Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Vernakalant

Proprietary Product Name: Brinavess

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

November 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Rejected
Date of Initial Decision:	5 August 2011
Date of Final Decision:	3 January 2012[1]
Active ingredient(s):	Vernakalant (as the hydrochloride)
Product Name(s):	Brinavess
Sponsor's Name and Address:	Merck Sharpe & Dohme (Australia) Pty Ltd Level 4, 66 Waterloo Road North Ryde NSW 2113
Dose form(s):	Concentrated injection
Strength(s):	500 mg/25 mL, 20 mg/mL
Container(s):	Type 1 glass vials with rubber stoppers
Pack size(s):	1 and 10 vials
Approved Therapeutic use:	Not applicable
Route(s) of administration:	Intravenous infusion
Dosage:	Complex-see *Product background* below.
ARTG Number (s)	Not applicable

Product background

Vernakalant is an antiarrhythmic medicine that acts preferentially in the atria to prolong atrial refractoriness and to rate-dependently slow impulse conduction. These anti-fibrillatory actions on refractoriness and conduction are thought to suppress reentry and are potentiated in the atria during atrial fibrillation. The relative selectivity of vernakalant on atrial versus ventricular refractoriness is postulated to result from the block of currents that are expressed in the atria, but not in the ventricles, as well as the unique electrophysiologic condition of the fibrillating atria. However, blockade of cationic currents, including hERG channels and cardiac voltage-dependent sodium channels, in the ventricles has been documented.

This AusPAR describes the evaluation of an application by Merck Sharp & Dohme (Australia) Pty Ltd (the sponsor) to register Vernakalant (Brinavess) for the treatment of

[1] The initial Delegate's decision was taken to be confirmed, in accordance with s.60(4) of the *Therapeutic Goods Act 1989* on 3 January 2012. For further details see the *Outcome* section of this AusPAR.

atrial fibrillation. The sponsor claims that targeted effects on atrial tissue coupled with frequency dependent late sodium channel ion current (INa) block may result in a lower risk of ventricular proarrhythmia for vernakalant than with drugs which predominately block sodium channels (for example, Class Ic agents such as flecainide) or potassium channels (for example, Class III agents such as ibutilide or dofetilide). Given the limitations of current pharmacological agents used to acutely convert atrial fibrillation (AF) and the necessity for conscious sedation or anaesthesia for electrical cardioversion, the sponsor states that there is a clinical need for better pharmacological approaches to convert AF to sinus rhythm. The sponsor claims that rapid pharmacological cardioversion by vernakalant injection, suitable for a broad-based AF population with typical cardiovascular co-morbidities, provides a much needed addition to the treatment algorithm for the acute conversion of AF.

The proposed indication is:

Brinavess is indicated for the rapid conversion of recent onset atrial fibrillation (≤ 7 days duration) to sinus rhythm.

Dosage recommendations are:

Brinavess should be administered in a monitored clinical setting appropriate for cardioversion. Brinavess is administered based on patient body weight. The standard recommended dose 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. Cumulative doses of greater than 5 mg/kg should not be administered. If conversion to sinus rhythm occurs during either the initial or second infusion, that infusion should be continued to completion. If haemodynamically stable atrial flutter is observed after the first dose, the second dose of Brinavess may be administered as patients may convert to sinus rhythm.

Brinavess vials are for single use only. Brinavess must be diluted prior to administration. Brinavess should only be administered by intravenous infusion.

Regulatory status

A similar application was approved in the European Union (EU) on 1 September 2010 and Switzerland on 16 March 2011. The indication in the EU 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*

The indication in Switzerland is:

Rapid conversion of recent onset atrial fibrillation to sinus rhythm in adult non-surgery and post-cardiac surgery patients

An application was submitted in the US on 19 December 2006 where it is under review. It was considered approvable but a further clinical study was recommended.

An application has been approved in New Zealand (17 November 2011).

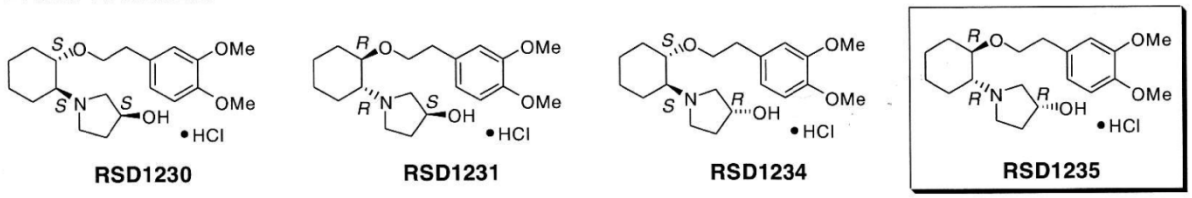
II. Quality findings

Drug substance (active ingredient)

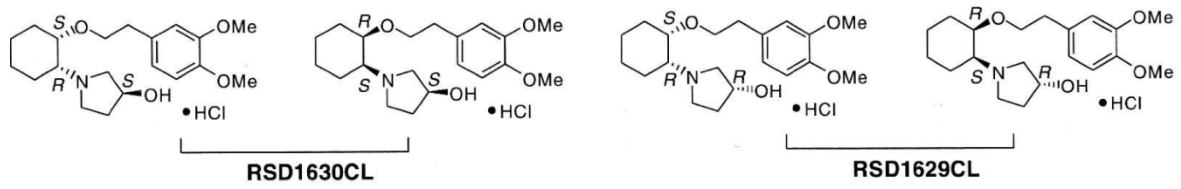
The drug substance contains 3 chiral centres, but is presented as a single diastereoisomer. The eight possible diastereoisomers are depicted below, RSD1235 being vernakalant

hydrochloride.

***Trans* Isomers:**



***Cis* Isomers:**



Vernakalant Hydrochloride details

*(1*R*,2*R*)-2-[(3*R*)-hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)cyclohexane monohydrochloride*

$C_{20}H_{31}NO_4.HCl$ *Molecular mass = 385.93 (349.46 free base)*

CAS # = [748810-28-8] *pK_a = 9.5 (i.e. pyrrole nitrogen is protonated at neutral pH)*

Aqueous solubility = 274-496 mg/mL (freely soluble) over pH range 1-13

Biopharmaceutical Classification System (BCS) Class not relevant to IV injections

Vernakalant hydrochloride is prepared completely by chemical synthesis in a five step process which ensures the chirality of each chiral centre. The route of synthesis leads to a single polymorphic form of the anhydrous, non-solvated material. No other polymorphs have been generated, but mono- and dihydrates have been isolated. The final material precipitates as fine crystals and further micronisation is not necessary. There are no compendial monographs for the drug substance or for finished products containing this drug substance.

The specifications include tests and limits for 5 specified impurities. Four of the limits are above the International Council on Harmonisation (ICH) qualification threshold, but the advice of the nonclinical evaluator was that these limits are qualified.[2] There is a limit of not more than (NMT) 0.2% for unspecified isomeric impurities. This is above the ICH qualification threshold and the sponsor was asked to specify the impurities or reduce the limit. The residual solvents present are limited to tighter than ICH levels and residual palladium (catalyst) is limited to 5 ppm which ensures ICH levels are met.

Drug product

Formulation and manufacture

The concentrated injections are to be manufactured by a single site: Hameln Pharmaceuticals GmbH in Germany. The process is typical and involves dissolution of ingredients, pH adjustment, filtration and filling. This process is performed under nitrogen

[2] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

and the filled vials are terminally sterilised by steam. The sterility aspects of the manufacture are controlled satisfactorily.

Specifications

The specifications have acceptable expiry limits and identical release limits which are acceptable as no changes occur on storage. The limits for related substances comply with ICH guidance.

Stability

Stability data were provided to support an unopened shelf life of 3 years when stored below 30°C. No other conditions are required.

Bioavailability

The product is a simple aqueous solution intended (after dilution) for intravenous administration only. As such the bioavailability can be considered 100%.

Advisory committee considerations

Details of this submission were presented at the 135th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in November 2010. The PSC expressed no requirement to review the submission again if all outstanding issues were resolved to the satisfaction of the TGA.

The PSC commented that the population pharmacokinetic model used was not necessarily appropriate and the conclusions relating to weight and gender may be in error, and that this analysis should be brought to the attention of the Delegate.

Quality summary and conclusions

Approval of the application was recommended with respect to chemistry and manufacturing control. Bioavailability is 100% for this route of administration. The recommendations of PSC in relation to the population pharmacokinetics were brought to the attention of the Delegate.

III. Nonclinical findings

Introduction

Overall, the quality of the submitted submission was adequate, although there were some shortcomings and primary pharmacodynamic study reports were relatively poorly documented in some cases.

Pharmacology

Primary pharmacodynamics

Primary pharmacology studies on vernakalant were extensive and included investigation of effects on cardiac ion channels and action potentials *in vitro* and its cardiovascular activity in a number of species *in vivo*. Several studies included comparators from

different classes in the Vaughan Williams classification of antiarrhythmic drugs, including flecainide, quinidine, propafenone and lignocaine (all class I sodium channel blockers), dofetilide, E-4031 and tedisamil (all class III potassium channel blockers) and verapamil (class IV calcium channel blocker). Studies in isolated guinea pig or canine myocytes and cloned ion channels (mainly human) expressed in HEK-293 cells showed that vernakalant inhibits both potassium and sodium channels but has little effect on calcium channels and overall suggested that vernakalant should exhibit the proposed activity, with some atrial over ventricular selectivity.

Sodium channel blockade is considered to be highly effective in terminating AF (Kneller *et al*., 2005).[3] Vernakalant inhibited the cloned human heart sodium channel (Nav1.5 = hH1) with median inhibitory concentration (IC_{50}) values of about 20-30 μM (1 Hz) or 10.8 μM (10 Hz), with the latter being similar to the expected maximal clinical plasma concentration (C_{max}) of about 13.2 μM. Further, 30 μM vernakalant inhibited each of the early, sustained and (to a greater extent) late components of the sodium current in the cloned human channel (by 50-70%), with an IC_{50} of 14 μM being obtained for the latter. Many of the electrophysiological properties of vernakalant in blocking human Nav1.5 channels were similar to those of the specific late sodium channel blocker, ranolazine, used as a comparator in some studies. The late component occurs at voltages approximating the action potential duration to 50% repolarization (APD_{50}) such that inhibition of this component may offset any potential QT prolongation or ventricular arrhythmias due to hERG channel inhibition.

Vernakalant inhibited several potassium currents with variable potencies: ultra-rapidly activating potassium channel current (I_{Kur}) (Kv1.5), the rapid potassium channel current (I_{Kr}) (hERG) and the inwardly rectifying potassium channel (I_{KACh}) (Kir3.1/3.2) for which IC_{50} values were less than or equal to the expected clinical plasma C_{max}. Vernakalant would be expected to show some atrial specificity compared to the ventricle, as I_{Kur} and I_{Kr} are considered to be limited to (or predominantly present in) the atria (Tamargo *et al*., 2004).[4] Inhibition of I_{Kr} (hERG) would be expected to be disadvantageous as it is known to be associated with prolongation of QT intervals and an increased risk of ventricular arrhythmias (discussed further below).

A number of *in vivo* models of AF were used in which intravenous (IV) vernakalant showed variable efficacy. High activity was seen in anaesthetised vagally stimulated dogs at 2 mg/kg and goats at 0.2-0.4 mg/kg/min, with the lowest plasma drug concentrations in dogs observed at times of AF termination of 0.8 – 9.1 μg/mL, that is, below the expected clinical C_{max}. Termination of AF was also seen in dogs in an atrial tachycardia model, with AF that was sustained or >20 seconds (s) but not with short lasting AF. Variable or little activity was noted in a dog chronic heart failure model and in anaesthetised pigs. In the species studied *in vivo* (dogs, goats, pigs, rats, guinea pigs and cynomolgus monkeys), effective refractory periods (ERP) were generally increased by vernakalant, as expected. Moreover, where both atrial and ventricular ERP were measured (dogs, pigs and cynomolgus monkeys), atrial values were increased to a greater extent than ventricular values, further suggesting some atrial specificity. In studies where atrial conduction velocity was measured (mostly in dogs but also in pigs) vernakalant reduced this parameter, an effect typical of class I antiarrhythmic drugs that are sodium channel blockers.

Vernakalant appeared to have low potential for proarrhythmic activity and it reduced the incidence of torsades de pointes (TdP) induced in rabbits by the predominantly class III antiarrhythmic drug, clofilium. This is consistent with its ability to suppress dofetilide

[3] Kneller J *et al.* Mechanism of atrial fibrillation termination by pure sodium channel blockade in an ionically-realistic mathematical model. Circ Res 2005; 96: e35-47.

[4] Tamargo J *et al.* Pharmacology of cardiac potassium channels. Cardiovasc Res 2004; 62: 9-33.

induced early after depolarisations (EAD) *in vitro*, as EAD are believed to trigger TdP (Tamargo *et al*., 2004).[4] The mechanism by which vernakalant reduced clofilium induced TdP was probably via its observed inhibition of clofilium induced increase in QTc.

Potential for proarrhythmic activity was also investigated in a coronary ischaemia model (left anterior descending coronary artery (LAD) occlusion) in anaesthetised pigs, in which 2/8 vernakalant treated pigs developed ventricular fibrillation (VF) compared with 6/7 controls, indicative of a protective effect. Although it was noted that a mortality of 60-70% was normal for this model, the report was not well documented and it was not clear whether control deaths occurred. However, by comparison, flecainide (1 or 2 mg/kg IV) and amiodarone (5 mg/kg/IV) respectively resulted in 9/9 lethal cases and 3/3 total cases (including one death) of VF. A similar protective effect of vernakalant (but not flecainide) was seen in a similar rat LAD occlusion model in which an arrhythmia score was determined from VF, ventricular tachycardia (VT) and premature ventricular contraction (PVC) data.

Electrocardiogram (ECG) intervals (PR, QRS and QT/QTc in dogs, goats, pigs, rats and guinea pigs, and cynomolgus monkeys) were generally found to be increased by vernakalant. However, the rat is not considered to be a suitable model for comparison with humans due to species differences in the cardiac ion channels contributing to cardiac repolarisation (TGA-adopted EU guideline) and effects on these parameters in the larger mammals (dogs, goats, pigs and cynomolgus monkeys) were generally of relatively small magnitude.[5] As noted above, inhibition of the late sodium current may contribute to offsetting the inhibition of the hERG channel current I_{Kr}.

In *in vitro* studies, force of contraction was not affected in rabbit atria or papillary muscles by vernakalant at concentrations up to 10 μM, but contractility ($+dP/dt_{max}$) was decreased in Langendorff-perfused guinea pig hearts (by up to 65% at 30 μM vernakalant). Like the sodium channel blocker, flecainide, vernakalant exhibited negative inotropic effects in pigs *in vivo*, and also rats, presumably associated with sodium channel blockade.

