, making it difficult to assess the natural history of the AF patients. For the responders group, HR at follow-up was 61.5 bpm compared to 84.7 bpm in non-responders. Vernakalant also significantly reduced the AF-related symptoms (50.2% vernakalant vs 73.0% placebo; P<0.0001). Efficacy was comparable when conducted for the per protocol population. No significant effect was shown in the long duration cohort, or in patients with AFL.

2.4.5.2.2.3. Ancillary analyses

Comparison of Efficacy Results in Subpopulations
Vernakalant injection was effective across a broad range of subgroups, including gender, age, background use of rate or rhythm control medication and relevant medical history (CHF, MI, hypertension, IHD, valvular heart disease, and structural heart disease). Additional analyses on the primary AF efficacy population were performed in the following subgroups: renal impairment, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 substrates, QT prolonging medications and patients with implanted pacemakers. Within the limits of these post-hoc analyses (subgroups were not pre-specified and no multiplicity adjustments were made), there were no significant differences in response to vernakalant injection within any subgroup. However, there are trends towards decreased efficacy in elderly patients (≥ 75 years old), those with a history of CHF, patients on digoxin and patients treated with Class I antiarrhythmics. The number of non-white patients was very low (n=9 in short-duration cohort) and does not allow an adequate assessment of efficacy by race. These findings are based on uni-variate logistic regression and no attempt to adjust for confounding factors was made.

Left Ventricular Ejection Fraction LVEF: EF data was available only in a minority of the Phase III short-duration AF patients that were treated with vernakalant (N = 185/498) and collection of EF data was not pre-specified. A post-hoc analysis was performed to investigate the relationship between efficacy of vernakalant and LVEF in patients from ACT II, ACT III and ACT IV. The percentage of patients converting from AF to sinus rhythm was similar for patients with normal LVEF function and mild LVEF dysfunction. Few patients had either moderate or severe LVEF dysfunction.

Implanted Rate Control Device: ACT I/III pooled pivotal data included 23 patients with pacemakers (12 vernakalant; 11 placebo). In the overall population, 4 patients with pacemakers (3 vernakalant; 1 placebo) had termination of AF within 90 minutes of first receiving study drug.

Renal and Hepatic Impairment: There were no significant differences in response to vernakalant injection in patients with hepatic impairment (47.9% in patients with normal hepatic function vs 36.8% in patients with abnormal hepatic function), but there was a lower response for renal impairment (55.5% in patients with normal renal function vs 34.1% in renal impairment). Conversion rates were significantly higher in the vernakalant group compared with placebo for all categories.

CYP2D6 Genotype: There were no significant differences in response to vernakalant injection by genotype. The treatment difference in the rate of conversion of AF to SR in the short duration cohort was 41.8% in extensive metabolisers vs 33.3% in poor metabolisers.

Concomitant medications: Conversion rates were significantly higher in the vernakalant group compared with placebo for all medication categories, with the exception of use of digoxin. The treatment difference for use vs. non-use of digoxin was 16.3% vs 51.9% respectively (P = 0.1897). For other rate control medications, no significant difference was seen. With rhythm control medications, the treatment difference for use vs non-use of Class I and Class III antiarrhythmic medications was 20.0% vs 50.7% for Class I antiarrhythmics (p= 0.9680), and 55.8% vs 45.3% for Class III antiarrhythmics. Although conversion rate is lower with vernakalant in the subgroups of patients co-administered digoxin or class I AADs, the conversion rate is still higher than that in the placebo group. The reason of such reduced efficacy is speculative, but may be related to the patient's condition e.g. longer duration of AF in patients on digoxin, or general refractoriness to AADs. A PK interaction is unlikely. Furthermore in the case of Class I AADs, the number of patients is too few (n=25) precluding robust assessment. There were no significant differences in response to vernakalant injection in patients taking concomitant CYP2D6 inhibitors, CYP2D6 substrates or QT prolonging medications compared to those not taking such medications.

Medical History: Patients with the following medical conditions were scarcely represented in ACT I/III: CHF (n=42), history of myocardial infarction (n=25), ischemic heart disease (n=50) or valvular heart disease (n=36) (table E3, above). Most of these medical conditions were adequately presented in ACT II, except for patients with CHF. These patients were poorly represented in the studies. In addition, no adequate information regarding their NYHA status is submitted. From the current results, the treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort for history vs. no history of the condition was 26.9% vs. 50.0% for CHF (NYHA I/II), raising concerns about the efficacy in these patients. Adequate warnings are currently implemented in the SPC. Within the primary safety population, information on LVEF available from echocardiography studies was

available for 162 of the 773 vernakalant-treated patients (n=150 LVEF ≥ 35% and n=12 LVEF < 35%) and 49 of the 335 placebo patients (n=44 LVEF ≥ 35% and n=5 LVEF < 35%). This indicates some inadequacies in the performance of the trials. Due to the limited experience in such patients, a warning is implemented in the SPC. Degrees of hepatic impairment were not adequately defined in the submitted clinical studies; and specifically patients with advanced hepatic impairment were not properly represented. A warning in the SPC is implemented against the use of vernakalant in such patients. Around half of the recruited patients suffered from renal impairment. The treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort was 55.5% in patients with normal renal function vs. 34.1% in the renally impaired. Recruited patients with pacemakers were very few to allow conclusions; a relevant warning is currently included in the SPC.

ACT II:

3.4.5.2.3 Methods

This was a phase III, multinational (Europe, North and South America and Asia), prospective, randomised, double-blind, placebo-controlled study in adult patients (≥ 18 years) with documented normal sinus rhythm prior to undergoing CABG and/or valvular surgery. Patients who developed sustained AF (or AFL) for a duration > 3 hours and ≤ 72 hours within 24 hours to 7 days after surgery qualified for study screening procedures and subsequent enrolment if entry criteria were met. As the duration of AF in ACT II is less than that of ACT I/III, relevant labelling in section 4.1 is currently implemented.

3.4.5.2.3.1 Study Participants

Apart from the target group of ACT II, the inclusion and exclusion criteria do not appear to vary from those employed in ACT I/III. The study plan called for 210 patients randomly assigned to treatment in a 2:1 ratio (vernakalant:placebo). Patients were recruited who had documented normal sinus rhythm within 2 weeks before CABG and/or valvular surgery, patients who had CABG and/or valvular surgery within the last 7 days, patients who had, at the time of randomization, documented AF or AFL (duration 3 to 72 hours) with onset of AF or AFL occurring between 24 hours and 7 days after CABG and/or valvular surgery.

3.4.5.2.3.2 Treatments

Same as in ACT I/III.

3.4.5.2.3.3 Objectives

The primary objective was to demonstrate the effectiveness of vernakalant injection (3.0 mg/kg + 2.0 mg/kg) compared to placebo in the conversion of atrial arrhythmia (AF or AFL) to SR in patients who developed the specified arrhythmia subsequent to recent CABG and/or valvular surgery. Secondary objectives were to examine the rate of conversion of arrhythmia to sinus rhythm and to assess the overall safety of vernakalant in this patient population.

3.4.5.2.3.4 Endpoints and Statistical methods

The primary and secondary endpoints were comprable to those used in ACT I/III. Consistent with the indication sought by this application, this section focuses on efficacy results supporting vernakalant injection for the rapid conversion of AF to sinus rhythm and excludes the patients with AFL.

3.4.5.2.4 Results

3.4.5.2.4.1 Patient disposition

The majority of the recruited patients were white (94%) and male (73.3%), with a mean age of 68.3. The treatment groups were comparable regarding the baseline demographics. Most patients had a baseline diagnosis of AF (150/161, 93.2%). Further results concern only AF patients. The surgery type (CABG versus valvular) was balanced between the groups. The majority were scheduled for CABG surgery (65.0% vernakalant, 66.0% placebo) with the rest undergoing valvular surgery (27.0% vernakalant, 20.0% placebo) or both surgeries (8.0% vernakalant, 14.0% placebo). No discontinuations were recorded in either group during the first dose. In the vernakalant group three

discontinuations due to adverse events (hypotension, complete AV-block, RBBB) occurred, of which the first two were followed by successful conversion. One case of discontinuation of unknown reason occurred in the placebo group. The use of rate control medications was balanced. LVEF was normal in more than half of the patients, patients with LVEF<35% were minimally represented.