Metabolites and diastereoisomers

The 4-O-demethyl metabolite (RSD1385) also showed ion channel blocking activity although there were considerable discrepancies in IC_{50} values, possibly related to the use of batches of different purity. Data for the most recent and purest batch showed that RSD1385 had lower activity (3 to 10 fold) than vernakalant in blocking Kv1.5, hERG and Nav1.5 channels but appeared to be of similar activity in blocking Kv4.2/Kv4.3 channels. The effect of RSD1385 on action potentials was qualitatively similar to vernakalant but quantitatively small. Similarly the 3-O-demethyl derivative (RSD1390) showed lower activity (2-20 fold) than vernakalant in blocking Kv1.5, hERG and Nav1.5 channels but appeared to be of similar activity in blocking Kv4.2/Kv4.3 channels. Both compounds were present at low levels in human plasma compared with vernakalant or metabolite glucuronide conjugates and would be expected to contribute little to pharmacological activity. RSD1385-glucuronide was inactive at blocking sodium (Nav1.5; IC_{50} >100 μM) or potassium channels (Kv1.5 and hERG; IC_{50} >1000 μM). According to the sponsor, RSD1390-glucuronide was also largely inactive at blocking Kv1.5 and hERG (respective IC_{50} values of 516 μM and 194 μM).

Pharmacological studies with the diastereoisomers RSD1230, RSD1231 and RSD1234 showed they had similar potency to vernakalant in blocking Nav1.5, hERG, Kv1.5 and Kv4.3 channels and each (like vernakalant) caused frequency dependent block of Nav1.5. Antiarrhythmic activity and effects of vernakalant and each of the diastereoisomers on

[5] EMEA, ICH Topic Q S 7 B, November 2005. Note for Guidance on the Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals, CPMP/ICH/423/02.

blood pressure, heart rate, ECG intervals and stimulation parameters were generally comparable when investigated in rats.

Safety and secondary pharmacology

Safety pharmacology studies were adequate, although not always compliant with Good Laboratory Practice, and included investigation of central nervous system (CNS) effects in mice and rats, respiratory effects in rats and cardiovascular effects in rats, guinea pigs, pigs and dogs. Cardiovascular effects were also extensively investigated in other studies included in the primary pharmacology section because of their intimate relationship to the mode of action of vernakalant.

Prominent CNS effects were observed in rats after continuous IV infusion, including pupil dilation, tremors, restlessness, compulsive chewing, lip smacking, head shaking and at higher doses, convulsions. These were probably due to potassium channel block and the 4-O-demethyl metabolite (RSD1385) showed broadly similar activity to that of parent drug. Respiratory changes were relatively minor (hyperpnoea in the above study with continuous IV infusion and transiently increased tidal volume at 20 mg/kg IV). CNS and respiratory changes were observed in the toxicity studies (*General toxicity*), in which there were no findings suggesting a need to extend safety pharmacology studies beyond the core battery.

The effects of vernakalant on blood pressure and ECG (discussed in *Primary pharmacodynamics*) parameters were determined in a number of studies, with broadly consistent results in the various species investigated. Reductions in blood pressure were consistently observed in all species investigated (dogs, pigs, rats, guinea pigs), except cynomolgus monkeys, in which there was little effect and in one study in conscious dogs in which transient (30 minutes) increases in blood pressure were observed at 20 mg/kg. Reductions in heart rate were also consistently observed in pigs, rats and guinea pigs, while again the exceptions were cynomolgus monkeys (little effect) and the dog study SPT05-027 (transient [5 minutes] increase at 20 mg/kg), together with dog study SPD06-004 (increases with 16 mg/kg).

Slight transient prolongation of the QRS complex and QTc interval were seen in the clinical trials and potential cardiovascular risks identified in the Risk Management Plan (RMP) were hypotension, bradycardia, ventricular arrhythmia and atrial flutter.

Although there were no indications of untoward effects on platelets and clotting in the toxicity studies, potential effects of vernakalant on platelet function were not investigated. Vernakalant and its diastereoisomer RSD1231, and the 4-O- and 3-O-demethyl metabolites (3-30 μM) did not induce, potentiate or inhibit histamine release from human whole blood or rat mast cells *in vitro*.

Pharmacokinetics and relative drug exposures

Following single IV administration, plasma vernakalant clearance values were higher in mice, rats, rabbits, dogs and cynomolgus monkeys (respectively about 9.4, 4.7-14.3, 2.0, 1.8 and 1.7 L/h/kg with doses of 10-24 mg/kg) than in humans (0.75 L/h/kg with 5 mg/kg). Elimination was not comprehensively investigated. Radioactivity mass balance data were available only for the rat, which showed a different excretion pattern to that in humans and it was not clear why elimination was not also examined in dogs. After single IV administration of [^{14}C]vernakalant respective rat urinary and faecal recoveries of radioactivity were about 26% and 64%, compared with mainly urinary recovery in humans (about 93% of the dose in extensive metabolisers). Similar results were obtained after oral (PO) administration, a route not proposed for the current application but being developed for chronic use in the prevention of atrial fibrillation (sponsor's *Clinical*

Overview). Results of a tissue distribution study suggested that faecal recovery in rats resulted from biliary excretion, with high radioactivity being present in bile as well as urine and kidneys after IV administration. Pharmacokinetic studies submitted using PO administration gave respective oral bioavailabilities of 18%, 56% and 16% in rats, dogs and cynomolgus monkeys.

In terms of potential untoward effects of the proposed single treatment regimen (3 mg/kg which may be followed by 2 mg/kg), peak drug concentrations would probably be more relevant than drug exposures based on area under the plasma concentration time curve (AUC). As summarised in Table 1, exposure ratios (ER) based on the C_{max} achieved in the repeat dose toxicity studies were low, and would be even lower by comparison with a human value of 7.53 µg/mL obtained in one clinical trial with post-surgery patients.

Table 1: Exposure ratios for various species

Species	Duration	Dose (mg/kg/day)	C_{max} (µg/mL)#	$AUC_{0-\infty}$ (µg.h/mL)#	ER (C_{max})*	ER (AUC)*
General toxicity (IV studies)						
Rat	2 wks	10, 20, 40	-	-	-	-
Rat	4 wks	10, 20, 40	5.54, 11.08, 25.85	1.86, 4.16, 9.66	1.2, 2.4, 5.6	0.2, 0.4, 0.8
Dog	2 wks	5, 10, 20&	-, 2.99, 5.82	-, 3.75, 10.6	-, 0.6, 1.3	-, 0.3, 0.9
Dog	4 wks	5, 10, 20&	2.46, 5.61, 10.3†	-, -, 11.45	0.5, 1.2, 2.3	-, -, 1.0
Reproductive toxicity (IV studies)						
Rat	GD 6-17	10, 20, 40	6.62, 13.9, 26.1 (GD 17)	2.96, 6.24, 15.3	1.4, 3.0, 5.7	0.3, 0.5, 1.3
Rabbit	GD 7-18	3, 10, 30	1.19, 3.37, 6.84 (GD 18)	1.39, 4.58, 7.49	0.3, 0.7, 1.5	0.1, 0.4, 0.6
Reproductive toxicity (PO studies, BID dosing)						
Rat	GD 6-17	100, 200, 400	0.67, 2.68, 12.17 (GD17)	1.79, 19.74^, 77.02^	0.1, 0.6, 2.6	0.2, 1.7, 6.6
Rabbit	GD 6-18	100, 200, 400	5.98, 10.29, 17.84 (GD18)	12.50, 30.25, 79.51	1.3, 2.2, 3.9	1.1, 2.6, 6.8

excluding the reproductive toxicity studies, values are means for the first (AUC0-∞) and last (AUC0-24 h or last) doses;

* exposure ratios (ER) relative to respective Cmax and AUC0-∞ human values of 4.6 µg/mL and 11.64 µg.h/mL (section 6.2.4),

& all doses given as 10 min infusions (2-3 min for rats, 5-8 min for rabbits) with the first sample times at 5 and 15 min (2 weeks) or 1-2 min post-infusion (4 weeks);

† mean of HD values from main and toxicokinetic groups;

^AUC0-tlast (but expected to be similar to 0-∞ values);

- = no data

Doses were generally limited by toxicity in these studies, expressed almost exclusively as clinical reactions including deaths (*General toxicity*). Although ER values based on plasma AUC were also low, adjustment for multiple dosing compared with the proposed single clinical treatment gave values for total cumulative exposures of >20 for rats and dogs in

the 4 week toxicity studies. There were no toxicokinetic data for the fertility and early embryonic development and pre/postnatal development studies in rats but these both used the same IV doses as the embryofetal development study in this species.

Exposure ratios for free drug would have been slightly higher (by about 30-55%) in rats, rabbits and dogs, based on a lower plasma protein binding in these species (respectively 35.5%, 24.9% and 38.6%) compared with humans (51.6%), as assessed *in vitro* at 5 µM (about 1.9 µg/mL).

Metabolism

Human data were more extensive than those in experimental animals. The latter were investigated in 2 *in vitro* studies (one of which used a goat preparation), a preliminary *in vivo* study involving rats but not dogs and standard assays for plasma 4-O-demethylated and 3-O-demethylated derivatives. *In vitro* experiments indicated that human Phase I vernakalant metabolism was mediated mainly by cytochrome P450 (CYP) 2D6 (with minor contribution by CYP3A4), with the formation of the 4-O- and to a slight extent 3-O-demethylated derivatives. CYP2D6 exhibits substantial polymorphism with the majority and minority of humans respectively being classified as extensive (EM) or poor (PM) metabolisers. Measurement of human plasma concentrations of these derivatives (plus the diastereoisomer RSD1231) and their glucuronide conjugates after IV [^{14}C]vernakalant administration showed the highest exposures to 4-O-demethylated vernakalant glucuronide (EM) or vernakalant and its glucuronide conjugate (PM). Two O-demethylated derivatives (one of which was more prominent) and their glucuronide conjugates were also present in rat plasma as the main metabolites, although this was determined only after PO administration in a preliminary metabolism study. Standard quantitative plasma measurements indicated low levels of the 4-O-demethylated derivative in rats and especially dogs but conjugates were not included in the assays. Minimal levels of the 3-O-demethylated derivative were also measurable in dogs. RSD1231 was present in human plasma with an exposure as measured by the area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) about 13% of that for the parent drug, but it was < limit of quantitation (mouse) or not detectable (rat) in the two studies in which it was measured. Because of its occurrence in humans (it is also a specified impurity), this compound was the subject of measurements of activity (*Primary pharmacodynamics*), as well as investigations of safety pharmacological activity and general toxicity and genotoxicity (*Impurities*).

Overall, proper inter-species comparison of metabolism was precluded by lack of data but the available information suggests similarities between humans and rats and dogs.

Toxicology

General toxicity

Repeat dose studies were of adequate duration considering the proposed single use in humans, although the intended 10 minute (min) infusion time was used only for dogs (versus 2-3 min injections for rats). Clinical signs in these studies notably involved the CNS (for example, uncoordinated gait, convulsions, tremors) but also included decreased activity and altered respiration (rats), deaths (rats) and aggressiveness (dogs) but little or no tissue toxicity. Similar prominent clinical signs (for example, ataxia, tremors, convulsions, splayed limbs, altered respiration) and deaths were also noted in rabbits, a species used for an embryofetal toxicity study (with a preliminary maximum tolerated dose study).

Some nervous system related reactions were seen in the clinical trials but these were of a different nature, for example, taste distortion, dizziness, headache and paraesthesia

(proposed Product Information). These adverse reactions were noted in the Risk Management Plan, together with the fact that adverse CNS effects occurred only with doses (40 mg/kg in rats, 20 mg/kg in dogs) respectively achieving ER values (based on C_{max}) of 6 and 2.5[6], which were considered to be 'good safety margins'. It is not clear why a higher C_{max} was obtained after a second infusion in a clinical trial with post-surgery patients, but use of this value (7.53 µg/mL) would substantially reduce these ER values. Additionally, adverse CNS reactions (and deaths) in the rabbit embryofetal toxicity study occurred with the high dose (HD) of 30 mg/kg/day which resulted in a relatively low C_{max} value (6.8 µg/mL).

As noted above (*Pharmacokinetics and relative drug exposures*), exposure ratios based on peak drug concentrations were not high, but the observed deaths and clinical reactions suggested that doses could not be appreciably increased, at least in rats. A high dose of 40 mg/kg was used in all (single dose, pilot, 2 week and 4 week) studies in this species, with 1/4 and 4/20 deaths being recorded in the pilot and 4 week studies respectively. A corresponding HD of 20 mg/kg was used in all dog studies (single dose, pilot, 2 week and 4 week), except a preliminary study in which a scheduled 30 mg/kg dose elicited severe clinical signs, although in this case the infusion was prematurely stopped and dogs would not have received the full dose. Some severe but transient reactions were seen with 20 mg/kg in the single dose study, although this dose was well tolerated in the two repeat dose studies. The lack of appreciable toxicity as assessed by clinical and tissue pathology at a high cumulative vernakalant exposure, in terms of plasma AUC over the dosing period (ER >20), suggests that the effects of vernakalant are probably restricted to cardiovascular and CNS activity.

Genotoxicity and carcinogenicity

Genotoxicity studies were adequate. There was a positive result for clastogenicity *in vitro* (Chinese hamster ovary cells). Significant increases in cells with aberrations were seen with and without S9 metabolic activation at the highest single concentrations that could be scored (0.386 mg/mL –S9, 3.86 mg/mL +S9). These concentrations were high relative to the expected clinical plasma C_{max} with the recommended dose and were associated with high but not excessive toxicity, as judged by viable cells/culture (63-80% reduction). The sponsor's *Nonclinical Overview* alluded to significant toxicity as the cause of these results and concluded that vernakalant did not show any genotoxicity in the assays. Vernakalant was not genotoxic in an *in vivo* mouse micronucleus assay and although the HD (50 mg/kg IV) was lethal, data from a pharmacokinetic study (20 mg/kg) suggested that drug exposure may not have been high. Dose extrapolation gave a C_{max} of 12.4 µg/mL (ER = 2.7) and an $AUC_{0-\infty}$ value of 4.8 µg.h/mL (ER = 1.0).

Although vernakalant is intended for single, rather than continuous use, it would have been prudent to have conducted another *in vitro* chromosomal aberration assay, preferably with a narrower concentration range, to confirm or refute the apparently positive results obtained. Carcinogenicity studies were not conducted and are not required for the proposed duration and exposure of vernakalant use.

Reproductive toxicity

A full range of adequate reproductive toxicity studies was conducted, with daily IV administration, plus PO embryofetal development studies in rats and rabbits, although placental transfer and excretion in milk were not investigated; placental transfer was assumed based on the findings discussed below. Twice daily oral dosing in embryofetal

[6] The sponsor's Nonclinical Overview used a human Cmax value of 4325 ng/mL for calculation of ER values.

development studies enabled the delivery of greater doses and thus exposure to vernakalant in both species than seen with IV dosing. There were no apparent effects on male or female fertility, or pre/postnatal development in rats at IV doses ≥40 mg/kg/day (extrapolated AUC based exposure ≥0.8-fold exposure at the recommended clinical dose). Increased postimplantation loss was seen with oral dosing of pregnant rats and rabbits, at respective AUC based exposures 10 and 3 times greater than exposure at the recommended clinical dose. Postimplantation loss occurred in rabbits at doses lower than those eliciting maternal toxicity.

Fetal variations and malformations were seen in rats and rabbits with dosing during organogenesis, particularly with greater exposure to vernakalant in the PO studies. Findings in PO studies in rats occurred at maternotoxic doses and included whole body oedema, cleft palate and micrognathia of the jaw and other skull bone abnormalities, small or absent thyroid, constricted trachea, increased renal pelvic cavitation, undescended testes and an increased incidence of dilated ureter. Several bones were also misshapen and/or bent and incomplete ossification was frequently observed. A marked incidence of most findings was seen at 200 mg/kg twice daily (bd) (exposure 7 times greater than exposure at the recommended clinical dose, based on AUC), with a low incidence of several findings at 100 mg/kg bd (exposure margin 1.7). In the IV studies, effects in rats were limited to a low incidence of umbilical omphalocoele at doses ≥ 20 mg/kg/day (exposure margin ≥1.5). Although the incidence was higher than that of historical control data, the near absence of this finding at higher exposures in PO studies (only one affected fetus at 100 mg/kg bd) suggests that this finding is unlikely to be of toxicological concern.

Malformations of the head (acrania, anophthalmia, misshapen tongue, dome-shaped head or meningocoele) were also seen at low incidence in rabbits at PO doses ≥200 mg/kg bd (AUC based exposure 7 times greater than exposure at the recommended clinical dose). Other findings included abnormal limb flexure, absent azygos lobe of the right lung and an increased incidence of common carotid artery arising from the innominate artery. These latter three findings occurred at an incidence within historical control ranges and were probably of minor toxicological significance. Effects on embryofetal survival and development occurred in rabbits at doses lower than those associated with maternal toxicity.

The clinical significance of these findings was uncertain in the context of the generally high exposure margins achieved with twice daily oral dosing in animals compared with the proposed single/intermittent use of vernakalant clinically. However, this risk assessment would need to be reconsidered, should the indicated patient population be expanded in the future to include more frequent and/or increased dosing with this product.

Local tolerance

Specific local tolerance studies were conducted only to determine blood compatibility with no adverse effects being observed. However, daily administration to dogs in the 2 week toxicity study used the intended 10 min IV infusion, and the HD of 20 mg/kg/day was without effect at the infusion site. This dose was delivered as a 10 mg/mL solution (2 mg/kg/min or 40 mg/m^2/min) compared with the intended 4 mg/mL solution in humans (0.3 mg/kg/min or 11.1 mg/m^2/min for a 70 kg person). Infusion site haemorrhages/subacute inflammation were however noted with all doses (5, 10, 20 mg/kg/day) in the corresponding 4 week study using a 4 mg/mL solution given over 10 min, although the relevance of this to the intended single use is questionable. Occasional local reactions (pain, paraesthesia) were sometimes seen in the clinical trials (proposed Product Information).

Impurities

RSD1231, a diastereoisomer of vernakalant, which is a specified impurity and also a minor human metabolite (*Pharmacokinetics and relative drug exposure*) was relatively extensively investigated. Besides assessment of pharmacological activity, studies included safety pharmacology, genotoxicity (with negative results) and a 4 week PO toxicity study in rats (with supporting toxicokinetic measurements) using doses of 25-150 mg/kg bd. In the latter study, mean (first and last dose) plasma 2x AUC from time zero to 10 hours ($AUC_{0\text{-}10\,h}$) values of 0.35-12.9 µg.h/mL (males) or 1.2-31.8 µg.h/mL (females) were achieved and a pronounced accumulation over the dosing period was observed. These exposures are comparable to or higher than those obtained in the corresponding study with the parent compound and there were few effects of treatment (increased food consumption, cholesterol and relative liver weights; minimal liver mononuclear cell infiltration).

Nonclinical summary and conclusions

In vitro experiments showed that vernakalant is a mixed sodium and potassium ion channel antagonist, but does not block calcium channels. It inhibited the sodium channel Nav1.5 (hH1) in a frequency dependent manner, with IC_{50} values at higher frequencies being below the expected clinical plasma C_{max}, which may confer atrial selectivity. Vernakalant inhibited the late sodium current at clinically relevant concentrations (IC_{50} = 14 µM) and inhibited several potassium channels *in vitro*, notably Kv1.5 (I_{Kur}), hERG (I_{Kr}) and Kir3.1/3.2 (I_{KACh}) channels, with IC_{50} values below the expected clinical plasma C_{max}. It also inhibited Kv4.2/Kv4.3 (I_{to}) and Kir6.1/6.2 (I_{KATP}) channels, but had little activity against I_{Ks} or I_{K1}. Inhibition of I_{Kur} and I_{KACh} may confer atrial selectivity while I_{Kr} inhibition may prolong QTc intervals. The 4-O- and 3-O-demethyl metabolites also showed ion channel blocking activities, while their glucuronide conjugates (where tested) were inactive.

Vernakalant prolonged atrial (and to a lesser extent ventricular) action potentials in rabbit cardiac muscle *in vitro*. It prolonged atrial (and to a lesser extent ventricular) effective refractory periods in dogs, pigs and cynomolgus monkeys, while QT interval prolongation in these species was relatively small. It also inhibited dofetilide induced early-after-depolarisations (EAD) *in vitro* and clofilium induced torsade de pointes in rabbits.

Vernakalant showed variable activity in different models of atrial fibrillation (AF) in dogs, pigs and goats. The models used suffered from some limitations, but good efficacy was shown against AF induced by vagal stimulation in anaesthetised dogs and in a model of persistent AF in goats. Plasma vernakalant concentration data were often limited.

Safety pharmacological studies with IV administration were generally adequate. Vernakalant elicited CNS activity, including convulsions and a transient increase in tidal volume, as well as cardiovascular changes. Although experimental conditions varied between studies, blood pressure, heart rate and contractility ($+dP/dt_{max}$) were normally reduced by vernakalant. Potential interactions with platelets were not investigated. An *in vitro* screening study showed selective vernakalant binding to sodium channel site 2 receptor (rat) and non-selective binding to sigma receptor (guinea pig).

Following single IV administration, plasma vernakalant clearance was relatively high in the experimental species examined, with associated short half-life ($t_{1/2}$) values (about 2-3 L/h/kg and 3 h in dogs). Excretion was not comprehensively investigated (there were no data for the dog) but recovery of radioactivity after IV administration of [^{14}C]-vernakalant to rats was primarily in the faeces (about 64% of the dose) compared with humans in which it was mainly urinary. Vernakalant was only partially plasma protein bound *in vitro*, with values varying from about 25% (rabbit) to 52% (human) in one study. Vernakalant was shown to be a substrate for p-glycoprotein in an *in vitro* assay.

In vitro studies with human preparations showed that vernakalant was metabolised mainly via CYP2D6 with the formation of 4-O-demethylated vernakalant and to a small extent the corresponding 3-O-demethylated derivative. Low levels of glucuronidation of the 4-O-demethyl derivative were also demonstrable. Proper inter-species comparison of *in vivo* metabolite exposures was precluded by a paucity of experimental animal data but the presence in plasma of both demethyl derivatives (dogs) or the 4-O-demethyl derivative (rats) was shown. Vernakalant inhibited CYP2D6 activity *in vitro* with a K_i value of 3 μM, and experiments indicated a potential for inhibition of vernakalant metabolism by the CYP2D6 substrates propafenone and fluoxetine.

Radioactivity was widely distributed after IV administration of [^{14}C]-vernakalant to rats, and there was evidence for biliary excretion and melanin binding. Placental transfer and excretion of parent drug or metabolites in milk were not investigated. Some pharmacokinetic data were also available following PO vernakalant administration, a route not proposed for the current application.

Repeat dose toxicity studies were conducted in rats and dogs, with respective doses of 10-40 and 5-20 mg/kg/day IV being used in studies of 2 and 4 weeks duration in both species, although administration was by 10 min infusion only in the dog. Little or no tissue toxicity was seen, although numerous clinical signs were elicited which were dose-limiting (for example uncoordinated gait, tremors, convulsions). High dose drug exposures based on C_{max} were about 6x (rats) or 2x (dogs) the expected human value, while those based on cumulative AUC over the 2-4 week study periods were >20 for both species.

Vernakalant showed a positive result in one *in vitro* genotoxicity assay (clastogenicity in Chinese hamster ovary cells) at high concentrations associated with substantial cellular toxicity. Negative results were obtained in other adequate tests (bacterial reverse mutation, forward mutation in mouse lymphoma cells, *in vivo* mouse micronucleus assay), but a repeat *in vitro* clastogenicity assay was not conducted. Carcinogenicity studies were not required for this acute indication.

There were no effects on male or female fertility or on pre/postnatal development in rats with repeated daily IV doses similar to maximum recommended clinical exposure levels. Possible excretion of vernakalant in milk was not investigated. Increased post-implantation loss was seen in rats and rabbits with twice daily oral dosing during organogenesis (exposure 10 and 3 fold maximum recommended clinical exposure); this occurred in rabbits at doses lower than maternotoxic doses.

Vernakalant administration during organogenesis resulted in fetal variations and malformations in rats and rabbits. Findings in rats occurred at maternotoxic doses (≥1.7 fold maximum recommended clinical exposure levels), and included whole-body oedema, cleft palate and micrognathia of the jaw, misshapen/bent bones, incomplete ossification, small or absent thyroid, constricted trachea, increased renal pelvic cavitation, undescended testes and dilated ureter. A low incidence of malformations of the head (acrania, anophthalmia, misshapen tongue, dome-shaped head or meningocoele) was seen in rabbits at doses lower than those eliciting maternal toxicity, but at high relative exposures (7 fold maximum clinical exposure). The clinical relevance of these findings is somewhat diminished by the generally high exposure margins achieved with twice daily oral dosing in animals compared with the proposed single/intermittent use of vernakalant in the clinic. However, the degree of concern would need to be reconsidered should the indicated patient population be expanded in the future to include more frequent and/or increased dosing with this product.

There were no nonclinical objections to the registration of vernakalant for the rapid conversion of recent onset atrial fibrillation to sinus rhythm.

IV. Clinical findings

Introduction

The clinical development program for vernakalant hydrochloride injection consisted of 12 clinical studies conducted at investigative sites in Argentina, Canada, Chile, Denmark, Hungary, India, Italy, Mexico, Netherlands, Poland, Slovakia, South Africa, Sweden and United States.

A total of 883 adult subjects received vernakalant injection (including 110 in Phase I and 773 in Phase II/ III studies) and 354 received placebo (including 19 in Phase I and 335 in Phase II/ III studies). There were 6 pharmacokinetic (PK)-pharmacodynamic (PD) studies with the proposed intravenous formulation of vernakalant**.** The pivotal Phase III studies are the Atrial Arrhythmia Conversion Trial (ACT) I [Study 1235-0703], ACT III [Study 04-7-010] and ACT II [Study 1235-0104]. There were 3 additional efficacy studies: CRAFT, (1235-1001), Scene 2 (1235-0703B) and an open label safety study (ACT-IV, 05-7-012).

All completed vernakalant injection trials were placebo controlled or open label. The current EU Guideline[7] supersedes the TGA-adopted EU guideline which was in place at the time of the Phase III program did not clearly assert that provision of active comparator data is mandatory for the approval of a new agent in AF.[8] Accordingly, the sponsor sought advice from the EU Scientific Advice Committee on the need for comparator data in 2007. Whilst the committee could not provide an assessment of the overall risk benefit of the product, it was confirmed that comparative data would be of use in order to establish the place of vernakalant injection in the current treatment options for AF. Accordingly, the sponsor initiated an active comparator study versus amiodarone (VERI-305-AMIO). Results of this Phase III active comparator study versus amiodarone (VERI-305-AMIO) were provided in this submission although the clinical summary and metanalyses do not include results of this study. Although there does not appear to be any specific scientific advice/protocol assistance given to the sponsor by the TGA, none was requested by the sponsors.

This marketing authorisation application is specific to vernakalant injection for the rapid conversion of AF to sinus rhythm. In a separate clinical program, an oral formulation of vernakalant is being evaluated for the prevention of recurrence of AF with completed enrolment in 8 PK-PD studies and 2 Phase II studies with plans for Phase III studies underway. A total of 694 subjects with AF have been exposed to oral vernakalant. Clinical study reports for completed studies with the oral vernakalant were provided in the submission and an application for orally administered vernakalant may be made at a future time. However, these studies do not relate to the current submission and have not been evaluated.

Vernakalant is also referred to as RSD1235 and this may appear on figures and tables in this AusPAR.

[7] EMEA, Committee for Medicinal Products for Human Use (CHMP), 24 July 2008. Note for Guidance on Antiarrhythmics. Addendum on Atrial Fibrillation (CHMP/EWP/ 352438/2008).

[8] pp. 297-306 0f Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC21, June 1996. Medicinal Products for the Treatment of Arrhythmias. http://www.tga.gov.au/pdf/euguide/vol3cc21aen.pdf

Pharmacokinetics

Introduction

Vernakalant injection is intended for intravenous use. Vernakalant hydrochloride concentrate for solution for infusion (also referred to as vernakalant concentrate) is a sterile, isotonic, buffered solution of vernakalant hydrochloride at a concentration of 20mg/mL. Prior to intravenous infusion, vernakalant concentrate is diluted with one of the following recommended diluents: 0.9% Sodium Chloride Injection, Lactated Ringers Injection, or 5% Dextrose Injection. The formulation used in the clinical trials is the formulation intended for commercial use and therefore no further bioequivalence studies were necessary. The pharmacokinetic evaluation for vernakalant injection includes data from 6 studies in healthy volunteers (with doses ranging from 0.1 to 5 mg/kg) and 6 studies in AF and/or atrial flutter (AFL) patients (doses ranging from 0.5 to 5 mg/kg total dose).

Absorption

Vernakalant is intended for intravenous infusion and hence no bioavailability or absorption studies were conducted.