3.4.5.2.4.2 Efficacy Results

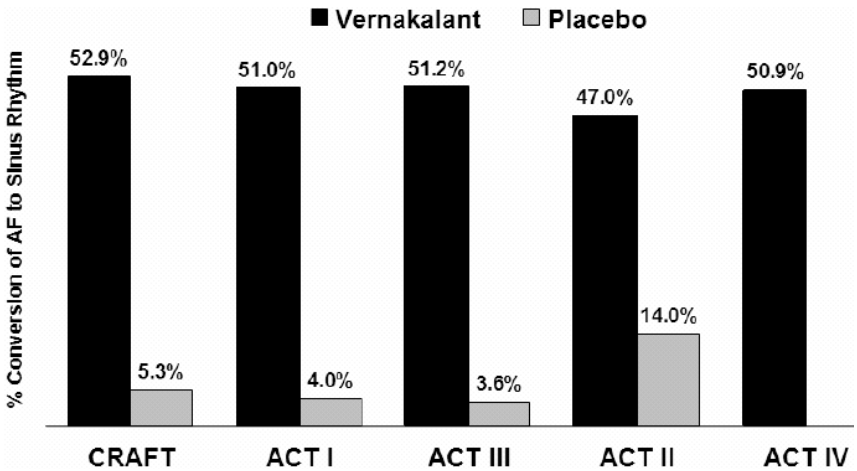
Significantly more patients in the vernakalant group (47%) converted to SR within 90 min than placebo group (14%)(difference of 33%; p= 0.0001; CI: 19.3- 46.7). The results are generally in line with those reported previously in ACT I/III. However, it is noted that the spontaneous conversion rate in the placebo group is higher in ACT II (14% vs 4% in the ACT I/III). This probably reflects the different etiology of the AF where temporary adrenergic stress could be playing an important role in the ACT II population; with time more spontaneous conversion is expected. Maintenance of SR beyond the 90 min limit shows more disappointing results in ACT II. The life-table estimate of maintenance of sinus rhythm at 24 hours or 7 days is 59.5% and 56.9 % in ACT II compared to 97.2% and 93% in ACT I/III respectively. This difference may again represent the different underlying pathology. Furthermore, vernakalant did not significantly improve AF-related symptoms compared to placebo (P=0.185). Although the results are less impressive that those reported in ACT I/III, efficacy of vernakalant in patients with post-cardiac surgery AF is still considered clinically relevant.

2.4.5.3. Analysis performed across trials

Efficacy Across All Phase II and III Studies

A comparison of conversion rates of short-duration AF to sinus rhythm across the phase II and III studies is shown in figure E3.

Figure E3: Conversion rates of short duration AF to sinus rhythm across the main studies.



CRAFT: dosing was 2 mg/kg + 3 mg/kg; data represents % in sinus rhythm at 1 hour post dosing. AF duration >3 to 72 hours. ACT I, III and IV: AF >3 hours to ≤ 7 days; ACT IV: a placebo group was not included in this open-label study; ACT II: AF post coronary artery bypass graft and/or valvular surgery; AF duration >3 to <72 hours.

Across the phase II/III, vernakalant administration did not affect the response of the patients to subsequent electric cardioversion, in case of vernakalant failure. Electrical cardioversion was successful in 90.2% (166/184) of patients in the placebo group and 87.8% (237/270) of patients in the vernakalant group.

2.4.5.4. Supportive studyies

ACT IV

The main objective of ACT IV was to evaluate the safety of vernakalant injection in the proposed dose to increase the safety database (n=236). However, the study did not include any special subgroups of interest not previously included in the pivotal studies e.g. more severe forms of CHF. The study was open- label and not controlled, limiting its value as an efficacy study. Still efficacy results are in line

with those reported previously in the pivotal studies: 50.9% (95% CI 43.3%, 58.5%) of the vernakalant treated patients experienced a treatment-induced conversion from AF to sinus rhythm. But as noticed with ACT II, the proportion of patients who maintained SR till 24 hours (76.5%) and 7 days (63.5%) was less than those reported with ACT I/III.

SCENE 2

SCENE 2 aimed to investigate the efficacy of vernakalant in AFL. The study design and endpoints followed that of the pivotal studies, but the target population were only AFL patients. The study results showed that vernakalant was not effective in the rapid conversion of AFL to sinus rhythm. Subsequently, further development of vernakalant focused on AF.

AVRO (VERI-305-AMIO)

The AVRO study design was submitted with the day 120 responses in answer to major objection requesting an actively-controlled study.

Methods
This was a phase 3, multicenter, randomized, double-blind, active-controlled, double-dummy study. Subjects were randomized to receive either vernakalant injection or amiodarone injection in a 1:1 ratio. The design of AVRO ——is considered appropriate to assess the efficacy of vernakalant in the rapid conversion of AF to SR. The duration of AF (3- 48 hours) is shorter than that examined in the other ACT pivotal studies, but is also considered clinically relevant, as in these patients anti-coagulation is not required. The applicant justified the choice of amiodarone as the active comparator as it can be used in the broad AF population. By hindsight, this choice was not optimal considering that patients with CHF were not included in this study as well. Considering the rapid onset of action of vernakalant, it would have been more appropriate to choose flecainide, rather than amiodarone, with its known slow onset of action and low initial conversion rates. The recruited patients are generally in line with those recruited in ACT I/III. Importantly, patients with SBP <100 mm Hg were excluded, whereas this limit was set to 90 mm Hg in the previous studies. This probably ensured the recruitment of more stable patients. Vernakalant administration followed the same scheme as that employed in the previous ACT studies. The administered dose of amiodarone was in accordance with the UK SPC as per the first 2 hours of administration, but not the 24 hours regimen. This was chosen in line with the aim of the study, which was mainly to show the rapidity of effect of vernakalant compared to amiodarone. According to the applicant the extra attention to the hydration status of the patients contributed to the lower number of hypotension events observed in AVRO compared to earlier ACT studies. Such recommendations are currently included in the adapted SPC. Choosing a time window till 90 minutes for the primary endpoint to detect conversion to SR could bias the results to vernakalant, considering that amiodarone is known for its delayed onset of action even following IV administration. Otherwise, the chosen endpoints are acceptable. Of note, no patients with NYHA III were recruited.
Results
Treatment with vernakalant resulted in a significantly greater proportion of subjects converting from AF to SR within the first 90 minutes compared to amiodarone. A total of 60 of 116 (51.7%) vernakalant subjects met the primary endpoint, compared to 6 of 116 (5.2%) amiodarone subjects (% difference: 46.6 % CI 95%: 36.6-56.5; p <0.0001). In the group of 60 subjects who responded to vernakalant, the median time to conversion was 11.0 minutes compared to 25.5 minutes in the 6 subjects who responded to amiodarone. This was also accompanied by significantly lesser AF-related symptoms by 90 minutes in the vernakalant group. By 4 hours post-dose, 54.4% of vernakalant subjects and 22.6% of amiodarone subjects had converted to SR. The results show that vernakalant was faster than amiodarone in conversion of recent onset AF to SR, with the caveats made above.

2.4.6. Conclusions on the clinical efficacy

In summary, vernakalant administration resulted in significantly more conversions of AF to SR. The results are of clinical relevance and SR was in most cases maintained till 24 hours. The results are at least comparable to those reported with other AADs in particular flecainide, amiodarone or ibutilide. The main advantage of vernakalant in terms of efficacy appears to be the rapid time to conversion. The results of AF in post cardiac surgery patients are significant but less than those reported in the general AF population. Efficacy in some patient populations is not clear, in particular patients with CHF (I/II).

2.4.7. Clinical safety

2.4.7.1. Patient exposure

Safety data of vernakalant injection is mainly based on six phase II and III efficacy and safety studies in which 773 patients received vernakalant injection and 335 patients received placebo (refer to table E1). Safety analysis of the AVRO study is discussed separately. Safety data from the oral vernakalant program is also considered. The safety database of vernakalant appears adequate with 507 patients administered the full dose and 241 patients administered the first dose (3 mg/kg) (Table S1). However, the actual representation of different subgroups of patients may not be sufficient, specially considering that vernakalant is a new chemical entity.

Table S1: Vernakalant Injection Exposure in Patient Populations With AF or AFL

Vernakalant Dose (mg/kg)	Patient Population		
	All Patients [a]	ACT I/III Pooled	ACT II
	n	n	n
0.5	1	0	0
1.5	17	0	0
2.0	7	0	0
3.0	241	112	38
5.0 (3.0 + 2.0)	507	227	69
Total	**773**	**339**	**107**

a [CRAFT, Scene 2, ACT I, ACT III, ACT IV, and ACT II].

There is no experience with repeat dosing and a warning with that effect is currently implemented in the SPC.

2.4.7.2. Adverse events

Due to the short half-life of vernakalant (about 3 hours in extensive metabolisers and 5.5 hours in poor metabolisers) focusing on the adverse events within the first 24 hours could be accepted as this is the most relevant period. The incidences of any treatment related treatment emergent adverse events (TRAE), serious related AE, withdrawals, drug discontinuation due to AE and related deaths were higher in the vernakalant compared to the placebo group respectively (table S2).

Table S2: Overview of Treatment Emergent Adverse Events in the phase 2-3 studies.

Population / Event	Number (%) of Patients			
	Placebo		Vernakalant	
	n	(%)	n	(%)
All Patients [a]				
N	335		773	
Any AE	197	(58.8)	577	(74.6)
Any related AE	31	(9.3)	398	(51.5)
Any serious AE	51	(15.2)	90	(11.6)
Any serious related AE	1	(0.3)	16	(2.1)
Withdrawals due to AE	0		5	(0.6)
Drug discontinuations due to AE [b]	1	(0.3)	28	(3.6)
Deaths	0		5	(0.6)
Related deaths	0		1	(0.1)

a Includes [ACT I, II, III, IV; CRAFT, and Scene 2].

b Includes temporary discontinuations.

The most common TRAEs in the vernakalant group in the first 2 hours were dysgeusia, sneezing, paraesthesia, nausea and hypotension (table S3).