Distribution

The objectives of the Phase I Study *04-0-195* were to define the pharmacokinetics and disposition of vernakalant and its metabolites, to obtain a mass balance estimate and to assess safety and tolerability after a single 240 mg IV and a single 240 mg oral dose of ^{14}C-labeled vernakalant in 8 healthy volunteers. The 240 mg dose was equivalent to 3.4 mg/kg for the minimum body weight requirement of 70 kg and 2.4 mg/kg for the maximum weight of 100 kg for this study. The mean terminal half-life of vernakalant (also called RSD1235) following the IV dose was 2.25 hours for extensive CYP2D6 metabolisers (n=5) and 8.20 hours for the poor CYP2D6 metabolisers (n=2).[9] The mean volume of distribution at steady state (V_{ss}) was 126.38 L for extensive metabolisers and 132.90 L for poor metabolisers. The apparent volume of distribution (V_{dz}) was 214.57 L for extensive metabolisers and 210.64 L for poor metabolisers. These results suggested that vernakalant was extensively distributed into tissue. The mean plasma clearance of vernakalant was higher for extensive metabolisers (65.66 L/h) compared to poor metabolisers (17.66 L/h). The mean renal clearance was 5.80 L/h for extensive metabolisers and 4.17 L/h for poor metabolisers.

Elimination (metabolism and excretion)

Metabolic profiling in Phase I Study *04-0-195* revealed that qualitatively, the metabolites after intravenous and oral dosing are similar. Two Phase I metabolites of vernakalant were detected, RSD1385 and RSD1390, both formed by O-demethylation. Vernakalant and these 2 metabolites each underwent Phase II metabolism primarily via glucuronidation. The primary plasma metabolite for extensive metabolisers was RSD1385G which formed rapidly and was measurable in all extensive metabolisers by the end of the 10 minute infusion. Direct glucuronidation of vernakalant is also relatively prominent, while sulphatation of the 4-O-demethylated metabolite, RSD1385, and/or the 3-demethylated metabolite, RSD1390, are minor metabolic pathways. In poor metabolisers of CYP2D6, the metabolism of vernakalant is slower and less extensive. Higher concentrations of

[9] CYP2D6 metaboliser status was based on a dextromethorphan to dextrophan (substrate to metabolite) ratio of 0.3 in the urine.

unchanged vernakalant are found in the systemic circulation and a higher proportion is also excreted unchanged in the urine. In these subjects, direct glucuronidation of vernakalant is an important route of elimination and RSD1235G is the primary metabolite for poor metabolisers.

Compared to poor metabolisers, the extensive metabolisers convert vernakalant to RSD1235G at a faster rate (T_{max}: 0.52 versus 1.67 hours [h]) but with a lower C_{max} (502 versus 886 ng/mL) compared to poor metabolisers. The T_{max} of RSD1385G for extensive metabolisers occurred slightly faster compared to poor metabolisers, (1.42 versus 2.17 h) with a much greater C_{max} (3737 versus 203 ng/mL). For RSD1390G, the T_{max} for extensive metabolisers occurred earlier (0.92 versus 2.17 h) and the C_{max} was lower (49.8 versus 128.8 ng/mL) compared to poor metabolisers.

Following the IV dose, urinary excretion of unchanged vernakalant averaged 8.49% for extensive metabolisers and 22.6% for poor metabolisers. Vernakalant was extensively and rapidly metabolised, as can be concluded from the low concentrations of unchanged drug in the plasma as early as 0.5 h and 1 h postdose, relative to the levels of its major metabolites. The high levels of vernakalant itself and of its metabolites in the urine within 2 hours of dosing shows that excretion is rapid.

The mean terminal elimination half-life for ^{14}C-vernakalant derived radioactivity was 4.59 h for extensive metabolisers and 9.46 h for poor metabolisers following the IV dose. Mean recovery of the radioactivity in urine was 92.9% for extensive metabolisers and 84.3% for poor metabolisers following the intravenous dose. Mean recovery of the radioactivity in faeces was 7.28% for extensive metabolisers and 5.64% for poor metabolisers following the intravenous dose. Measurable levels of radioactivity in the plasma, urine, and faeces could not be detected at 168 h.

Dose-proportionality and time dependency

In the Phase I, placebo-controlled, dose-ascending study 1235-1-04-12-01 involving 29 healthy volunteers**,** vernakalant showed linear pharmacokinetics within the 0.10 mg/kg to 5.0 mg/kg dosing range following a 10 minute IV infusion. Dose normalized $AUC_{(0\text{-}inf)}$ values were similar between all dose levels, although it appeared to be higher for the 4 mg/kg dose compared to the other doses**.** However, one subject who was later determined to be a phenotypical CYP2D6 poor metaboliser in the 4 mg/kg group may have been responsible for the AUC to be higher at this dose level. Mean peak concentrations (C_{max}) increased proportionally with increased dose level. The vernakalant elimination half-life was approximately 2 h. The volume of distribution was about 2 L/kg, indicating extensive deep tissue and/or peripheral tissue binding. Total body clearance of vernakalant ranged from 649 to 938 mL/min, and renal clearance (CLr) ranged from 37 mL/min to 170 mL/min. The percent of vernakalant dose excreted unchanged in urine was approximately 11.6%, with individual values ranging from 5.4% to 25.8%.

The Phase I Study *6517-CL-0011* evaluated the pharmacokinetics and dose proportionality of 1.25, 2.5 and 5.0 mg/kg intravenous (IV) vernakalant in 14 healthy volunteers. With each increase in vernakalant dose, an associated increase was observed in total vernakalant exposure as estimated by the area under the plasma concentration time curve from time zero to the last measurable time point (AUC_{last})(approximate 2 fold increase with 2 fold increase in dose). Mean time to maximum plasma vernakalant concentration was approximately 9-10 minutes over the 1.25, 2.5, and 5.0 mg/kg dose levels and mean elimination half-lives ranged from 1.7 to 1.9 h. The mean volume of distribution, clearance values and terminal rate constant values were similar at each vernakalant dose level. Dose normalized AUC_{last}, and AUC_{inf} for plasma vernakalant concentrations suggest that increases in C_{max}, AUC_{last}, and AUC_{inf} were dose proportional; however, dose proportionality for C_{max} could not be concluded statistically since the 95% confidence

intervals (CI) for the slope of C_{max} did not contain the value 1. Lack of dose proportionality for C_{max} using the power model probably results from variations in sample collection at the end of infusion coupled with rapid distribution into a large volume of distribution (122 L – 145 L; approximately 3 times the total body water volume of a 70 kg human). RSD1385 was the major quantifiable metabolite in plasma; concentrations of RSD1385 were much lower than parent drug. Increases in RSD1385 C_{max} and AUC_{inf} were not tested using the power model but appeared to be dose-proportional. Metabolite RSD1231 was measurable in only 2 subjects as was metabolite RSD1390. Mean time to maximum plasma RSD1385 concentration was 1 h following the 1.25 mg/kg dose, 40 minutes (min) following vernakalant 2.5 mg/kg, and 65 min following the 5.0 mg/kg dose. The mean RSD1385 elimination half-life was approximately 4 h, 3 h and 2.5 h for the 1.25, 2.5, and 5.0 mg/kg doses, respectively. With each increase in vernakalant dose, an associated increase was observed in total RSD1385 exposure as estimated by mean $AUC_{last.}$

Intra- and inter-individual variability

After IV treatment the inter-individual variability was limited; after oral treatment the inter-individual variability was somewhat larger than after IV treatment.

Pharmacokinetics in target population

Following stepwise doses of vernakalant injection in 35 patients with recent onset AF in the CRAFT study**,** C_{max} and $AUC_{0\text{-}inf}$ increased with increasing dose and elimination half-life (t½) was similar for each dosing group. Mean peak vernakalant plasma levels were 5.43 µg/mL (range: 4.0 to 8.6 µg/mL) in the 2.0/3.0 mg/kg vernakalant group and 3.00 µg/mL (range: 0.1 to 23.5 µg/mL) in the 0.5/1.0 mg/kg vernakalant group. Mean peak plasma vernakalant concentrations were 1870.94 ng/mL (range: 596.34 to 3428.09 ng/mL) in the 0.5/1.0 mg/kg group and 5503.49 ng/mL (range: 2816.66 to 8551.86 ng/mL) in the 2.0/3.0 mg/kg group. Mean vernakalant $AUC_{0\text{-}inf}$ values were 5369 ng.h/mL (range: 1718 to 15803 ng. h/mL) in the 0.5/1.0 mg/kg group and 9686 ng. h/mL (range: 5808 to 16597 ng.h/mL) in the 2.0/3.0 mg/kg group. Mean t½ values were 3.88 h (0.5/1.0 mg/kg group) and 2.71 h (2.0/3.0 mg/kg group). CYP2D6 genotypes were determined for 25 of 35 patients in the PK analysis group; t½ was approximately 2.7 h and 8.5 h in the extensive and poor metabolisers, respectively and exposure to vernakalant ($C_{max}$and AUC) were much higher in the poor metabolisers.

In the pivotal Study *ACT-I,* mean plasma vernakalant concentration peaked at the end of the 10 min infusion for subjects who received a single infusion of vernakalant and at the end of the second 10 min infusion for subjects who received both vernakalant infusions. Vernakalant plasma concentrations decreased sharply following the end of infusion. At 24 h following the start of the first vernakalant infusion, mean plasma concentration had decreased to close to the lowest level of quantification (LLOQ) of 5 ng/mL in both dose groups. Vernakalant exposure was dose proportional based on the areua under the plasma concentration time curve from time zero to 90 min ($AUC_{0\text{-}90min}$) between subjects who received one infusion and subjects who received two infusions; median C_{max} was similar in the two dose groups. Median C_{max} and $AUC_{0\text{-}90min}$ were generally similar between subjects who converted to sinus rhythm and nonconverters. RSD1385 was the major quantifiable metabolite in plasma and peaked at 35-50 min (average C_{max} = 31 ng/mL after one dose and 45 ng/mL after 2 doses). RSD1390 in plasma was generally not quantifiable. Approximately 9% of vernakalant was excreted unchanged in urine over the first 24 h.

In Study *1235-0703B (Scene 2)* involving 53 adult patients with atrial flutter, $C_{max\ of}$ plasma vernakalant was 3113 ng/mL after one infusion (3 mg/kg), and 4847 ng/mL after two infusions (3+2 mg/kg). $AUC_{0\text{-}90min}$ was dose proportional between subjects who had received one infusion and those who received both infusions within this study. RSD1385 was the major plasma metabolite and peaked at 90 min after infusion; whereas RSD1390

was not quantifiable in plasma. Plasma RSD1385 concentrations were about 1% of those of the parent drug. Urinary excretion of unchanged drug was about 7% to 10% over the first 24 h period following dosing.

In pivotal study *ACT-II* involving 161 subjects with atrial fibrillation or atrial flutter following valvular and/or coronary artery bypass graft surgery, mean and median $AUC_{0\text{-}90min}$ of vernakalant appeared to be relatively dose proportional between subjects who received one infusion (3 mg/kg) and subjects who received two infusions of vernakalant (3+2 mg/kg). RSD1385 was the major quantifiable unconjugated metabolite in plasma. Maximum concentrations of RSD1385 were observed between 35 and 90 min. C_{max} and $AUC_{0\text{-}90min}$ values of RSD1385 were similar for subjects who received either one or two infusions. The metabolite RSD1390 in plasma was generally not quantifiable**.**

In study *ACT-IV***,** involving 89 patients with AF**,** mean plasma vernakalant concentrations at 25 min postdose were 1766 ± 638 ng/mL and 2289 ± 1474 ng/mL in patients who received one or two doses, respectively. Elimination half-lives were similar for those who received 3 mg/kg or 3+2 mg/kg. RSD1385 was the major metabolite, which was rapidly formed with higher concentrations observed for the group that received the second infusion. RSD1231 appears to be a slowly formed minor metabolite and its highest plasma concentration was observed at 6 h in both dose groups. RSD1390 appears to be a rapidly formed minor metabolite, but plasma RSD1390 was generally not quantifiable. The elimination half-life of vernakalant for the poor metabolisers was longer than that of the extensive metabolisers and ultra-rapid metabolisers.

Special populations

Effect of intrinsic factors

Effect of renal impairment

The Phase I, open label study *VERO-106-REN* evaluated pharmacokinetics and safety of vernakalant injection and vernakalant (oral) in 24 subjects with mild, moderate and severe renal impairment compared to subjects with normal renal function. After IV dosing (with 2 mg/kg 10 min infusion), there were no clear differences in geometric mean values and ranges for vernakalant C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$ between the groups of subjects with mild, moderate or severe renal impairment and normal renal function group. The mean vernakalant urinary excretion to 48 hours ($A^e_{0\text{-}48}$) and CL_R were lower in all renal impairment groups compared to the normal renal function group, with the lowest values in the moderate and severe renal impairment groups. RSD1385 remained at low exposure levels and there were no significant differences in RSD1385 C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, between the groups with different renal functional status. RSD1390 and RSD1231 were detected in a very limited number of plasma and urine samples and the data were too limited to detect any differences between the different renal function groups. After oral dosing, for the subjects with moderate and severe renal impairment geometric mean values for vernakalant C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ were approximately 2 fold higher than for the subjects with normal renal function with no clear change in $t_{1/2}$. The mean values for $A^e_{0\text{-}48}$ and CL_R were lower for all renal impairment groups compared to the normal renal function group and the lowest values for CL_R were observed in the moderate and severe renal impairment groups.

Evaluator's comments

The statistical analysis yielded relatively wide 90% CI for most comparisons, which fell outside the commonly used 0.8-1.25 (AUC) and 0.7-1.43 (C_{max}) no effect boundaries in all cases. In the majority of cases, the 90% CI included the value "1", indicating that in this exploratory study a statistically significant difference could not be determined. Since the distribution of male/female subjects and intermediate CYP2D6 metaboliser (IM)/ extensive CYP2D6 metaboliser (EM) subjects was not the same for the different renal

function groups at baseline, possible influence of gender and genotype on the outcome of the study should also be taken into account. Statistical analysis showed no effect of gender on vernakalant C_{max} and AUC. Following IV treatment, no or a small effect of CYP2D6 metaboliser status on the PK parameters was observed; however a larger effect of genotype was observed following oral vernakalant (which is not the subject of this application), with on average 2 fold higher vernakalant C_{max} and 3 fold higher vernakalant $AUC_{0\text{-}inf}$ in IM subjects. The dose of IV vernakalant evaluated in this study (2 mg/kg) was not the proposed dose for this submission.

Effect of hepatic impairment

The Phase I, open label study *VERO-107-HEP* evaluated pharmacokinetics and safety of vernakalant injection and vernakalant (oral) in 24 subjects with mild, moderate and severe hepatic impairment compared to subjects with normal hepatic function.

Following treatment with 2 mg/kg vernakalant (IV) as a 10 min infusion, the peak vernakalant plasma concentrations observed at the end of infusion declined rapidly within the first hour after dosing. Thereafter the plasma concentrations declined more slowly. On average, the elimination rate appeared to be somewhat slower for the group of patients with severe hepatic impairment than for the other groups. By 24 h after dosing, in the majority of the healthy subjects and patients with mild or moderate hepatic impairment vernakalant plasma concentrations were below LLOQ. At 36 h after dosing, 2 out of 6 patients with severe hepatic impairment showed no detectable levels, while in the other 4patients very low vernakalant concentrations could still be measured (ranging from 6.82 to 18.6 ng/mL). Geometric mean values for vernakalant $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{½}$ and $A_{e\ 0\text{-}48}$ were higher in the severe hepatic impairment group compared to the healthy control group. There was no clear difference in C_{max}. The non renal clearance (CL_{NR}) was lower. Compared to the healthy subjects, vernakalant C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ all tended to be slightly lower in subjects with mild and moderate hepatic impairment. Following oral vernakalant, there was a distinct increase in exposure to drug in subjects with severe hepatic impairment; C_{max} was 2.36 fold (90% CI 1.51-3.68) higher, $AUC_{0\text{-}last}$ 3.59 fold (90% CI 2.24-5.76) higher and $AUC_{0\text{-}inf}$ 3.53 fold (90% CI 2.26-5.50) higher. The effect of gender and CYP2D6 genotype on IV vernakalant was not evaluated in this study (only the effect on oral vernakalant was evaluated). For most subjects, the main metabolite RSD1385 appeared in plasma within 10 to 20 min after start of the infusion. Geometric mean plasma concentrations of RSD1385 were much lower than of the parent compound, with the highest mean peak plasma concentration observed for the moderate hepatic impairment group (less than 2% of the mean peak plasma concentration of vernakalant for this group). RSD1385 remained detectable for the longest period of time in plasma of the patients with severe hepatic impairment (up to 12 to 24 h postdose). RSD1231 was detected in limited number of samples after IV vernakalant, while RSD1390 could not be detected in any of the plasma samples after either IV or oral treatments.

Evaluator's comments

Due to the wide 90% CI, the absence of an effect of mild and moderate hepatic impairment on vernakalant PK could not be concluded formally in this study. The dose of IV vernakalant evaluated in this study (2 mg/kg) was not the proposed dose for this submission.

Effect of age, gender and race

Study ACT-III population PK model data set included 362 vernakalant plasma concentration measurements from 128 subjects. Of these subjects, 39 received one infusion of vernakalant injection, whereas 89 received two infusions. Eighty four percent of plasma samples were drawn within one h of the start of either infusion; 4% were collected after 6 h from the start of either infusion. The PK model that best described the data was a two compartment model with first order elimination from the central

compartment. Typical clearance of vernakalant for the patient population was estimated to be 31.2 L/h. The typical volume of the central compartment in males was estimated to be 46.2 L and that in females was approximately half that value (23.9 L). The lower volume of the central compartment in females may reflect lower body weights of females (median 75 kg) compared with males (median 89 kg) in the study population. However, the acute exposure (C_{max} and $AUC_{0\text{-}90min}$) and half-life were similar in males and females.

In the ACT-III population PK analysis, age, renal function, history of congestive heart failure and concomitant medications that were CYP2D6 inhibitors or beta blockers did not significantly influence the PK of vernakalant in this study population. In addition, no difference was seen with race, although this must be interpreted cautiously because of the small number of non-Whites in the study.

In the population PK analysis from five Phase II/ III studies, age and creatinine concentrations were identified as significant covariates for vernakalant central clearance. Elderly patients or patients with high serum creatinine would be expected to have higher maximum vernakalant plasma concentration than young patients. Body weight was not found to influence vernakalant pharmacokinetics, probably because vernakalant was administrated in accordance with body weight.

Effect of CYP2D6 genotype

In the population PK analysis with data from five Phase II/ III studies, a total of 16 subjects (9 in ACT I, 5 in ACT IV, and 2 in study 04-0-195) were classified as poor CYP2D6 metabolisers (PMs). The peak plasma concentration and the volume of distribution values of parent (active) drug were similar in both PMs and EMs. The exposure of the drug increased in PMs compared to EMs. The vernakalant clearance was found to be 50% lower for PMs (0.41 L/h/kg versus 0.20 L/h/kg or 32.7 L/h versus 16.4 L/h for 80 kg patient) compared to EMs increasing the terminal half-life from 3 h to 5.5 h for CYP2D6 PMs. As a result of reduced clearance, C_{max} values would be approximately 8.1% higher in PMs relative to EMs after a 10 min infusion at a dose of 3 mg/kg followed by a 15 min observation and a second 10 min infusion at a dose of 2 mg/kg.

Effect of extrinsic factors

No formal studies evaluating the effect of extrinsic factors (example, concomitant medications) on the PKs of vernakalant injection were performed. A Population PK approach was taken for the analysis of extrinsic factors on the PKs of vernakalant injection [VERI-Pop-PK]. The pharmacokinetics of vernakalant injection in plasma were evaluated in 597 patients with atrial fibrillation or flutter from five studies; data from 8 healthy volunteers in the 04-0-195 who had full PK profiles were also included in the analysis. A two compartment pharmacokinetic model with first order elimination adequately described the time-course of the observed vernakalant concentrations in plasma following 3+2 mg/kg 10 min IV infusions separated by 15 min.

CYP2D6 inhibitors, beta blockers and the four most commonly used concomitant medications (warfarin, metoprolol, furosemide and digoxin) were not found to influence vernakalant pharmacokinetics. Race did not appear to influence the clearance of vernakalant in this study population, although it should be noted that 96% of study participants were White.

Interactions

No formal clinical drug interaction studies with vernakalant injection were conducted.

The effects of CYP2D6 inhibitor medications on the PKs of vernakalant injection were evaluated in two ways: 1) a combined PK analysis of ACT I and Scene 2 data and 2) a population pharmacokinetic analysis that used data from the following studies: ACT I, ACT II, ACT III, ACT IV and Scene 2.

In the pooled ACT I and Scene 2 PK analysis, patients who received CYP2D6 inhibitors compared to patients who did not receive CYP2D6 inhibitors had percent ratios of 105.5% and 102.8% for the $AUC_{0\text{-}90min}$ and C_{max} (geometric mean values), respectively.[10] This suggested that concomitant CYP2D6 inhibitors did not significantly influence plasma levels in this patient population [ACT 1-Scene2].

In the population PK analysis across studies [VERI-Pop-PK], the ratio of acute exposure was very close to unity by concomitant use or non use of CYP2D6 inhibitors for subjects receiving 1 or 2 infusions of vernakalant. These minimal effects on exposure did not result in increased adverse events in subjects receiving CYP2D6 inhibitors. When only patients on potent CYP2D6 inhibitors (paroxetine, fluoxetine and bupropion) were considered in this analysis (n=11; 3 with one infusion and 8 with two vernakalant infusions), the ratio for AUC was 0.95 (95% CI, 0.74 to 1.22) and for C_{max} was 0.93 (95% CI, 0.71 to 1.22). In the population PK analysis, beta-blockers, and the four most commonly used concomitant medications (warfarin, metoprolol, furosemide and digoxin) were not significant covariates of acute exposure ($AUC_{0\text{-}90min}$ and C_{max}) of vernakalant.

Vernakalant is not highly bound to human serum proteins and *in vitro* evidence suggests a lack of competition/interaction with warfarin, propranolol, acebutolol, diltiazem, verapamil or quinidine for binding sites. Vernakalant injection has been administered with concomitant medications known to inhibit CYP2D6 in several patients to date, with no safety implications related to drug-drug interactions noted. Furthermore, clinical data demonstrate that vernakalant injection has been safely administered to subjects receiving concomitant warfarin.

Drug interactions studies have been conducted as part of the vernakalant oral development program; a study with the CYP2D6 substrate metoprolol, and a study with the CYP2D6 inhibitor, paroxetine. 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 C_{max} and $AUC_{0\text{-}90min}$ following acute IV administration. While the terminal elimination phase may be slowed by CYP2D6 inhibitors, rapid and extensive distribution is the main determinant of C_{max} with IV dosing.

Exposure relevant for safety evaluation

In the Phase I, dose proportionality study 6517-CL-0011**,** the QT interval corrected by the Fridericia formula (QTcF) increased with increased vernakalant plasma concentration. Vernakalant at all three doses elicited increases in the mean PR and QT intervals in a dose dependent manner. All doses of vernakalant elicited an increase in QRS with the highest increase observed with 5 mg/kg. The risk of hypotension appeared to increase after the second dose of vernakalant as suggested by the increased risk of hypotension detected at vernakalant plasma levels of 4,000 ng/ml (VERI-POP-PK-PD).

Evaluator's overall conclusions on pharmacokinetics

ADME profile

Vernakalant is intended for intravenous infusion. It is extensively and rapidly distributed in the body with a volume of distribution of approximately 2 L/kg. The free fraction of vernakalant in human serum is 53-63% at a concentration range of 1-5 µg/ml. In patients,

[10] CYP2D6 inhibitors: amiodarone, amiodarone hydrochloride, benadryl, buproprion, celecoxib, chlorpromazine, chlorpheniramine, cimetidine, citalopram, citalopram, clomipramine, cocaine, diphenhydramine, doxepin, doxorubicin, duloxetine, escitalopram, fluoxetine, halofantrine, haloperidol, hydroxyzine, levomepromazine, metoclopramide, methadone, mibefradil, moclobemide, Nytol, paroxetine, quinidine, ranitidine, sertraline, terbinafine.

average peak plasma concentrations of vernakalant were 3.9 µg/ml following single 10 min infusion of 3 mg/kg and 4.3 µg/ml following a second infusion of 2 mg/kg (with a 15 min interval between doses). The C_{max} and AUC were dose proportional between 0.5 and 5 mg/kg. Vernakalant is extensively and rapidly metabolised, as can be concluded from the low concentrations of unchanged drug in the plasma as early as 0.5 h and 1 h postdose, relative to the levels of its major metabolites. In CYP2D6 EMs, vernakalant was mainly metabolised by CYP2D6 mediated O-demethylation at the 4-position followed by glucoronidation of the resulting O-demethylated metabolite (RSD1385G). In CYP2D6 PMs, direct glucoronidation of vernakalant is a more important metabolism pathway. Major metabolites circulating in human plasma were RSD1385G in EMs or the glucuronic acid conjugate of vernakalant itself (RSD1231) in PMs, neither of which was pharmacologically active. The high levels of vernakalant itself and of its metabolites in urine within 2 h after dosing showed that excretion was rapid. The mean elimination half life of vernakalant was approximately 3 h and 5.5 h in CYP2D6 extensive and poor metabolisers, respectively.

PKs in target patient population

The vernakalant PKs in the target patient population were similar to that in healthy subjects with a dose proportional increase in ($AUC_{0\text{-}90min}$) in patients who received both the 3 mg/kg and 2 mg/kg infusions compared to those who received only a single infusion of 3 mg/kg.

Effect of CYP2D6 genotype

Population PK analysis suggested that CYP2D6 metaboliser status influences vernakalant clearance. However, acute exposure ($AUC_{0\text{-}90min}$) of vernakalant was only 15.5% higher and C_{max} was only 8.1% higher in CYP2D6 PMs than in EMs after the proposed clinical dose. The most apparent difference between extensive and poor metabolisers was that extensive metabolisers had higher mean concentrations of RSD1385G, lower vernakalant and RSD1231 $AUC_{0\text{-}inf}$, a shorter vernakalant half-life and lacked any measurable levels of RSD1231 and RSD1231G in plasma and urine. Overall, no dosing adjustments may be necessary for CYP2D6 genotype for the proposed acute IV infusion of vernakalant.

Effect of age, sex, race, renal/ hepatic impairment

Age, sex, race did not have a significant effect on vernakalant pharmacokinetics following acute IV infusion. Although the mean CL_R of vernakalant was decreased in all renal impairment groups, the C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ of vernakalant and its main metabolite RSD1385 for the subjects with mild, moderate and severe renal impairment were similar to those for the subjects with normal renal function. Similarly, elimination rate appeared to be somewhat slower in patients with severe hepatic impairment compared to the other groups (mild/ moderate hepatic impairment or normal hepatic function) but vernakalant exposure (C_{max} and AUC) was similar in all groups. However, due to wide 90% confidence intervals in both the renal/hepatic impairment studies, there was no conclusive evidence for lack of effect of renal/hepatic impairment on vernakalant pharmacokinetics. It is important to note that both the studies in subjects with renal/hepatic impairment only used a dose of 2 mg/kg and the proposed dose of 3+2 mg/kg was not evaluated. Furthermore, patients with severe renal/hepatic impairment were excluded from the Phase III studies and hence due precautions should be taken before administration of IV vernakalant in these patients.

Drug interactions

In the population PK analysis, beta-blockers, and the four most commonly used concomitant medications (warfarin, metoprolol, furosemide and digoxin) were not significant covariates of acute exposure ($AUC_{0\text{-}90min}$ and C_{max}) of vernakalant. Vernakalant is not highly bound to human serum proteins and *in vitro* evidence suggests a lack of competition/interaction with warfarin, propranolol, acebutolol, diltiazem, verapamil or

quinidine for binding sites. Vernakalant injection has been administered with concomitant medications known to inhibit CYP2D6 in several patients to date, with no safety implications related to drug-drug interactions noted. Furthermore, clinical data demonstrate that vernakalant injection has been safely administered to subjects receiving concomitant warfarin.

Pharmacodynamics

Introduction

Vernakalant has demonstrated relative selectivity on atrial electrical activity in preclinical studies and in animal models of AF. Mechanistic studies have indicated that vernakalant prolonged atrial refractoriness and slowed atrial conduction in a rate dependent manner. There is only one PD study evaluating effects of vernakalant on electrophysiological parameters.

Mechanism of action

Vernakalant acts on the heart by blocking early activating potassium channels that predominantly affect atrial repolarisation. The concentration, voltage and frequency dependent blockade of sodium channels by vernakalant (during atrial fibrillation) allows selective action on the rapidly activating and partially depolarised atrial tissue rather than toward the normally polarised ventricle beating at lower heart rates. Furthermore, the ability to block the late component of sodium current suggests that vernakalant may have lower risk of ventricular proarrhythmia. The net result is prolonged atrial refractoriness and rate dependent slowing of atrial conduction [Fedida 2005].[11] Vernakalant does not substantially inhibit (at < 100 uM) I_{Ks}, I_{K1} or the L type calcium current (I_{CaL}). *In vivo* effects of vernakalant include significant prolongation of atrial refractoriness and rate dependent slowing of atrial impulse conduction, with only minimal effects on ventricular electrophysiological parameters.