Table S3: Most frequently reported treatment emergent related adverse events in the Vernakalant group in the first 24 Hours Post-dose- All Patients in Phase 2 and Phase 3 Studies

SYSTEM ORGAN CLASS Preferred Term	0 to 2 Hours, N (%)		2 to 24 Hours, N (%)	
	Placebo (N=335)	Vernakalant (N=773)	Placebo (N=335)	Vernakalant (N=773)
ANY RELATED AE				
CARDIAC DISORDERS				
Atrial flutter	0	8 (1.0)	0	0
Bradycardia	0	12 (1.6)	0	2 (0.3)
GASTROINTESTINAL DISORDERS				
Dry mouth	0	9 (1.2)	0	0
Nausea	0	35 (4.5)	0	2 (0.3)
Vomiting	0	10 (1.3)	0	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Feeling hot	2 (0.6)	20 (2.6)	0	0
Infusion site pain	0	17 (2.2)	0	0
NERVOUS SYSTEM DISORDERS				
Dizziness	1 (0.3)	19 (2.5)	1 (0.3)	1 (0.1)
Dysgeusia	8 (2.4)	155 (20.1)	0	1 (0.1)
Paraesthesia	3 (0.9)	60 (7.8)	0	0
Paraesthesia oral	1 (0.3)	17 (2.2)	0	0
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Cough	1 (0.3)	26 (3.4)	0	0
Nasal discomfort	0	19 (2.5)	0	0
Sneezing	0	113 (14.6)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	1 (0.3)	24 (3.1)	0	2 (0.3)
Pruritus	0	27 (3.5)	0	0
VASCULAR DISORDERS				
Hypotension	1 (0.3)	31 (4.0)	1 (0.3)	0

The AEs were generally described as mild or moderate and were not treatment-limiting. From 2 to 24 hours after initiation of infusion, the incidence of these adverse events in the vernakalant group decreased to a level comparable to that reported in the placebo group. The current data show that the main safety issues occur within 2 hours vernakalant injection.

2.4.7.3. Serious adverse event/deaths/other significant events

The incidence of related SAEs during the 24 hours post-dose was slightly higher in the vernakalant group (2.1%) than in the placebo group (0.3%). Hypotension was the most frequently related SAE (8 vernakalant, 1.0%; 1 placebo, 0.3%). Other related SAEs included bradycardia (3 patients, 0.4%) and complete AV block (2 patients, 0.3%). No new SAE's were identified in ACT II which is reassuring considering the more vulnerable patient population recruited in this study.

Deaths. Five cases of deaths were reported of which only one was considered related to vernakalant. This concerns a 64-year old white male with a history of aortic stenosis. At the time of admission he was also suffering from ACS with ST elevation. The recruitment of such a patient and his management further represent protocol violations. The patient was first administered IV and oral metoprolol and later 2 infusions of vernakalant despite his hypotension. Consequently, the patient suffered from ventricular fibrillation and resuscitation was unsuccessful. This death strongly indicates a deleterious effect of vernakalant in haemodynamically unstable patients (including patients with severe aortic stenosis), justifying their inclusion as contraindications. Also, a possible deleterious effect of vernakalant on severely hypotensive patients *per se* can not be excluded, which are currently contraindicated (< 100 mm Hg).

Adverse Events of Special Significance: Based on the safety profile of other AAD and following review of the safety data for vernakalant, certain adverse events of interest were identified (ventricular arrhythmia, hypotension, bradycardia and AFL).

Ventricular arrhythmia. Clinically meaningful ventricular arrhythmias had a slightly higher frequency in the vernakalant group (0.6%) compared to placebo (0). The five reported cases occurred in the first 2 hours post-dose, three of whom had a history of CHF. Generally, ventricular arrhythmia events occurred more frequently in patients with a history of CHF who were treated with vernakalant.

Two cases of VF are reported. One case is discussed under Deaths. The other is a case of VF that is considered un-related to vernakalant but due to non-synchronised cardioversion due technical malfunction.

Torsade de pointes (TdP). Four events of TdP occurred (3 in the vernakalant and 1 in placebo) of which one might have a temporal relation to vernakalant. The case was asymptomatic and was captured on the Holter as a nine beat run of a ventricular arrhythmia monitored 2 hours and 20 minutes after initiation of the infusion of vernakalant injection and immediately after an infusion of ibutilide. According to the applicant, the ibutilide injection confounds the causal relation between vernakalant and TdP. It should be noted that the ventricular arrhythmias associated with ibutilide usually occur within the first 40 minutes of injection. A contraindication is currently implemented in the SPC regarding the administration of vernakalant till 4 hours, following intravenous Class I and III antiarrhythmics. The most valid candidates that could be administered before vernakalant, are probably flecainide or ibutilide, both rapidly distributed following iv administration. For both agents, there is no contraindication for prior use of iv AADs. Importantly, there is already a contraindication to the administration of vernakalant in case of prolonged QT (uncorrected > 440 msec; also implemented in the ibutilide SPC). This contraindication is considered sufficient to guard against excessive prolongation of QT interval which is the main risk when AADs are co-administered. There is also limited experience with administration of AAD (class I/III) 4-24 hours prior to vernakalant, and a warning with that message is currently implemented in the SPC (section 4.4).

Thorough analysis of the QT data. Prolongation of QTcF was observed with placebo-subtracted peaks of +22.1 msec (95% CI: 18.9-25.3) at minute 10 and +18.8 msec (95% CI: 15.6-22) at minute 35, returning to baseline by 50 minutes. Substantially more patients in the vernakalant group were observed with QTcF prolongations of ≥30 msec and ≥60 msec compared to the placebo group till the second hour, although the absolute number of patients with a QTcF prolongation of ≥60 msec was low. Afterwards, as plasma levels of vernakalant were low and other medications were allowed as well, such differences were not noticed. Likewise, increases in mean QTcF of >480 msec and >500 msec were more frequently recorded in the vernakalant group than the placebo group but the incidence was low and lasted only till minute 50, after which the frequencies appear comparable. The PK-PD modeling predicts an increase of around 20 msec in QTcF at the expected Cmax of 4100 ng/ml. This data shows that vernakalant is associated with a higher risk of prolonging QTcF which is probably associated with its pharmacological action. It suggests an effect on the action potential on a ventricular level, precluding absolute atrial selectivity. This partial atrial selectivity and the effect on QT are adequately depicted in section 5.1. This is also described for other AADs as well e.g ibutilide. The current clinical program is too limited precluding any realistic estimation of the risk of TdP. No correlation between prolonged QTcF at baseline and further QTcF prolongation was observed. However, a contraindication for patients with prolonged QT at baseline is implemented as these patients were excluded from the clinical studies. This is in line with the labeling of other AAD. There was no foreseen need for a thorough QT study during the iv program but before the submission of the oral formulation, such study will be conducted according to the applicant. A better evaluation of the pro-arrhythmic potential of vernakalant and other important AE (e.g hypotension) are expected from the data of the post-approval PASS registry study, which is an integral part of the RMP.

Hypotension. The overall incidence of hypotension in the first two hours following infusion was comparable between the vernakalant (7.6%) and the placebo groups (5.1%), however the incidence of associated AEs was higher (5.4% versus 1% respectively). Outliers with a greater degree of hypotension post-dose (< 80 mmHg) were numerically more frequent among vernakalant-treated patients (n=22 of 771, 2.9%) than placebo-treated (n=5 of 332, 1.5%). SAEs of hypotension were also more frequently reported among vernakalant-treated patients than with placebo (9 vernakalant, 1.2%; 1 placebo, 0.3%). Meantime, mean SBP population-response among vernakalant-treated patients actually showed a slight but significant increase in comparison to placebo. The PK-PD modeling predicts a maximum of 3.05 mmHg increase in SBP with EC50 of 1141 ng/ml (much below the expected Cmax). However no AEs related to hypertension were reported. A logistic regression analysis showed that a low baseline SBP (<105 mmHg) and a history of CHF were the most important factors that correlated to approximately a 3-fold and 1.8-fold increased risk of hypotension, respectively. The SPC contraindicates the use of vernakalant in patients with SBP <100 mm Hg. This also reflects the experience in the AVRO study, where patients with SBP <100 mm Hg were excluded. The hypotension could be attributed to the observed negative inotropic effect shown in experimental studies, however the mechanism of the recorded hypertension is not fully explained, but can be attributed to the normalization of the rhythm, as a comparable increase in BP was also recorded in placebo patients following conversion to SR by other methods.

Bradycardia The incidence of bradycardia in the 0-2 hour period was slightly higher in the vernakalant group (5.4%) compared to placebo (3.8%) [percent risk difference 1.6 (95% CI:-1.1, 4.3)]. This could have been mainly driven by patients who converted to sinus rhythm in the vernakalant group within the first 90 minutes: where bradycardia was reported in 8.2% of the patients in the vernakalant group compared to 0 in placebo. For patients who did not convert to sinus rhythm within the first 90 minutes, the incidence of bradycardia events was comparable in both groups (3.8% and 4% respectively). Also in patients who did not convert within the first 90 minutes, but who subsequently underwent electrical cardioversion or other therapy 2 hours post-dose, the rate of bradycardia events from 2-24 hours post-dose was 14.4% in the placebo group and 7.7% in the vernakalant group supporting the claim that these bradycardia events are probably primarily associated with termination of AF rather than drug treatment. Clinically significant bradycardia was reported more frequently in the vernakalant group (1.3%) compared to the placebo group (0) in the first 2 hours. Thereafter the incidence was comparable (0.4% and 0.6% respectively). Patients with a known history of sinus node dysfunction or severe bradycardia (not corrected by a pacemaker) were excluded from the vernakalant clinical trials, as conversion from AF by pharmacological or electrical means has an associated risk for sinus pause in these patients. These patients are contraindicated in the SPC. There is little data regarding the effect of vernakalant on PR interval. Available data suggest that vernakalant has mild effects on the PR interval in subjects with normal nodal conduction, with a possible dose dependent effect.