Primary pharmacology

1235-SMHI was a Phase IIb, open label, single centre study in 19 subjects undergoing electrophysiology testing for suspected or documented ventricular or supraventricular arrhythmias or radiofrequency ablation for supraventricular arrhythmias. The primary objective of this study was to assess the effect of vernakalant on the atrial effective refractory period (AERP). The secondary objectives were to assess the effect of vernakalant on: PA interval, AH interval, HV interval, PR interval, QRS duration, QT interval, QT interval corrected by Bazett's formula for heart rate (QTcB), sinus node recovery time (SNRT), time to 90% repolarisation of the atrial monophasic action potential (AMAP90), restitution of atrial action potential duration (APD), stimulus artifact to local depolarization (S1-A and S1-V) intervals, Wenckebach cycle length, atrial and ventricular repolarisation times (ART and VRT, respectively), ventricular effective refractory period (VERP), ratio of AERP change to VERP change, as well as heart rate, blood pressure, and oxygen saturation. Each subject served as their own control as all protocol specified endpoint measurements were conducted at baseline and during drug infusion and drug effect was measured as the difference.

The loading infusion of Dose Level 1 (2 mg/kg) was selected based on the observed effective dose in 50% of the population (ED_{50}) for AF conversion in subjects with recent

[11] Fedida D, Orth PMR, Chen JYC *et al.* The mechanism of atrial antiarrhythmic action of RSD1235. J Cardiovasc Electrophysiol 2005; 16: 1-12.

onset AF [Study Report 1235-1001]. Dose Level 1 loading and maintenance doses were estimated to achieve vernakalant blood concentrations in the range of 1-3 μμg/mL during the electrophysiology measurements. The loading infusion of Dose Level 2 (4 mg/kg) was selected as a dose that was demonstrated to be well tolerated in normal healthy volunteers with only transient, mild adverse events reported [Study Report 1235-1-04-12-01]. Dose Level 2 loading and maintenance doses were estimated to achieve vernakalant blood concentrations in the range of 2-5μg/mL during the electrophysiology measurements.

All the 19 subjects who were enrolled completed the study. Two of the 19 subjects met the protocol defined dose-stopping criteria and for these subjects drug infusion was terminated early.[12] The mean change in AERP increased significantly ($p<0.05$) from baseline at all atrial pacing cycle length (PCLs) during infusion of vernakalant 4 mg/kg (Dose Level 2). At Dose Level 1 (2 mg/kg), an increase in the mean change in AERP above baseline was observed during atrial pacing at 600 milliseconds (ms) cycle length (CL). The effect on mean AERP at each atrial PCL tended to be greater for Dose Level 2 than for Dose Level 1, although no statistical test was applied to this difference. PR interval values increased significantly from baseline during atrial pacing at 600 ms in the Dose Level 2 group. There was no significant increase in QT interval from baseline during atrial pacing. There was no significant increase in mean QRS duration from baseline during atrial or ventricular pacing, although values tended to increase in the Dosing Level 2 group. Although there was no difference in the mean change in PA interval, AH interval, and HV interval from baseline during atrial pacing, there was a trend to prolongation in all these parameters and the increase in PR interval may be due to small decreases in intra atrial, AV nodal and His Purkinje conduction. The increases in the mean SNRT and Wenckebach CL from baseline measurements reached significance in the Dosing Level 2 group during atrial pacing at 400 ms. There was no significant difference in the mean change in time to 50% repolarisation of the atrial monophasic action potential (AMAP50), the diastolic interval (DI) and S1-A from baseline during atrial pacing, although little data was available at the higher pacing rates and for subjects in the Dosing Level 2 group.

Overall, results from this study showed that vernakalant prolonged AERP in a dose dependent manner. It exhibited a small conduction slowing effect in the atrium and AV node at the higher dose level. Vernakalant (2 and 4 mg/kg) had no significant effects on ventricular refractoriness, or repolarisation and tended to slow conduction in ventricular tissue at the higher dose level. The dosing regimen successfully maintained median vernakalant plasma levels during electrophysiological testing at concentrations that approached those demonstrated to convert AF to sinus rhythm in patients. However, the proposed maximum dose of 5 mg/kg (3+2 mg/kg) was not evaluated in this study.

Secondary pharmacology

Invasive haemodynamic testing was not done for vernakalant.

In the Phase III studies, the effects of vernakalant on QT interval were mild and predictable; vernakalant treated patients showed 22 ms and 18 ms increases over placebo after the first and second infusions, respectively and the difference from placebo was reduced to 8 ms by 90 min after start of the infusion.

[12] Dose-stopping criteria included the occurrence of any of the following events: Torsade de pointes; Allergic reaction; Uncorrected QT of 0.550 sec or QT prolongation >25% of baseline; HR <40 bpm; Systolic BP <90 mmHg systolic or decrease in systolic BP >25% of baseline; QRS prolongation of >50% from control (baseline); Any polymorphic VT; Intolerable side effects as determined by the Investigator or any changes in cardiac rhythm or AV conduction that, in the Investigator's opinion, was a threat to subject safety.

Relationship between plasma concentration and effect

In study 1235-SMHI, the median plasma concentration of vernakalant in subjects receiving Dose Level 1 (2 mg/kg) was 1675 ng/mL at the end of the loading infusion (T=10 min) and 1090 ng/mL at T=45 min. In the Dose Level 2 (4 mg/kg) group, the median plasma level was 3110 ng/mL at T=10 min and 2190 ng/mL at T=45 min. At discharge, median plasma levels had fallen to 12.1 ng/mL and 18.3 ng/mL in subjects having received Dose Level 1 and Dose Level 2, respectively. For those electrophysiology parameters that reached statistical significance, there did not appear to be a consistent correlation to plasma levels of vernakalant. While there were several significant correlations, they lacked dose relatedness. This apparent lack of a significant pharmacokinetic/pharmacodynamic relationship may be a result of the limited sample size and variability between subjects. Furthermore, the proposed maximum dose of 5 mg/kg was not evaluated in this study.

Genetic differences in pharmacodynamic response

A population PK analysis suggested that CYP2D6 metaboliser status affects vernakalant clearance. However, acute exposure ($AUC_{0\text{-}90min}$) of vernakalant was only 15% higher and C_{max} was only 8% higher in PMs than in EMs after the recommended dose. The effects of CYP2D6 status on the primary and secondary pharmacodynamic effects of vernakalant were not specifically evaluated but it appears that dose adjustment may not be necessary for IV vernakalant.

Evaluator's overall conclusions on pharmacodynamics

Preclinical studies suggested vernakalant blocks currents in all phases of the atrial action potential, including potassium currents that are expressed specifically in the atria (the ultra rapid delayed rectifier and the acetylcholine dependent potassium currents). Furthermore, the ability to block the frequency and voltage dependent sodium channels and also the late component of the sodium channel limits risk of ventricular proarrhythmia.

Invasive electrophysiological testing of vernakalant in the Phase IIb open label study 1235-SMHI showed that vernakalant prolonged AERP in a dose dependent manner. It exhibited a small conduction slowing effect in the atrium and AV node at the higher dose level (4 mg/kg). Vernakalant at the doses studied (2 and 4 mg/kg), had no significant effects on ventricular refractoriness, or repolarisation and it tended to slow conduction in ventricular tissue at the higher dose level. However, the proposed maximum dose of 5 mg/kg was not evaluated in this study.

Invasive haemodynamic testing was not done for vernakalant.

Efficacy

Introduction

The efficacy of vernakalant injection was evaluated in three controlled clinical studies that specifically tested the activity of vernakalant to rapidly convert AF to sinus rhythm. Another Phase III active controlled (IV amiodarone) study *(AVRO)* evaluated efficacy of vernakalant in patients with AF (3 to 48 hours duration). The three randomised, double blind, placebo controlled studies included two pivotal Phase III studies, Atrial arrhythmia Conversion Trial [ACT I and ACT III], in which the cohort of short duration AF patients constitutes the primary efficacy population; and one pivotal Phase III study that expands the efficacy profile to include post cardiac surgery AF patients [ACT II]. In addition, supportive safety and/or efficacy data is available from a Phase II study in patients with

AF, Cardiome Recent onset Atrial Fibrillation Trial [CRAFT]; a Phase III open label safety study in patients with AF [ACT IV] that included efficacy assessments with results that were consistent with the controlled studies; and another Phase III study (Scene 2) that assessed the safety and efficacy of vernakalant injection in the conversion of atrial flutter (AFL) to sinus rhythm.

All clinical studies (Table 2) were multinational, were well conducted and complied with Good Clinical Practice guidelines with adequate ethical approval.

Table 2: Clinical efficacy studies with vernakalant injection

Study Number (Acronym) [a]	Phase	Population /Duration	Vernakalant Dose [b]	Design	Number of Patients by Treatment		
					Pbo	Vkt	Total
1235-0703 (ACT I) **PIVOTAL**	3	AF >3hours to ≤45 days	3.0 mg/kg, + 2.0 mg/kg if required [d]	Randomised, Double-blind, Placebo-controlled	115	221	336
1235-0504/04-7-010 (ACT III) **PIVOTAL**	3	AF or AFL[c] >3hours to ≤45 days	3.0 mg/kg, + 2.0 mg/kg if required [d]	Randomised, Double-blind, Placebo-controlled	131	134	265
1235-0104 (ACT II) **PIVOTAL**	3	AF or AFL post cardiac surgery [c] >3hours to ≤72 hours	3.0 mg/kg, + 2.0 mg/kg if required [d]	Randomised, Double-blind, Placebo-controlled	54	107	161
1235-1001 (CRAFT) SUPPORTIVE	2	AF >3hours to ≤72 hours	2.0 mg/kg, + 3.0 mg/kg if required [d]	Randomised, Double-blind, Placebo-controlled	20	36	56
05-7-012 (ACT IV) SUPPORTIVE	3	AF >3hours to ≤45 days	3.0 mg/kg, + 2.0 mg/kg if required [d]	Open-label	0	236	236
1235-0703B (Scene 2) SUPPORTIVE	2/3	AFL >3hours to ≤45 days	3.0 mg/kg, + 2.0 mg/kg if required [d]	Randomised, Double-blind, Placebo-controlled	15	39	54
VERI-305-AMIO (AVRO)[e] Safety and efficacy SUPPORTIVE	3	AF >3hours to ≤48 hours	3.0 mg/kg, + 2.0 mg/kg if required [d]	Randomised, Double-blind, Active-controlled	120[f]	120	240

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; Pbo, placebo; Vkt, Vernakalant.

a In general, study acronyms are used when referencing individual studies throughout the Summary of Clinical Efficacy.

b Patients assigned to the control group received placebo (saline).

c 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.

d 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.

e This study is currently ongoing.

f Amiodarone, and not placebo, is the comparator in the AVRO study.

Dose response studies

1235-1001 (CRAFT) was a Phase IIa, randomized, double blind, placebo controlled, step dose, three arm parallel design study. The selection of the dose regimen was based upon safety and PK results of the Phase I study of vernakalant in healthy human volunteers (protocol 1235-1001) which had shown linear pharmacokinetics within the dosing range of 0.10 mg/kg to 5.0 mg/kg following IV infusion over 10 min. The dose range of 0.5 mg/kg to 3.0 mg/kg was given in two stepping dose regimens, 0.5 mg/kg stepping to 1.0 mg/kg (0.5-1 mg/kg), and 2.0 mg/kg stepping to 3.0 mg/kg (2-3 mg/kg). The 0.5/1.0 mg/kg group had one patient (5.6%) who terminated AF either during or following Dose 1

(0.5 mg/kg) with the remaining 17 patients receiving Dose 2 (1 mg/kg). In the 2.0 - 3.0 mg/kg group, 7 patients (38.9%) required only Dose 1 (2 mg/kg) and 11 patients received Dose 2 (3 mg/kg). The baseline demographics were similar in the 3 treatment groups. Prior to dosing, the mean and median duration of AF was longer in the 2.0-3.0 mg/kg group (mean: 1479.3 min, median 1171.0 min) than in the 0.5-1.0 mg/kg group (mean: 1418.9 min, median: 690.0 min) or in the placebo group (mean: 1067.1 min, median: 800.0 min). The number and percentage of patients who terminated AF (for at least 1 minute) during infusion or in the 30 minute follow up period was significantly greater in the 2-3 mg/kg vernakalant group compared to placebo (11/18, 61.1% versus 1/19, 5.3%, p = 0.0003) (Table 3). Significant results in favour of vernakalant 2/3 mg/kg compared to placebo were also shown for the percentage of patients in normal sinus rhythm (NSR) at 0.5 h post dose (vernakalant versus placebo: 55.6% versus 5.3%, p = 0.0008) (Table 4) and at 1.0 hour post-dose (52.9% versus 5.3%, p= 0.0014) (Table 5). Although the percentage of patients in NSR at 24 hours was numerically greater in the vernakalant 2-3 mg/kg group, the difference from placebo and 0.5-1mg/kg groups was not statistically significant. Vernakalant showed a rapid response with significantly shorter median time to conversion to NSR compared with placebo (14.0 min versus 162.0 min, p = 0.016). Vernakalant 0.5 to 1 mg/kg showed minimal efficacy with no difference from placebo and the 2/3 mg/kg dose was significantly better than both placebo and the 0.5 to 1 mg/kg dose for the primary and secondary efficacy endpoints.

Table 3: Summary of termination of AF during infusion or in the 30 min post infusion follow up period

Termination of AF		Placebo	0.5 and 1.0 mg/kg RSD1235	2.0 and 3.0 mg/kg RSD1235
During dose 1 infusion or in the 30-minute follow-up n, (%)	N	19	18	18
	Yes	0	1 (5.6)	8 (44.4)
	No	19 (100.0)	17 (94.4)	10 (55.6)
During dose 2 infusion or in the 30-minute follow-up n, (%)	N	19	17	11
	Yes	1 (5.3)	1 (5.9)	4 (36.4)
	No	18 (94.7)	16 (94.1)	7 (63.6)
Total termination of AF during dose 1 or dose 2 or in the 30-minute follow-up periods n, (%)	N	19	18	18
	Yes	1 (5.3)	2 (11.1)	11 (61.1)
	No	18 (94.7)	16 (88.9)	7 (38.9)
Treatment	**P-value***	**Risk****	**Lower 95% CI**	**Upper 95% CI**
Placebo		0.053	0.001	0.260
0.5 and 1.0 mg/kg RSD1235		0.111	0.014	0.347
2.0 and 3.0 mg/kg RSD1235		0.611	0.358	0.827
Placebo vs. 0.5 and 1.0 mg/kg RSD1235	0.5148	-0.058	-0.289	0.172
Placebo vs. 2.0 and 3.0 mg/kg RSD1235	0.0003	-0.558	-0.859	-0.258
2.0 and 3.0 mg/kg vs. 0.5 and 1.0 mg/kg RSD1235	0.0018	-0.500	-0.824	-0.177

Data Source: Table 3.1.1 and 3.1.2

* P-value corresponds to Cochran-Armitage trend test, ** Risk is the probability of termination of AF

Note: N = total number of patients, n, % = number and percentage of patients analyzed

Table 4: Summary of number of patients in NSR at 0.5 h post infusion

		Placebo	0.5 and 1.0 mg/kg RSD1235	2.0 and 3.0 mg/kg RSD1235
Patients in NSR at 0.5 hour post-dose n, (%)	N	19	18	18
	Yes	1 (5.3)	2 (11.1)	10 (55.6)
	No	18 (94.7)	16 (88.9)	8 (44.4)
	P-value*	Risk**	Lower 95% CI	Upper 95% CI
Placebo		0.053	0.001	0.260
0.5 and 1.0 mg/kg RSD1235		0.111	0.014	0.347
2.0 and 3.0 mg/kg RSD1235		0.556	0.308	0.785
Placebo vs. 0.5 and 1.0 RSD1235	0.5148	-0.058	-0.289	0.172
Placebo vs. 2.0 and 3.0 mg/kg RSD1235	0.0008	-0.503	-0.808	-0.198
2.0 and 3.0 mg/kg vs. 0.5 and 1.0 mg/kg RSD1235	0.0047	-0.444	-0.772	-0.117

Data Source: Tables 3.2.1 and 3.2.2

* P-value corresponds to Cochran-Armitage trend test

** Risk is the probability of conversion to normal sinus rhythm at 0.5 hours post infusion

Note: N = total number of patients, n, % = number and percentage of patients, NSR = normal sinus rhythm, CI = confidence interval

Table 5: Summary of number of patients in NSR at 1.0 h post infusion

		Placebo	0.5 and 1.0 mg/kg RSD1235	2.0 and 3.0 mg/kg RSD1235
Patients in NSR at 1.0 hour post-dose n, (%)	N	19	18	17
	Yes	1 (5.3)	2 (11.1)	9 (52.9)
	No	18 (94.7)	16 (88.9)	8 (47.1)
	P-value*	Risk**	Lower 95% CI	Upper 95% CI
Placebo		0.053	0.001	0.260
0.5 and 1.0 mg/kg RSD1235		0.111	0.014	0.347
2.0 and 3.0 mg/kg RSD1235		0.529	0.278	0.770
Placebo vs. 0.5 and 1.0 mg/kg RSD1235	0.5148	-0.058	-0.289	0.172
Placebo vs. 2.0 and 3.0 mg/kg RSD1235	0.00147	-0.477	-0.790	-0.163
2.0 and 3.0 mg/kg vs. 0.5 and 1.0 mg/kg RSD1235	0.0077	-0.418	-0.754	-0.083

Data Source: Tables 3.2.3 and 3.2.4

* p-value corresponds to Cochran-Armitage trend test

** Risk is the probability of conversion to normal sinus rhythm at 1.0 hour post infusion

Note: N = total number of patients, n, % = number and percentage of patients, NSR = normal sinus rhythm, CI = confidence interval

Evaluator's comments

It was not clear why the sponsor reversed the regimen used in the CRAFT study (2+3 mg/kg) to the current proposed regimen (3+2 mg/kg) in the Phase III studies. No specific reason was provided for this switch.

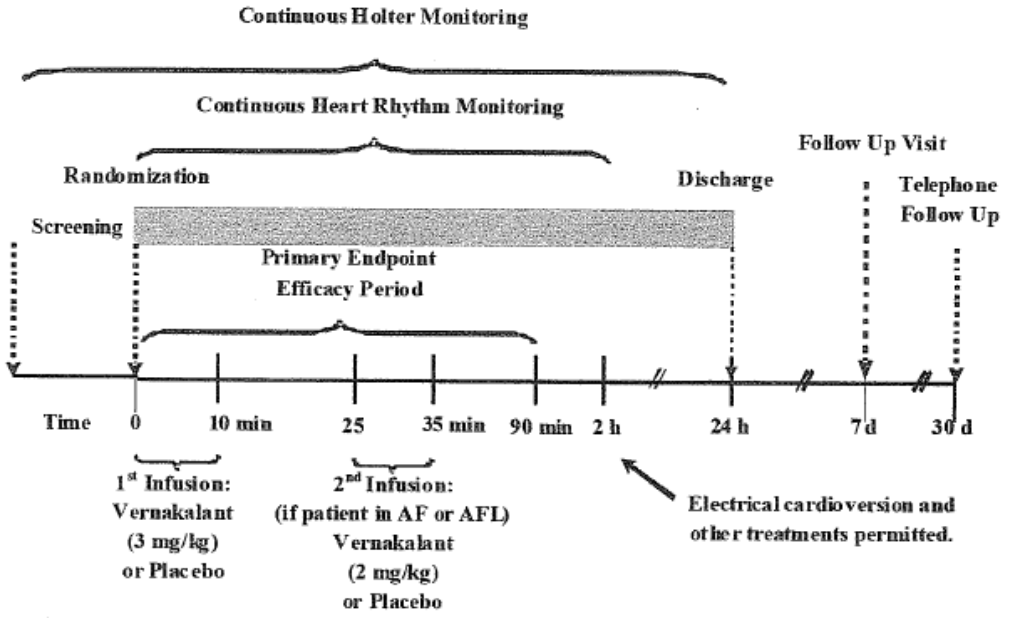
Main (Pivotal) studies

The clinical efficacy of vernakalant in the treatment of patients with AF was evaluated in three large, randomised, double blind, placebo controlled studies (ACT-I, ACT-II, ACT-III) and in an active controlled study versus intravenous amiodarone (AVRO).

Methods, objectives and study treatment

The study design for pivotal studies ACT-I and ACT-III is shown in Figure 1.

Figure 1: Design of Phase III Studies in Patients with Atrial Arrhythmia (ACT I and ACT III)



The ACT II study design was generally consistent with that of ACT I and ACT III up to Hour 24 with the" discharge" follow-up visit occurring at discharge or any time up to 14 days post discharge, and a follow up telephone call at 30 days post dose. The study design of the active controlled study (AVRO) was also similar.

The primary study objective of these pivotal studies was to demonstrate the efficacy of vernakalant in the conversion of AF to sinus rhythm. In the three placebo controlled studies, patients were to receive a 10 min infusion of vernakalant injection (3.0 mg/kg) or placebo (normal saline). The infusion was followed by a 15 min observation period after which a second 10 min infusion of vernakalant 2.0 mg/kg or placebo (normal saline infusion) was administered if the patient was in AF or AFL at the end of the observation period. Patients randomised to amiodarone in the AVRO study received a 60 min infusion of 5 mg/kg amiodarone followed by a maintenance infusion of 50 mg amiodarone over an additional 60 min (equivalent to approx 15 mg/kg over 24 hours). For patients who weighed > 113 kg, the dose was to be based on a weight of 113 kg (not higher). Dose stopping safety criteria were included in each protocol and were documented by the investigator on the case report form. Treatment compliance was assessed from data on duration of the study drug infusion, drug accountability records and results of study drug assays.

Study participants (inclusion and exclusion criteria)

The study population in the pivotal Phase III studies ACT-I and ACT-III consisted of adults (≥ 18 years) who had an atrial arrhythmia with dysrhythmic symptoms.[13] The pivotal study ACT-I included patients with AF (in which the atrial activity was either absent or chaotic both in amplitude and in rate) or other related atrial arrhythmia including non-typical forms of atrial flutter. Study ACT-III included patients with AF and typical atrial

[13] The investigator specifically queried subjects for the following AF or AFL symptoms: shortness of breath, palpitations, chest tightness/pains, dizziness, oedema, fatigue, rapid heartbeats, diaphoresis, orthopnoea, paroxysmal nocturnal dyspnoea, nausea, syncope, irregular pulse, vomiting, cough, and headaches.

flutter (AFL).[14] In studies ACT-I/ III, the current arrhythmia episode was > 3 h and ≤ 45 days. Study ACT-II included adults (≥ 18 years) with documented normal sinus rhythm prior to undergoing coronary artery bypass surgery (CABG) and/or valvular surgery, but developed sustained AF (or AFL) for a duration > 3 h and ≤ 72 h within 24 h to 7 days after surgery. In the active controlled study (AVRO), patients had symptomatic AF of 3 to 48 h duration at baseline.

In studies ACT-I/ III, patients were stratified on the basis of AF duration of either 3 h 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 h 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 h 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).

In all four Phase III studies, patients had to be haemodynamically stable (systolic blood pressure >90 mmHg and <160 mmHg and diastolic blood pressure <95 mmHg at screening and at baseline). Identification of the baseline rhythm, initial therapy (if needed), and post-treatment care was according to standard clinical procedures and the investigator's judgement. Other inclusion criteria were a body weight between 45 and 136 kg and adequate anticoagulant therapy as defined by the clinical practice of the investigator. If AF or AFL lasted more than 48 h, subjects were managed in accordance with standard of practice as recommended by the American College of Cardiology/American Heart Association/European Society of Cardiology practice guidelines [Fuster, *et al.*, 2001].[15]

Patients with pacemakers were included in the studies, as 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). 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.

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;
- evidence of significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis and those with prolonged QT syndromes, myocardial infarction or cardiac surgery within the past 30 days (except in study ACT-II), or acute coronary syndrome.

Other exclusion criteria were:

- known bradycardia or sick sinus syndrome unless controlled by a pacemaker;

[14] was limited to "typical" AFL based on the following criteria: AFL with a regular atrial rate of 220-320 beats per minute (bpm) with a typical sawtooth pattern in leads II, III and aVF and predominantly negative flutter waves in V6 and positive or biphasic in V1. Non-typical forms of AFL were categorized as AF.

[15] Fuster V, Rydén LE, Cannom DS, *et al.* ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006; 48: e149 –246.

- QRS interval >0.14 seconds unless the subject had pacemaker;
- uncorrected QT interval >0.440 seconds as measured on a 12 lead ECG;
- ventricular rate less than 50 beats per minute (bpm) as documented by a 12 lead ECG;
- reversible causes of AF such as alcohol intoxication, hyperthyroidism, acute pericarditis or pulmonary embolism;
- serious pulmonary, hepatic, metabolic, renal, gastrointestinal, central nervous system (CNS) or psychiatric disease;
- end stage disease states;
- or any other disease that could interfere with the conduct or validity of the study or compromise subject safety;
- had failed electrical cardioversion;
- had uncorrected electrolyte imbalance (serum potassium of less than 3.5 mEq/L [3.5 mmol/L] must have been corrected prior to enrolment);
- had clinical evidence of digoxin toxicity;
- had received intravenous Class I or Class III antiarrhythmic drugs or intravenous amiodarone within 24 hours prior to dosing; or
- any other surgical or medical condition that, in the judgment of the clinical investigator might warrant exclusion or be contraindicated for safety reasons.

The patient inclusion and exclusion criteria were similar in the AVRO study. Inclusion/ exclusion criteria were also similar in study ACT-II in post-cardiac surgery patients with the exception that patients who had acute coronary syndrome (including AMI) or patients who had cardiac surgery within past 30 days were not excluded.

Efficacy endpoints and statistical considerations

Cardiac monitoring for conversion from AF to sinus rhythm included 12 lead ECG tracings and Holter monitor recordings. Baseline atrial arrhythmia was established by 12 lead ECG, which was performed at screening and in triplicate at baseline (two within 10 min of the start of the infusion, one at infusion start [time = 0]). A 12 lead ECG was subsequently performed every 5 min thereafter up to 50 min, at 90 min and at 2, 4, and 8 h. Holter monitoring was performed continuously from screening to 24 hours post dose. The Clinical Events Committee (CEC made up of members with expertise in arrhythmia) which was blinded to the study treatment was responsible for verification of conversion to sinus rhythm, verification of termination of AF or atrial flutter (AFL) and verification of cardiac rhythm at baseline.

The primary efficacy endpoint for all the Phase III pivotal trials was the proportion of patients with AF of > 3 h to ≤ 7 days duration who had treatment induced conversion to sinus rhythm for a minimum duration of 1 min within 90 min of first exposure to the study drug.[16]

Key secondary endpoints included time to conversion of AF to sinus rhythm in patients with short-duration AF (> 3 h to ≤ 7 days duration), time to termination of AF in patients in the overall study population (AF duration of > 3 h to ≤ 45 days) and proportion of patients in the overall population who had treatment induced conversion of AF to sinus rhythm. In study ACT-III, secondary endpoints also included proportion of subjects with

[16] Treatment-induced conversion for the primary endpoint was defined as conversion that occurred within 90 minutes of the study drug administration and before any electrical cardioversion or other pharmacologic conversion (other than vernakalant).

short duration, long duration AF or AFL who had treatment induced AF or AFL termination (minimum duration of one min) within 90 min of first exposure to the study drug and proportion of patients with AFL (>3h and <45 days) who had treatment induced termination of AFL. All secondary endpoints were pre-specified and a multiplicity adjustment approach taken. The approach used to preserve the Type I error was via a pre-specified order of testing each secondary endpoint. The primary and secondary efficacy endpoints of the amiodarone-controlled (AVRO) study were similar.

The primary analysis set for all efficacy analyses was the full analysis set (FAS) and supportive evidence for efficacy results was provided by the results of the per protocol analyses (PPS).[17] The Cochran Mantel-Haenszel (CMH) test stratified by centre was used to compare the proportion of subjects with short duration AF who had treatment induced conversion of AF to sinus rhythm for a minimum duration of one min within 90 min of first exposure to the study medication. For the time from first exposure to the study medication until conversion of AF to sinus rhythm, the Product-Limit method was used to obtain estimates of the median time to conversion, the associated 95% CI and the survival curves for subject with short duration AF associated with each treatment group. The two treatment groups were compared using the Log Rank test and the time was censored in subjects who did not convert to sinus rhythm for a minimum of one min within 24 h. In addition, subjects who withdrew prior to conversion to sinus rhythm or who were electrically converted were censored at the time of withdrawal or electrical conversion. The CMH test stratified by centre was used to compare the proportion of subjects in the overall population who had treatment induced termination of AF, lasting a minimum of one min within 90 min of first exposure to the study drug. Exploratory efficacy analysis included logistic regression to investigate the effect of age (<65 years versus >65 years), gender and the use of rate control medications on the conversion of AF to sinus rhythm (short duration AF cohort) and the termination of AF (overall population; long duration AF cohort) within the first 90 min.