AFL. The risk of developing AFL was significantly higher following vernakalant (6.1%) than placebo (1.6%)(percent risk difference 4.5: 95% CI 2.3 to 6.7), but only one serious adverse event of AFL within the first 24 hour post-dose was reported. No patient with AFL following treatment with vernakalant injection developed 1:1 atrioventricular conduction to date in the clinical trials. Further analysis of data showed that in some cases, this secondary developing AFL may be a transitional phase and some patients may revert to SR without further intervention.

2.4.7.4. Laboratory findings

No clinically meaningful changes from baseline were noted for haematology or clinical chemistry parameters for vernakalant or placebo treatment. Shifts to potentially clinically meaningful high or low baseline chemistry and other laboratory values, where they occurred were small and similar for vernakalant and placebo at hour 24 and follow-up. No association between laboratory value shifts and vernakalant treatment has been identified.

2.4.7.5. Safety in special populations

Risk for the AEs of interest with vernakalant was not affected by age category (age<65 n= 528; age≥65 n= 524) (age<75 n= 836; age≥75 n= 216) or sex (males n=720 and females= 332). The recruited numbers of patients "non-white" (30/773, 3.9%) or poor metabolisers (2.2%, 17/773) are too few precluding any conclusion about the risk of AEs in these groups.

The medical history of patients had an effect on their risk of AEs.
Congestive heart failure (CHF). In patients with CHF, an increased risk of hypotension and ventricular arrhythmia was observed compared to patients with no CHF. These results pertain specifically to NYHA I/II with minimal representation of NYHA III, whereas NYHA IV were excluded from the clinical studies [Of the 68 patients for whom NYHA classification is known, there were 7 patients (3 placebo, 4 vernakalant) who had class III heart failure, 36 patients (12 placebo, 24 vernakalant) with class II heart failure, and 25 patients (6 placebo, 19 vernakalant) with class I heart failure]. This highlights the deficiency of the PD studies, which did not further explore these mechanisms in humans. The current SPC warnings are considered adequate to reflect these results regarding NYHA I/II. The requested post-registry safety study should be able to better identify the risks in these patients. In light of the results in patients with NYHA I/II, and the very limited experience in NYHA III/IV, (even in the AVRO study) the benefit/risk of vernakalant in these latter groups is not adequately defined and these patients are accordingly contraindicated.
Hypertension (HTN) and ischaemic heart disease (IHD). Risk for the AEs was not changed in patients with HTN or IHD.
Valvular heart disease. In patients with valvular heart disease, an increased risk of ventricular arrhythmia was observed in the first 2 hours post-dose in patients who received vernakalant. The exact mechanism is not identified, though it is acknowledged that in the two cases of serious VA, there were multiple co-morbidities complicating the causation. A warning in the SPC is implemented.

Myocardial infarction (MI). There was a trend towards an increased risk of ventricular arrhythmia and AFL in patients with a history of myocardial infarction (n=117). Patients with a history myocardial infarction within the last 30 days were excluded from the main studies. This is reflected in section 4.3 in the SPC.
Cardiac surgery. Patients with recent cardiac surgery (ACT II; n=161) had a higher risk of ventricular arrhythmia and a trend towards increased risk of hypotension compared to other patients (Pooled ACT I/III n= 575). The applicant explained that this trend can be due to characteristics inherent to the different studies. Also this trend was mainly seen in post cardiac surgery patients with CHF, where CHF is already identified as a risk group for hypotension. In addition, events recorded as clinically significant were actually comparable between the groups. These arguments refute the need for further warnings in this special cohort.
Impaired renal function. The risk of AEs appeared comparable in patients with normal renal function compared to those with moderate to severe renal impairment. This is further confirmed by PK study performed with vernakalant infusion (VERO-106-REN) that showed that vernakalant injection was safe and well tolerated in healthy subjects and in volunteers with mild, moderate and severe renal impairment. There does not appear to be a higher risk of ventricular arrhythmia, hypotension, bradycardia or AFL in patients with different degrees of renal impairment.
Hepatic impairment. Degrees of hepatic impairment were not adequately defined in the submitted clinical studies. The applicant used one method (APRI score) of classifying these patients. The applicability of this method to the current population was questioned, as APRI score is used to detect hepatic fibrosis following hepatitis C. Using this method showed that there is an adequate representation of patients with mild hepatic impairment (n=104). In these patients, the risk of VA appears comparable to the general population. In patients with advanced hepatic impairment (n=18), a risk of higher incidence of VA is noticed. However, confounding factors like: low number of placebo patients, and patients with multiple co-morbidities, preclude robust conclusions. PK data in all hepatically impaired patients show an increase of Cmax and AUC that reaches 20-25% respectively by the second dose compared to exposure in normal patients, which is within the expected limits (reflected in section 5.2). No dose reductions are accordingly recommended. A trend for higher incidence of VA with the highest exposure can not be excluded. A warning regarding the limited data and against the use in such patients is implemented.
Electrical cardioversion (ECV). The data show that in patients subsequently undergoing ECV, vernakalant did not increase the risk of ventricular arrhythmia (1.8% vs 2.8 for placebo), bradycardia (5.5% vs 11.6% for placebo) or hypotension (3.1% vs 6.1 in placebo).
There was also an unexplained increased risk of AFL in patients from Europe. There was no difference of background use of Class I/III AADs to explain the difference in the risk of AFL in EU vs non-EU population. The risk may have been amplified by a difference in the placebo reported rate of AFL.

Safety in AVRO study. The reported TEAE with vernakalant in particular dysgeusia, sneezing, cough and nausea are in line with those previously reported in the ACT studies. One case of death was reported in the study, in the vernakalant group, in which causality was assessed as not related. This decision is endorsed. The incidence of related SAEs during the 24 hours post-dose was slightly higher in the vernakalant group (2.6%) than the amiodarone group (0.9%). Cardiac disorders were the most frequently reported SAE. Events of hypotension were comparable in the vernakalant and the amiodarone groups. The incidence of hypotension in AVRO is much lower than that reported in the previous studies (overall incidence of 7.6% and 5.1% in the vernakalant and placebo groups respectively). Measures taken in AVRO, in particular excluding patients with BP lower than 100 mm Hg (unlike the ACT studies, which used a lower limit of 90 mm Hg) and ensuring proper patient's hydration have probably minimized the risk of hypotension. The incidence of ventricular arrhythmias was generally low in both groups. There was one case of ventricular arrhythmia (VA) reported as a SAE in the vernakalant group. The Ventricular Events Committee considered the arrhythmia as supraventricular tachycardia with aberrant conduction, but they did identify two brief episodes of monomorphic ventricular tachycardia approximately one hour later. This is different to the initial diagnosis of VA made by the investigator. This event was associated with a prolongation of QTc. The event was recorded in one patient with NYHA II (1/11) patients. The predisposition of the heart failure to the incidence of arrhythmia can not be excluded. A warning is already implemented in the SPC. No events of TdP or ventricular fibrillation were recorded. In the vernakalant group, QTcF was elevated maximally at 10 minutes post-dose (23.7 msec), comparable with amiodarone after 4 hours (21.7 msec), and then decreased over time. This was in line with the previous data from the ACT studies. This resulted in a slightly higher frequency of reported QTcF prolongations >450 msec in the vernakalant group compared to amiodarone during the first hour. Also a higher incidence of prolongations of QTcF >30 msec are reported in the same time. This negates the claim that vernakalant acts exclusively on the atria, although it has to be acknowledged that this prolongation of QTcF did not translate into serious ventricular arrhythmias. The incidence of AFL is higher in the vernakalant group (8.6%) compared to the amiodarone group (0.9%). No patient with AFL following

treatment with vernakalant injection developed 1:1 atrioventricular conduction. No events of AFL were reported as an SAE within 24 hours postdose or led to discontinuation of study drug.

2.4.7.6. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with intravenous vernakalant, which could be acceptable considering the route of administration and the short half-life. However some interaction studies have been performed to fulfill these requirements for the submission of the oral formulation. Of the rate control drugs, only in patients co-administered vernakalant with beta-blockers a higher risk of hypotension was observed. This was explained by the higher incidence of CHF in these patients. Background use of rhythm control agents was associated with a higher risk of developing AFL (percent risk difference of 6.8, 95% CI 4.0 to 9.7). This higher risk is stated in the SPC. The other AEs were not significantly affected. This is reflected as a warning regarding the lack of data regarding concomitant administration, till 4 hours after administration of vernakalant, while oral agents can be resumed after 2 hours. Use of iv class I and III AADs 4 hours prior to vernakalant administration is currently included as a contraindication, and warning for the use of these agents 4-24 hours prior to vernakalant, due to the lack of data. Vernakalant 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. No increased risk of AEs was reported in the users of CYP2D6 inhibitors or CYP2D6 substrates, which is further confirmed by a PK study performed with the oral preparation. No increased risk of AEs of interest was observed when vernakalant was administered concomitantly with QT prolonging agents. No significant differences were noticed in the risk of haemorrhagic or thromboembolic events between the vernakalant and placebo groups administered vitamin K antagonists (VKA). The presented data from the available iv, the oral and preclinical studies suggest that vernakalant does not increase the risk of haemorrhagic events or changes in INR.

2.4.7.7. Discontinuation due to adverse events

The rate of withdrawal from the clinical studies was low and slightly higher in the vernakalant group 1.3% (n=10) compared to the placebo group 0.9% (n=3). Five withdrawals due to AEs were recorded, all in the vernakalant group. Vernakalant was permanently or temporarily discontinued due to an adverse event for 28 vernakalant patients (3.6%) and 1 placebo patient (0.3%). The main reasons were hypotension (n=7) and bradycardia (n=2).

2.4.8 Conclusions on the clinical safety

In summary, the main safety issues associated with vernakalant infusion occur within the first 2 hours of administration. The most frequently reported AEs: dysgeusia, sneezing, paraesthesia and nausea are not considered serious. The AEs associated with the cardiovascular system are more worrisome and include hypotension, bradycardia and potential proarrhythmic effects. The risk of hypotension is higher in patients with initial hypotension or with a history of CHF. In the former group, this can be minimized by proper precautions as implemented in the AVRO study. Cases of ventricular arrhythmia were infrequently reported, but that may also reflect the limited database. The risk profile in certain patients groups is not well defined in particular patients with NYHA III/IV as they were not properly represented in the clinical studies. Several SPC adaptations were implemented to improve the safety profile of vernakalant infusion, in particular contraindication of vernakalant within 4 hours following use of class I/ III AADs, patients with severe hypotension, patients with NYHA III/IV, bradycardia and prolonged QT at baseline.

2.5. Pharmacovigilance

The CHMP considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.5.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.5.2. Risk management plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

SUMMARY OF THE EU RISK MANAGEMENT PLAN

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important identified risk Hypotension	1. Routine pharmacovigilance 2. Post-authorisation registry study: significant hypotension evaluated as a medically important adverse reaction of special interest	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Risk of hypotension and appropriate advice to prescribers for patient selection and minimization of this risk are provided in the proposed SmPC in sections 4.3 (Contraindications), 4.4 (Warnings and special precautions for use), and 4.8 (Undesirable effects). Section 4.3 (Contraindications): Patients with severe aortic stenosis, patients with systolic blood pressure < 100 mm Hg). [Additional text providing further specifics about patients with NYHA class III or IV heart failure will be included when the final, approved Brinavess SmPC is available.] Section 4.4 (Special warnings and precautions for use): Patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during and after administration of Brinavess, until clinical and ECG parameters have stabilized. Prior to attempting pharmacological cardioversion, ensure that patients are adequately hydrated and haemodynamically optimized. During infusion of Brinavess, if patients develop clinically meaningful bradycardia and/or hypotension or develop ECG changes (such as a

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), the administration of Brinavess should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of Brinavess, patients should not receive the second dose of Brinavess. <u>Hypotension</u> Hypotension can occur in a small number of patients (vernakalant 7.6%, placebo 5.1%). Hypotension typically occurs early, either during the infusion or early after the end of the infusion, and can usually be corrected by standard supportive measures. Patients with congestive heart failure (CHF) have been identified as a population at higher risk for hypotension. (See section 4.8). <u>Congestive Heart Failure</u> Patients with CHF showed a higher overall incidence of hypotensive events, during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (16.1% vs. 4.7%, respectively). In patients without 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 (5.7% vs. 5.2%, respectively). Hypotension reported as a serious adverse experience or leading to medicine discontinuation occurred in CHF patients following exposure to Brinavess in 2.9% of these patients compared to 0% in placebo. Due to the higher incidence of the adverse events of hypotension and ventricular arrhythmia in patients with CHF, vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II. There is limited experience with the use of vernakalant in patients with previously documented LVEF ≤ 35%, its use in these patients is not recommended. The use in CHF patients corresponding to NYHA III or

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		NYHA IV is contraindicated (see section 4.3). Section 4.8 (Undesirable effects): Vascular disorders *Common*: Hypotension Description of selected adverse reactions: Clinically significant adverse reactions observed in clinical trials included hypotension and ventricular arrhythmia. (See section 4.4 Hypotension, Congestive Heart Failure). 2. Additional Risk Minimisation Activities Proposed Healthcare Professional Education Programme Materials will identify the risk of hypotension with vernakalant use, and provide appropriate advice to minimise this risk. Risk of hypotension in patients with congestive heart failure will be identified, and guidance for appropriate patient selection will be provided.
Important identified risk Bradycardia	1. Routine pharmacovigilance 2. Post-authorisation registry study: significant bradycardia evaluated as a medically important adverse reaction of special interest	1. Routine Risk Minimisation Activities Proposed SmPC Risk of bradycardia and appropriate advice to prescribers for patient selection and minimization of this risk are provided in the proposed SmPC in sections 4.3 (Contraindications), 4.4 (Warnings and special precautions for use), and 4.8 (Undesirable effects). Section 4.3 (Contraindications): Patients with prolonged QT at baseline (uncorrected >440 msec), or severe bradycardia, sinus node dysfunction in the absence of a pacemaker. [Additional text providing further specifics about patients with heart block will be included when the final, approved Brinavess SmPC is available.] Section 4.4 (Special warnings and precautions for use): Patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during and after administration of Brinavess, until clinical and ECG parameters have stabilized. During infusion of Brinavess, if patients develop

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		clinically meaningful bradycardia and/or hypotension or develop ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), the administration of Brinavess should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of Brinavess, patients should not receive the second dose of Brinavess. Section 4.8 (Undesirable effects): Cardiac disorders *Common*: Bradycardia *Uncommon*: Sinus arrest, complete AV block, first degree AV block, sinus bradycardia Description of selected adverse reactions: Bradycardia was observed predominantly at the time of conversion to sinus rhythm. With a significantly higher conversion rate in patients treated with Brinavess, the incidence of bradycardia events was higher within the first 2 hours in vernakalant treated patients than in placebo-treated patients (5.4% vs. 3.8%, respectively). Of the patients who did not convert to sinus rhythm, the incidence of bradycardia events in the first 2 hours postdose was similar in placebo and vernakalant treated groups (4.0% and 3.8%, respectively). In general, bradycardia responded well to discontinuation of Brinavess and/or administration of atropine. 2. Additional Risk Minimisation Activities Proposed Healthcare Professional Education Programme Materials will identify the risk of bradycardia with vernakalant use, and provide appropriate advice to minimise this risk.
Important identified risk Ventricular arrhythmia in patients with	1. Routine pharmacovigilance 2. Post-authorisation	1. Routine Risk Minimisation Activities Proposed SmPC Risk of ventricular arrhythmia in patients with heart failure, and appropriate advice to

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
history / evidence of CHF	registry study: ventricular arrhythmia evaluated as a medically important adverse reaction of special interest; medical history of heart failure and NYHA class collected at baseline	prescribers for patient selection and minimization of this risk are provided in the proposed SmPC in sections 4.3 (Contraindications), 4.4 (Warnings and special precautions for use), and 4.8 (Undesirable effects). Section 4.3 (Contraindications): [Specific text describing contraindication of use in patients with NYHA class III and IV heart failure will be included when the final, approved Brinavess SmPC is available.] Patients with prolonged QT at baseline (uncorrected > 440 msec) Use of IV rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to Brinavess administration. Acute coronary syndrome (including myocardial infarction) within the last 30 days. Section 4.4 (Special warnings and precautions for use): Patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during and after administration of Brinavess, until clinical and ECG parameters have stabilized. In patients with uncorrected hypokalaemia (serum potassium of less than 3.5 mmol/l), potassium levels should be corrected prior to use of Brinavess. During infusion of Brinavess, if patients develop clinically meaningful bradycardia and/or hypotension or develop ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), the administration of Brinavess should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of Brinavess, patients should not receive the second dose of Brinavess.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		<u>Congestive Heart Failure</u> Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (7.3% for Brinavess compared to 1.6% in placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. By contrast, ventricular arrhythmias were reported with similar frequencies in patients without a history of CHF who were treated with either Brinavess or placebo (3.2% for Brinavess vs. 3.6% for placebo). Due to the higher incidence of the adverse events of hypotension and ventricular arrhythmia in patients with CHF, vernakalant should be used cautiously in haemodynamically stable patients with CHF functional classes NYHA I to II. There is limited experience with the use of vernakalant in patients with previously documented LVEF ≤ 35%, its use in these patients is not recommended. The use in CHF patients corresponding to NYHA III or NYHA IV is contraindicated (see section 4.3). <u>Use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS</u> BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data. BRINAVESS should not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3). 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 (see above). There is limited experience with the use of intravenous rhythm control anti-arrhythmics (class I and class III) in the first 4 hours after BRINAVESS administration, therefore these agents should be used cautiously within this period. Resumption or initiation of oral maintenance antiarrhythmic therapy can be considered starting 2 hours after vernakalant

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		administration. <u>Valvular Heart Disease</u> In patients with valvular heart disease, there was a higher incidence of ventricular arrhythmia events in vernakalant patients. These patients should be monitored closely. Section 4.8 (Undesirable effects): <u>Cardiac disorders</u> *Uncommon*: ventricular extrasystoles, ventricular tachycardia <u>Description of selected adverse reactions</u>: Clinically significant adverse reactions observed in clinical trials included hypotension and ventricular arrhythmia. (See section 4.4 Hypotension, Congestive Heart Failure). <u>2. Additional Risk Minimisation Activities</u> <u>Proposed Healthcare Professional Education Programme</u> Materials will identify the risk of ventricular arrhythmia with vernakalant use in patients with heart failure, and provide appropriate advice to minimise this risk.
Important potential risk Ventricular arrhythmia in patients without CHF	1. Routine pharmacovigilance 2. Post-authorisation registry study: ventricular arrhythmia evaluated as a medically important adverse reaction of special interest	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Risk of ventricular arrhythmia, and appropriate advice to prescribers for patient selection and minimization of this risk are provided in the proposed SmPC in sections 4.3 (Contraindications), 4.4 (Warnings and special precautions for use), and 4.8 (Undesirable effects). Section 4.3 (Contraindications): Patients with prolonged QT at baseline (uncorrected > 440 msec) Use of IV rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to Brinavess administration. Acute coronary syndrome (including myocardial infarction) within the last 30 days Section 4.4 (Special warnings and precautions

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		for use): Patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during and after administration of Brinavess, until clinical and ECG parameters have stabilized. In patients with uncorrected hypokalaemia (serum potassium of less than 3.5 mmol/l), potassium levels should be corrected prior to use of Brinavess. During infusion of Brinavess, if patients develop clinically meaningful bradycardia and/or hypotension or develop ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), the administration of Brinavess should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of Brinavess, patients should not receive the second dose of Brinavess. <u>Congestive Heart Failure</u> Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (7.3% for Brinavess compared to 1.6% in Placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. By contrast, ventricular arrhythmias were reported with similar frequencies in patients without a history of CHF who were treated with either Brinavess or Placebo (3.2% for Brinavess vs. 3.6% for Placebo). <u>Use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS</u> BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data. BRINAVESS should not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3).

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		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 (see above). There is limited experience with the use of intravenous rhythm control anti-arrhythmics (class I and class III) in the first 4 hours after BRINAVESS administration, therefore these agents should be used cautiously within this period. Resumption or initiation of oral maintenance antiarrhythmic therapy can be considered starting 2 hours after vernakalant administration. <u>Valvular Heart Disease</u> In patients with valvular heart disease, there was a higher incidence of ventricular arrhythmia events in vernakalant patients. These patients should be monitored closely. Section 4.8 (Undesirable effects): <u>Cardiac disorders</u> *Uncommon*: ventricular extrasystoles, ventricular tachycardia <u>Description of selected adverse reactions</u>: Clinically significant adverse reactions observed in clinical trials included hypotension and ventricular arrhythmia. (See section 4.4 Hypotension, CHF).
Important potential risk Atrial flutter	1. Routine pharmacovigilance 2. Post-authorisation registry study: atrial flutter evaluated as a medically important adverse reaction of special interest	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Risk of atrial flutter, and appropriate advice to prescribers for patient selection and minimization of this risk are provided in the proposed SmPC in sections 4.2 (Posology and method of administration), 4.4 (Warnings and special precautions for use), and 4.8 (Undesirable effects). Section 4.2 (Posology and method of administration): If haemodynamically stable atrial flutter is observed after the initial infusion, the second infusion of Brinavess may be administered as patients may convert to sinus rhythm. (See 4.8)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		Section 4.4 (Special warnings and precautions for use): <u>Atrial Flutter</u> Brinavess was not found to be effective in converting typical primary atrial flutter to sinus rhythm. Patients receiving Brinavess have a higher incidence of converting to atrial flutter within the first 2 hours post-dose. This risk is higher in patients who use Class I antiarrhythmics (see section 4.8). If atrial flutter is observed as secondary to treatment, continuation of infusion should be considered (see 4.2). Section 4.8 (Undesirable effects): <u>Cardiac disorders</u> *Common*: Atrial flutter <u>Description of selected adverse reactions</u>: <u>Atrial Flutter</u> Atrial fibrillation patients receiving Brinavess have a higher incidence of converting to atrial flutter within the first 2 hours postdose (10% vs. 2.5% in placebo). With continuation of the medicine infusion as recommended above, the majority of these patients continue to convert to sinus rhythm. In the remaining patients, electrical cardioversion can be recommended. No patient with atrial flutter following treatment with Brinavess developed 1:1 atrioventricular conduction.
Important potential risk Overdose / Medication error	1. Routine pharmacovigilance 2. Post-authorisation registry study: data will be collected to assess vernakalant dosing	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Detailed instructions for preparation, dosing and administration of vernakalant are provided in the proposed SmPC in section 4.2 (Posology and method of administration). Information about human experience with overdose is provided in section 4.9 (Overdose) Section 4.2 (Posology and method of administration): Brinavess is dosed by patient body weight, with a maximum calculated dose based upon 113 kgs. The recommended initial infusion is 3 mg/kg to be infused over a 10 minute period. For patients weighing ≥ 113 kg, do not exceed the

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		maximum initial dose of 339 mg (84.7 ml of 4 mg/ml solution). If conversion to sinus rhythm 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, do not exceed the maximum second infusion of 226 mg (56.5 ml of 4 mg/ml solution). Cumulative doses of greater than 5 mg/kg should not be administered within 24 hours. There are no clinical data on repeat doses after the initial and second infusions. [Further detailed instructions for preparation, dosing, and administration of Brinavess will be included when the final, approved Brinavess SmPC is available.] Section 4.9 (Overdose): No case of overdose with Brinavess has been reported in clinical trials. One patient who received 3 mg/kg of Brinavess over 5 minutes (instead of the recommended 10 minutes) developed haemodynamically stable wide complex tachycardia which resolved without sequelae. <u>2. Additional Risk Minimisation Activities</u> <u>Proposed Healthcare Professional Education Programme</u> Materials will provide specific instructions for preparation, dosing, and administration of vernakalant injection.
Important missing information Patients with heart failure NYHA class III and IV	1. Routine pharmacovigilance 2. Post-authorisation registry study: heart failure status and NYHA class of registry patients will be evaluated	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Risk of hypotension and ventricular arrhythmia in patients with heart failure NYHA class III or IV, and appropriate advice to prescribers for patient selection and minimization of these risks are provided in the proposed SmPC in sections 4.3 (Contraindications), and 4.4 (Warnings and special precautions for use). Use of vernakalant injection in heart failure NYHA class III and IV is specifically contraindicated. Section 4.3 (Contraindications): [Text describing contraindication of use in patients with heart failure NYHA class III and IV

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		will be included when the final, approved Brinavess SmPC is available.] Section 4.4 (Special warnings and precautions for use): <u>Hypotension</u> Hypotension can occur in a small number of patients (vernakalant 7.6%, placebo 5.1%). Hypotension typically occurs early, either during the infusion or early after the end of the infusion, and can usually be corrected by standard supportive measures. Patients with congestive heart failure (CHF) have been identified as a population at higher risk for hypotension. (See section 4.8). <u>Congestive Heart Failure</u> Patients with CHF showed a higher overall incidence of hypotensive events, during the first 2 hours after dose in patients treated with vernakalant compared to patients receiving placebo (16.1% vs. 4.7%, respectively). In patients without 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 (5.7% vs. 5.2%, respectively). Hypotension reported as a serious adverse experience or leading to medicine discontinuation occurred in CHF patients following exposure to Brinavess in 2.9% of these patients compared to 0% in placebo. Patients with a history of CHF showed a higher incidence of ventricular arrhythmia in the first two hours post dose (7.3% for Brinavess compared to 1.6% in placebo). These arrhythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias. By contrast, ventricular arrhythmias were reported with similar frequencies in patients without a history of CHF who were treated with either Brinavess or placebo (3.2% for Brinavess vs. 3.6% for placebo) Due to the higher incidence of the adverse events of hypotension and ventricular arrhythmia in patients with CHF, vernakalant should be used cautiously in haemodynamically

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		stable patients with CHF functional classes NYHA I to II. There is limited experience with the use of vernakalant in patients with previously documented LVEF ≤ 35%, its use in these patients is not recommended. The use in CHF patients (corresponding to NYHA III or NYHA IV) is contraindicated (see section 4.3). 2. <u>Additional Risk Minimisation Activities</u> <u>Proposed Healthcare Professional Education Programme</u> Materials will identify the risk of hypotension and ventricular arrhythmia with vernakalant use in patients with heart failure, and provide appropriate advice to minimise this risk. Guidance for appropriate patient selection will be provided, including the contraindication of vernakalant in patients with NYHA class III and IV heart failure, and precautions regarding patients with hemodynamically stable NYHA class I to II heart failure (use with caution).
Important missing information Diseases / Conditions not studied in clinical trials: • Patients with prolonged QT (uncorrected > 440 msec) • Patients with severe bradycardia, sinus node dysfunction, and second and third degree heart block (without	1. Routine pharmacovigilance 2. Post-authorisation registry study: medical history data will be collected	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Information regarding limited experience with vernakalant injection in specific patient groups, and appropriate advice for the prescriber regarding patient selection are provided in the proposed SmPC in sections 4.3 (Contraindications), and 4.4 (Warnings and special precautions for use). Section 4.3 (Contraindications): Patients with prolonged QT at baseline (uncorrected >440 msec), or severe bradycardia (without pacemaker), sinus node dysfunction in the absence of a pacemaker. [Additional text providing further specifics about patients with heart block will be included when the final, approved Brinavess SmPC is available.] Section 4.4 (Warnings and special precautions for use): <u>Other Diseases and Conditions not Studied</u> Furthermore, Brinavess has not been evaluated in patients with clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
pacemaker) • Patients with clinically meaningful valvular stenosis • Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis		constrictive pericarditis, and its use can not be recommended in such cases. 2. Additional Risk Minimization Activities Proposed Healthcare Professional Education Programme Materials will 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).
Important missing information Off label use • Patients with severe aortic stenosis, or systolic blood pressure < 100 mm HgPatients with recent myocardial infarction or acute coronary syndrome • Patients treated for arrhythmias other than atrial fibrillation	1. Routine pharmacovigilance 2. Post-authorisation registry study: indication for vernakalant treatment will be evaluated	1. Routine Risk Minimisation Activities Proposed SmPC Information about the recommended indication for use of vernakalant injection, and contraindication against use in patients with severe aortic stenosis hypotension, or recent myocardial infarction or acute coronary syndrome are provided in the proposed SmPC in sections 4.1 (Therapeutic indications), and 4.3 (Contraindications). Section 4.1 (Therapeutic indications): 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 Section 4.3 (Contraindications): Patients with severe aortic stenosis, patients with systolic blood pressure < 100 mm Hg Acute coronary syndrome (including myocardial infarction) within the last 30 days 2. Additional Risk Minimisation Activities Proposed Healthcare Professional Education

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		Programme Materials will identify key patient selection criteria, including indication for vernakalant use, contraindications, and information about patient populations at special risk.
Important missing information Use of intravenous antiarrhythmic drugs (class I and class III) within 4-24 hours prior to vernakalant administration Use of oral antiarrhythmic drugs (class I and class III)	1. Routine pharmacovigilance 2. Post-authorisation registry study: concomitant medication utilization data will be collected	1. Routine Risk Minimisation Activities Proposed SmPC Appropriate advice to prescribers regarding use of antiarrhythmic drugs prior to vernakalant administration is provided in the proposed SmPC in sections 4.3 (Contraindications) and 4.4 (Warnings and special precautions for use). Section 4.3 (Contraindications): Use of intravenous rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to Brinavess administration. Section 4.4 (Warnings and special precautions for use): Use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III) 4-24 hours prior to vernakalant, due to lack of data. BRINAVESS should not be administered in patients who received intravenous AADs (class I and III) within 4 hours prior to vernakalant (see section 4.3). 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 (see above). 2. Additional Risk Minimisation Activities Proposed Healthcare Professional Education Programme Materials will reinforce key patient management considerations, including contraindication of use of intravenous class I and class III antiarrhythmic agents within 4 hours prior to vernakalant infusion, and warnings and special precautions for use which state that BRINAVESS can not be recommended in patients previously administered intravenous AADs (class I and III)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		4-24 hours prior to BRINAVESS, due to lack of data and that BRINAVESS should be used with caution in patients on oral AADs (class I and III), due to limited experience.
Important missing information Use of intravenous antiarrhythmic drugs (class I and class III) in the first 4 hours after vernakalant administration	1. Routine pharmacovigilance 2. Post-authorisation registry study: concomitant medication utilization data will be collected	1. Routine Risk Minimisation Activities Proposed SmPC Appropriate advice to prescribers regarding use of antiarrhythmic drugs following vernakalant administration is provided in the proposed SmPC in section 4.4 (Warnings and special precautions for use). Section 4.4 (Warnings and special precautions for use): There is limited experience with the use of intravenous rhythm control anti-arrhythmics (class I and class III) in the first 4 hours after Brinavess administration, therefore these agents should be used cautiously within this period. 2. Additional Risk Minimisation Activities Proposed Healthcare Professional Education Programme Materials will reinforce key patient management considerations, including advice to exercise caution when using intravenous class I and class III antiarrhythmic agents in the first 4 hours following vernakalant infusion.
Important missing information Patients with pacemakers	1. Routine pharmacovigilance 2. Post-authorisation registry study: medical history data will be collected	1. Routine Risk Minimisation Activities Proposed SmPC Information regarding limited experience with use of vernakalant injection in patients with pacemakers is provided in the proposed SmPC in section 4.4 (Warnings and special precautions for use). Section 4.4 (Warnings and special precautions for use): There is limited experience with Brinavess in patients with pacemakers.
Important missing information Hepatic impairment	1. Routine pharmacovigilance 2. Post-authorisation	1. Routine Risk Minimisation Activities Proposed SmPC Information regarding limited experience with

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	registry study: medical history data, and results of laboratory testing conducted as part of usual medical care will be collected	vernakalant injection in patients with advanced hepatic impairment, and appropriate advice for the prescriber regarding patient selection and dosing are provided in the proposed SmPC in sections 4.2 (Posology and method of administration), 4.4 (Warnings and special precautions for use), and 5.2 (Pharmacokinetic properties). Section 4.2 (Posology and method of administration): *Hepatic impairment* No dose adjustment necessary (see sections 4.4 and 5.2). Section 4.4 (Special warnings and precautions for use): As the clinical trial experience in patients with advanced hepatic impairment is limited, use of vernakalant is not recommended in these patients. Section 5.2 (Pharmacokinetic properties): *Special patient groups* Acute exposure is not significantly influenced by gender, history of congestive heart failure, renal impairment, or concomitant administration of beta blockers and other medications, including warfarin, metoprolol, furosemide and digoxin. In patients with hepatic impairment, exposures were elevated by 9 to 25%. No dose adjustment of Brinavess is required for these conditions, nor on the basis of age, serum creatinine or CYP2D6 metaboliser status. <u>2. Additional Risk Minimisation Activities</u> <u>Proposed Healthcare Professional Education Programme</u> Materials will reinforce key patient management considerations, including guidance that use of vernakalant in patients with advanced hepatic impairment is not recommended.
Important missing information Use in pregnant or lactating women	1. Routine pharmacovigilance	<u>1. Routine Risk Minimisation Activities</u> <u>Proposed SmPC</u> Information regarding lack of human experience in pregnancy and/or lactation, and observations of fetal malformations in animal studies using the oral formulation of vernakalant are provided

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		in the proposed SmPC in sections 4.6 (Fertility, pregnancy and lactation), and 5.3 (Preclinical safety data). Section 4.6 (Fertility, pregnancy and lactation): <u>Pregnancy</u> There are no data from the use of vernakalant hydrochloride in pregnant women. Animal studies have shown malformations after repeated oral exposure (see section 5.3). As a precautionary measure, it is preferable to avoid the use of vernakalant during pregnancy. <u>Breast-feeding</u> It is unknown whether vernakalant /metabolites are excreted in human milk. There is no information on the excretion of vernakalant /metabolites in animal milk. A risk to the suckling child cannot be excluded. Caution should be exercised when used in breastfeeding women. <u>Fertility</u> Vernakalant was not shown to alter fertility in animal studies. Section 5.3 (Preclinical safety data): With respect to reproduction no effects on pregnancy, embryofoetal development, parturition or postnatal development were observed after intravenous administration of vernakalant at exposure levels (AUC) similar or below the human exposure levels (AUC) achieved after a single intravenous dose of vernakalant. In embryofetal 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 intravenous 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 embryofetal lethality, increased number of fetuses with fused and/or additional sternebrae were seen in rabbits at the highest doses tested.
Important missing information	1. Routine pharmacovigila	<u>1. Routine Risk Minimisation Activities</u>

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Paediatric use		<u>Proposed SmPC</u> Information regarding lack of experience in paediatric patients and appropriate advice to the prescriber to avoid use in children and adolescents are provided in the proposed SmPC in section 4.2 (Posology and method of administration). Section 4.2 (Posology and method of administration): Paediatric population: There is no relevant use of Brinavess in children and adolescents < 18 years of age in the current indication and therefore should not be used in this population.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The Marketing Authorisation Holder shall ensure that all Healthcare Professionals (HCP) involved in the administration of Brinavess are provided with a healthcare professional information pack containing the following:

Educational material for Healthcare Professionals
Summary of Product Characteristics, Package Leaflet and Labelling

Key elements to be included in the educational material:

1. Brinavess should be administered by intravenous infusion after dilution, by qualified medical personnel in a monitored clinical setting appropriate for cardioversion.

2. Appropriate measures to manage and minimize 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:
  - Patients with prolonged QT at baseline (uncorrected > 440 msec), or severe bradycardia, sinus node dysfunction or second degree and third degree heart block in the absence of a pacemaker.
  - Use of intravenous rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to BRINAVESS administration.
  - Acute coronary syndrome (including myocardial infarction) within the last 30 days
  - Patients with severe aortic stenosis, patients with systolic blood pressure <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 adverse events, which may occur after Brinavess administration, including hypotension, bradycardia, atrial flutter, or ventricular arrhythmia.
- Alert HCP for use of AADs (anti-arrhythmic drugs) prior to or after BRINAVESS.
    - BRINAVESS can not be recommended in patients previously administered intravenous 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 be used cautiously 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.

User consultation

A readability test has been performed by Luto Research Ltd, Leeds, UK. The testing process involved: 1 a pilot test on 2 participants, 2 main tests on ten participants each. Twelve questions about the most critical parts of the package leaflet and one general question about the package leaflet were asked. There were sufficient questions about the critical sections. Taking into account the results for each question more than 90 % of the participants finds the section and answered the question correctly. The conclusions are clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The patient information leaflet has been adapted sufficiently taking into account the results of the test.

2.6 Benefit-risk balance

2.6.1 Benefits

2.6.1.1 Beneficial effects

In the pooled data of the general AF population (ACT I/III, n=390), vernakalant administration resulted in significantly higher conversion rate to SR (51.1%) compared to the placebo treated group (3.8%) (% difference 47.3% 95% CI: 40.2- 54.4), within the first 90 minutes. Median time to conversion in the vernakalant group was 10 minutes compared to 31.5 minutes in the placebo group. For the patients who converted, rate of maintenance of sinus rhythm was 97.2% at 24 hours and 93% at 7 days. In the subgroup of patients with AF duration <48 hours, the rate of conversion to SR was significantly higher in the vernakalant group (61.2%) compared to the placebo group (4.9%). Vernakalant administration did not affect the response of the patients to subsequent electric cardioversion, in case of vernakalant failure. In post-cardiac surgery patients (ACT II, n=150), vernakalant administration resulted in significantly higher conversion rate to SR (47%) compared to the placebo treated group (14%) (% difference 33% 95% CI: 19.3- 46.7). The median time to conversion was 12.4 minutes in the vernakalant group compared to 29.7 minutes in the placebo group. For the 48 patients with AF (AFL) who converted to sinus rhythm, rate of maintenance of sinus rhythm at 24 hours was 59.5% and 56.9% at 7 days compared to 50.0% in the placebo group at 24 hours and time of hospital discharge (or within 14 days).

2.6.1.2 Uncertainty in the knowledge about the beneficial effects.

No robust claims can be made on maintenance of SR beyond 24 hours as no continuous ECG monitoring was available beyond that time. In the three placebo-controlled studies, the recruitment criteria were quite broad, but that did not translate into adequate representation of some subgroups of interest, in particular patients with NYHA III/IV, and those co-administered rate or rhythm control

AADs. These subgroups are currently contraindicated in the SPC. The efficacy endpoint was measured at 90 minutes, thereafter other interventions were allowed. A specific study was conducted to assess conversion in post-cardiac surgery patients. Recruited patients were of shorter duration AF, this difference in duration is currently reflected in the indication. Results of the general population of AF are better than those reported in post-cardiac surgery patients, but these were still significantly better than placebo. The actively-controlled study against amiodarone showed vernakalant to be more rapid than amiodarone, with the caveat that amiodarone may not have been the best comparator considering its known delayed onset of action. Still, compared with historical data, the overall rate of conversion to SR reported with vernakalant appears at least comparable to that reported with amiodarone, flecainide or ibutilide with a shorter time to conversion, but definite conclusions are not possible without direct comparative data with those latter agents.

2.6.2 Risks

2.6.2.1 Unfavourable effects

The safety database of vernakalant appears adequate with 507 patients administered the full dose (3 mg/kg followed by 2 mg/kg) and 241 patients administered the first dose (3 mg/kg). Due to the short half-life of vernakalant, most of the AEs are observed during the first 2 hours of administration. The most common treatment-related AEs reported during this period are dysgeusia, sneezing, parasethesia, nausea and hypotension. These AEs were described as mild or moderate and were not treatment-limiting. The most frequently reported serious related AEs were hypotension (1% vernakalant vs 0.3% in placebo), bradycardia (0.4% in vernakalant vs 0 in placebo) and AV block (0.3% vernakalant vs 0 in placebo). One case of death related to vernakalant was reported, however, the patient was erroneously recruited and afterwards administered vernakalant in spite of the stopping rules. Death was preceded by hypotension and ventricular fibrillation. An important issue is the proarrhythmic potential. Data clearly show QTcF prolongation with placebo-subtracted peaks of +22.1 msec (95% CI: 18.9-25.3) at minute 10 and +18.8 msec (95% CI: 15.6-22) at minute 35, returning to baseline by 50 minutes. Substantially more patients in the vernakalant group were observed with QTcF prolongations of ≥30 msec and ≥60 msec compared to the placebo group till the second hour after administration, although the absolute number of patients with a QTcF prolongation of ≥60 msec was low. Only one event of TdP was recorded in which the causation is confounded by the co-administration of ibutilide. The risk of developing AFL was significantly higher following vernakalant (6.1%) than placebo (1.6%)(percent risk difference 4.5: 95% CI 2.3 to 6.7), but no patient with AFL following treatment with vernakalant injection developed 1:1 atrioventricular conduction. Background use of rhythm control agents was associated with a higher risk of developing AFL (percent risk difference of 6.8, 95% CI 4.0 to 9.7).

2.6.2.2 Uncertainty in the knowledge about the unfavourable effects

The actual representation of different subgroups of patients in safety database (e.g non-white, slow metabolisers or with associated medical conditions) may not be sufficient. Also clinical and non-clinical data on repeat administration is lacking. Non-clinical data support a lower potential of vernakalant to induce TdP than other AADs. However, the current safety database is too limited to give a realistic estimation of the risk. Also, patients with CHF did show an increased incidence of ventricular arrhythmias compared to placebo, although the incidence was low and VF was noted only once in a patient who should have been contraindicated. In summary, the proarrhythmic potential of vernakalant appears low, but in high-risk patients the risk is still present and more clinical data will show whether the risk for TdP is indeed as low as now suggested. Patients with congestive heart failure appear to be also at more risk for hypotension. The experience is mainly based on patients with NYHA I/II, whereas NYHA III were minimally represented and NYHA IV excluded. In turn, a low baseline SBP (<105 mmHg) and a history of CHF were the most important factors that increased risk of hypotension. The incidence of bradycardia in the 0-2 hour period was slightly higher in the vernakalant group (5.4%) compared to placebo (3.8%) (percent risk difference 1.6; 95% CI:-1.1, 4.3), but this is probably driven by patients who converted to SR.

2.6.2.3 Benefit-risk balance

Vernakalant, concentrate for solution for infusion, is effective in converting AF of short duration to SR in non-surgical as well as post-cardiac surgery patients. The conversion rate is in line with that reported with other AADs such as flecainide, ibutilide and amiodarone. Median time to conversion is

very short making it a relevant option for highly symptomatic patients, especially when compared to amiodarone with longer time to conversion, as observed in the AVRO study. However the target group is probably different from that of amiodarone. Efficacy was accompanied by AEs mainly during the first 2 hours of administration. The most frequently reported AE (dysegeusia, sneezing and parasthesia) did not impact on the tolerability of the drug, but their mechanism is not studied. The more serious AEs: hypotension or bradycardia are well defined for the general population, though also the mechanism is not known. Patients with low blood pressure or bradycardia at baseline appear to be at higher risk for developing these AEs. Patients with congestive heart failure (NYHA I/II) are another population at risk, showing a higher risk of hypotension and ventricular arrhythmia. There is limited experience in severer forms of CHF, but based on the current experience in NYHA I/II, vernakalant use is contraindicated in these patients. The arrhythmogenic potential of vernakalant appears limited based on both clinical and non-clinical data, however no robust conclusions can be made due to the limited experience. Compared to flecainide, there is also a higher incidence of conversion of AF to AFL, but this was not accompanied with 1:1 conduction.

2.6.2.4 Discussion on the benefit-risk balance

In summary the benefit-risk balance of vernakalant for the claimed indication is considered positive. Questions remain regarding its safety in patients with moderate and severe heart failure and its concomitant administration with other anti-arrhythmic agents, but these issues are addressed by appropriate labelling. More clinical data are needed before final conclusions can be drawn on its proarrhythmic potential. For all identified and potential risks a Post-authorisation Registry study is requested. The aim of this PASS is to better characterise the safety profile of vernakalant in the context of normal clinical use of the product. Amongst others, the incidence of hypotension and ventricular arrhythmia will be estimated. In addition to the identified and potential risks, the following events of special interest will be collected: atrial flutter with 1:1 atrioventricular conduction of duration >10 seconds and ventricular rate >200 and bradycardia requiring mechanical pacing (temporary or permanent). The study is a prospective, observational study of vernakalant iv that will be conducted in multiple European countries. Countries under consideration include Denmark, France, Germany, Italy, the Netherlands, and Spain but final selection is conditional on a number of factors, including, but not limited to, the actual date of product launch in each country and rate of market uptake of vernakalant iv. The list of countries selected for the registry will be included in the draft registry protocol submitted to the CHMP by October 2010. Patients will receive vernakalant iv at the discretion of their physicians. Data collection will be performed during and shortly following vernakalant administration. The registry will enrol 2,000 patients across participating EU countries. The sample size was selected in order to have sufficient statistical precision as expressed by a 2-sided, 95% confidence limit around the expected incidence rate for each medically significant health outcomes of interest (HOIs).

The incidence of each medically significant HOI during the first 24 hours post-vernakalant administration among subjects randomised to receive vernakalant iv in the pooled clinical trial database (n=889, including the AVRO Study) ranged from 0% to 0.22% for each HOI.

2.6.2.5 Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

plus

the following additional risk minimisation activities were required: all Healthcare Professionals (HCP) involved in the administration of Brinavess are provided with a healthcare professional information pack.

2.6.3 Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Brinavess in the 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 was favourable and therefore recommended the granting of the marketing authorisation.