Results of pivotal study ACT-I

Patient disposition, baseline patient characteristics, treatment compliance

In study ACT-I, a total of 360 subjects were to be randomized 2:1 (vernakalant: placebo) of whom 240 were planned to have short duration AF and 120 subjects were to have long duration AF. For the subject cohort with short duration AF, the study had a power of 97% to detect a significant difference (at 5% level based on two sided chi-square test) assuming a conversion rate of 25% in the placebo and 50% in the vernakalant group. For patients with long duration AF, the study had 93% power to detect a significant difference (at 5% level based on two sided chi-square test) assuming a conversion rate of 5% in the placebo and 30% in the vernakalant group. The assumptions for a conversion rate of 25% in placebo patients with AF ≤7 days were estimated using a range of results from a number of published manuscripts. These included Kochiadakis et al. (1998) (placebo rate of 28% at 1 h); Vardas (2000) (placebo rate of 25% at 1 h) Capucci et al (1992) (placebo rate of 29% at 3 h) and Donovan et al (1995) (placebo rate of 22% at 2 h).[18,19,20,21] The

[17] The FAS was defined as all randomized subjects who received any amount of study medication (active drug or placebo) The per protocol analysis set (PPS) was defined as all subjects in the full analysis set who had no significant protocol deviation or subjects that were electrically cardioverted prior to the 90 min time point.

[18] Kochiadakis GE, Igoumenidis NE, Solomou MC *et al.* Conversion of atrial fibrillation to sinus rhythm using acute intravenous procainamide infusion. Cardiovasc Drugs Ther 1998; 12: 75-81.

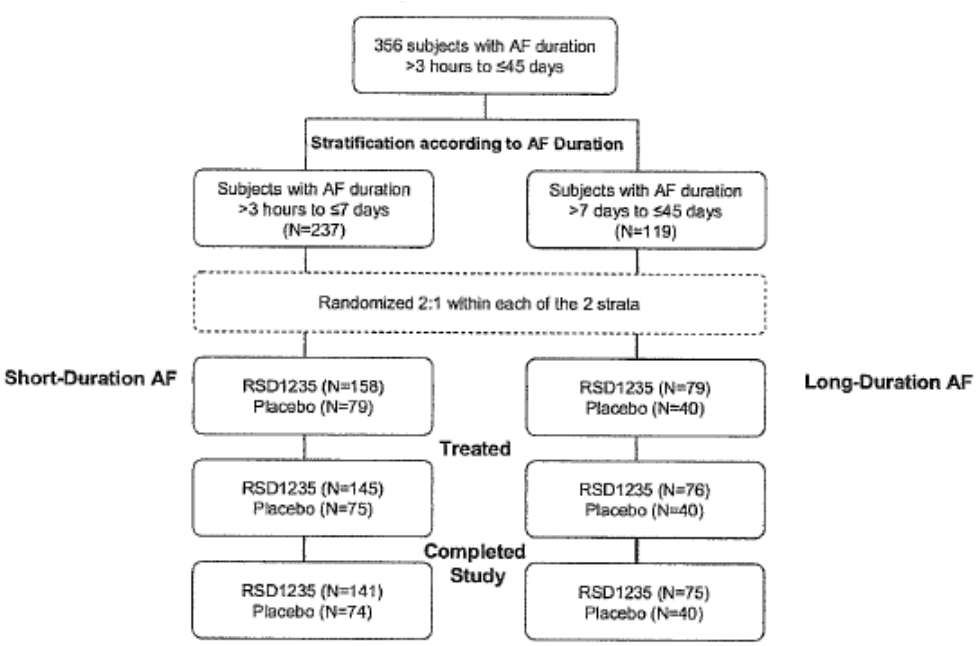
[19] Vardas PE, Kochiadakis GE, Igoumenidis NE, Tsatsakis AM, Simantirakis EN, Chlouverakis GI. Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. Chest 2000; 117: 1538-45.

[20] Capucci A, Aschieri D. Antiarrhythmic drug therapy: what is certain and what is to come. Eur Heart J 2003; 5: H8-H18.

vernakalant rate for the controlled Phase III studies was based on the results of the Phase IIa CRAFT study. In the AVRO study, the estimated conversion rates were in fact 25% and 45% in the amiodarone and vernakalant groups, respectively. Details can be found in section 12.1 of the study protocol. The manuscript from Martinez Marcos (2000) was the basis for estimating amiodarone conversion rates, while the vernakalant rate was estimated using subgroup analyses of patients with AF ≤48 h from the ACT I study.[22]

ACT-I was conducted at 44 sites in Denmark, Sweden, Canada and USA from 1 August 2003 to 1 November 2004. The disposition of the subjects is described in Figure 2.

Figure 2: Disposition of subjects (ACT-I)



Treated: Received any amount of study drug.

Completed Study: Derived from page 47 of case report form.

Three subjects (all in the vernakalant group) failed to complete the study due to an adverse event that resulted in death: rupture of a dissecting aortic aneurysm on Day 2; deterioration of dyspnoea, gastric pain, pain in general and fever resulted in death on Day 26; and pneumonia and respiratory arrest resulted in death on Day 8. None of the deaths were related to the study drug according to the investigator.

The incidence of spontaneous conversion to sinus rhythm before study drug administration was slightly higher in the vernakalant group compared to the placebo group (4.6% versus 2.5%). The primary efficacy analysis dataset included 336 of the 356 (94.4%) randomized subjects. The PP analysis dataset was similar to the FAS with exception of 4 subjects (one vernakalant recipient and three placebo recipients) who were not eligible for inclusion in this population. Protocol deviations were considered to be minor and did not result in a subject being excluded from a data set.

In the overall subject population and in both the short and long duration subgroups, the two treatment groups were similar in terms of demographics (age, gender, racial distribution), other baseline characteristics (height, body weight, body mass index [BMI]

[21] Donovan KD, Power BM, Hockings BEF, Dobb GJ, Lee KY. Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation. Am J Cardiol 1995; 75: 693-7.

[22] Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernández-Gómez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. Am J Cardiol 2000; 86: 950-3.

and tobacco use) and also in terms of duration of AF and duration of AF clinical symptoms. ***It is very important to note that the mean duration of AF symptoms was only 36-45 h (which is less than 2 days) and hence it appears that most of the patients with short duration AF had recent onset AF of <2-3 days.*** In the overall population, almost 78-82% of all patients presented with AF clinical symptoms with similar incidence and profile of symptoms in the two groups at both screening and baseline assessments. In the subgroup of subjects with short duration AF, the incidence of fatigue was significantly higher in the vernakalant group as compared to the placebo group (vernakalant versus placebo: 40.7% versus 22.7%, chi-square p-value=0.008), while incidence of headache was significantly higher in the placebo group (8.3% versus 17.3%, p=0.045). In the subgroup of patients with long duration AF, baseline incidence of all AF symptoms was higher in the placebo group (61.8% versus 82.5%, p=0.22). The baseline blood pressure (BP), heart rate, respiration rate and oxygen saturation were similar in both treatment groups. The two treatment groups were similar in terms of background use of the pre-selected antiarrhythmics in the overall population and in both the short duration and long duration AF subgroups. Concomitant medications defined as those medications used prior to administration of the study drug that continued during the study or those medications begun following administration of the study drug were comparable in the two treatment groups; the most frequently used concomitant medications in both groups were vitamin K antagonists. The most frequently administered medications after the first infusion were also similar in both groups with "other general anaesthetics" (sedatives administered prior to electrical cardioversion) being the most common in both groups. All subjects in the placebo group (100%) and 215/221 (97.3%) subjects in the vernakalant group received the complete Dose 1; 99.1% (113/114) placebo treated subjects and 98.7% (148/150) vernakalant treated subjects completed Dose 2.

Primary efficacy results

In subjects with short duration AF, a statistically and clinically significantly (p<0.0001) greater proportion of vernakalant recipients (75/145, 51.7%) compared with placebo recipients (3/75, 4.0%) converted to sinus rhythm within 90 min and met the primary efficacy endpoint (vernakalant – placebo=47.7%, 95% CI: 38.5, 57; odds ratio= 24.0, 95% CI: 6.9, 83.6). The PP analysis showed similar results (51.4% versus 4.2%; diff= 47.2%, 95% CI: 37.8%, 56.6%, p< 0.0001; odds ratio= 22.6, 95% CI: 6.4, 79.7).

Secondary efficacy results

In subjects with short duration AF, vernakalant treated patients experienced a statistically and clinically significantly (p < 0.0001) shorter time from first study drug exposure to first conversion of AF to sinus rhythm (minimum duration of 1 min) within 24 h of first exposure to the study drug compared with placebo recipients (Table 6) with similar results in the overall population (Table 7). In the overall population in the full analysis set, a statistically significant greater proportion of vernakalant treated patients (83/221, 37.6%) compared with placebo recipients (3/115, 2.6%) had treatment induced termination of AF within 90 min after receiving study drug (vernakalant – placebo=34.9, 95% CI: 27.9, 42.0, p<0.0001; odds ratio: 21.3, 95% CI: 6.5, 69.6).

Table 6: Summary of time to first treatment induced conversion of AF to sinus rhythm (short duration AF)

	Time (minutes) from First Study Drug Exposure to Conversion†				
Treatment Group	25th Percentile	50th Percentile	75th Percentile	95% CI	P-value‡
Placebo (N = 75)	264.3	>1440	>1440	>1440 - >1440	<0.0001
RSD1235 (N = 145)	10.4	75.5	>1440	>33.0 - 1439.0	

Subject base: All randomized subjects who received any amount of study drug (full analysis set/safety set).
CI: Confidence interval.
† Method: Simon and Lee. Cancer Treatment Report 66:37-42, 1982.
‡ P-value from log-rank test.

Table 7: Time to first treatment induced termination of AF (overall subject population)

Treatment Group	Time (minutes) from First Study Drug Exposure to Termination†				P-value ‡
	25th Percentile	50th Percentile	75th Percentile	95% CI	
Placebo (N = 115)	474.4	>1440	>1440	>1440 - >1440	<0.0001
RSD1235 (N = 221)	19.4	>1440	>1440	>1440 - >1440	

Subject base: All randomized subjects who received any amount of study drug (full analysis set/safety set).
CI: Confidence interval.
† Method: Simon and Lee, Cancer Treatment Report 66:37-42, 1982.
‡ P-value from log-rank test.

Patients with long duration AF did not show any difference in the time to termination of AF between treatment groups. In the long duration AF sub-group, treatment induced termination of AF within 90 min after exposure to the study medication was observed only in vernakalant treated subjects (vernakalant versus placebo: 7.9% versus 0%, diff=7.9, 95% CI: 1.8, 14, p<0.0918).

Exploratory efficacy results

The median time to conversion for the 80 subjects in the overall AF population and the 75 subjects with short duration AF who converted from AF to sinus rhythm within 90 min of infusion was approximately 11.0 min (11.5 min overall; 11.0 min short duration AF) in the vernakalant group and 29.0 min in the placebo group. In subjects with short duration AF, a statistically and clinically significantly greater proportion of vernakalant treated patients (77/145, 53.1%) compared with placebo treated subjects (3/75, 4.0%) had termination of AF (defined as the absence of AF and atrial flutter) within 90 min (p<0.0001, diff= 49.1, 95% CI: 39.8, 58.4).

Life table estimates of the maintenance of sinus rhythm for subjects with short duration AF treated with vernakalant who converted within 90 min (n=75) indicates 98.6% maintenance at 2 h, 4 h and 8 h, 97.0% maintenance at 24 h, and 92.0% maintenance at 7 days. There was 66.7% maintenance for the 3 subjects in the placebo group at all time points. ***However, it is important to note that this was only a post hoc analysis and was not a pre-defined efficacy endpoint.***

A statistically significant greater decrease in the median number of AF clinical symptoms was observed at 90 min in vernakalant treated patients compared with placebo recipients in subjects with short duration AF and in the overall population. At 90 min, the incidence of all AF clinical symptoms which had been present at baseline decreased considerably in vernakalant treated patients with short duration AF with a >10% reduction in incidence from baseline observed for irregular pulse, palpitation, rapid heart rate and shortness of breath. While the incidence of AF clinical symptoms also showed slight reduction (1-7%) in placebo recipients, the incidence of fatigue increased slightly (5.3%) (Table 8).

Table 8: Summary of individual AF symptoms at baseline and 90 min in subjects with short duration AF

	Treatment Group			
	Placebo (N = 75)		RSD1235 (N = 145)	
Parameter	Baseline	90 Minutes	Baseline	90 Minutes
Any AF symptom	61 (81.3%)	57 (76.0%)	125 (86.2%)	75 (51.7%)
AF Symptom				
Irregular Pulse	37 (49.3%)	34 (45.3%)	76 (52.4%)	30 (20.7%)
Palpitation	34 (45.3%)	32 (42.7%)	72 (49.7%)	30 (20.7%)
Rapid heart beat	28 (37.3%)	23 (30.7%)	47 (32.4%)	21 (14.5%)
Shortness of breath	14 (18.7%)	11 (14.7%)	30 (20.7%)	14 (9.7%)
Fatigue	17 (22.7%)	21 (28.0%)	59 (40.7%)	46 (31.7%)
Dizziness	11 (14.7%)	9 (12.0%)	19 (13.1%)	6 (4.1%)
Chest tightness/Pain	11 (14.7%)	10 (13.3%)	14 (9.7%)	7 (4.8%)
Headache	13 (17.3%)	11 (14.7%)	12 (8.3%)	8 (5.5%)
Cough	3 (4.0%)	3 (4.0%)	11 (7.6%)	5 (3.4%)
Paroxysmal nocturnal dyspnea	1 (1.3%)	1 (1.3%)	5 (3.4%)	0
Orthopnea	1 (1.3%)	0	5 (3.4%)	2 (1.4%)
Diaphoresis	4 (5.3%)	2 (2.7%)	5 (3.4%)	4 (2.8%)
Edema	2 (2.7%)	1 (1.3%)	4 (2.8%)	3 (2.1%)
Nausea	2 (2.7%)	1 (1.3%)	3 (2.1%)	2 (1.4%)
Vomiting	0	0	0	0
Syncope	0	0	0	0

Subject base: All randomized subjects who received any amount of study drug (full analysis set/safety set).
Adapted from MedDRA v6.1.

There were no statistically significant results for the effects of age, gender, baseline use of any rate control medication, beta blockers, calcium channel blockers and digoxin on the proportion of subjects with conversion from AF to sinus rhythm within 90 min of first study drug exposure for subjects with short duration AF, long duration AF or overall study population.

Overall, results from this study were robust and consistent and demonstrated that vernakalant (3+2 mg/kg) rapidly (with median 11min time to conversion) converted AF to sinus rhythm in subjects with short duration AF (3h to <7 days). Furthermore, there was a 10% reduction in symptoms, specifically irregular pulse, palpitations, rapid heartbeat and shortness of breath observed in subjects with short duration AF who received vernakalant which was most probably related to more patients attaining sinus rhythm. A *post hoc* analysis showed that most subjects who achieved sinus rhythm with vernakalant treatment maintained sinus rhythm up to 7 days after first exposure to vernakalant. Vernakalant was not effective in patients with long-duration AF (>7 to <45days).

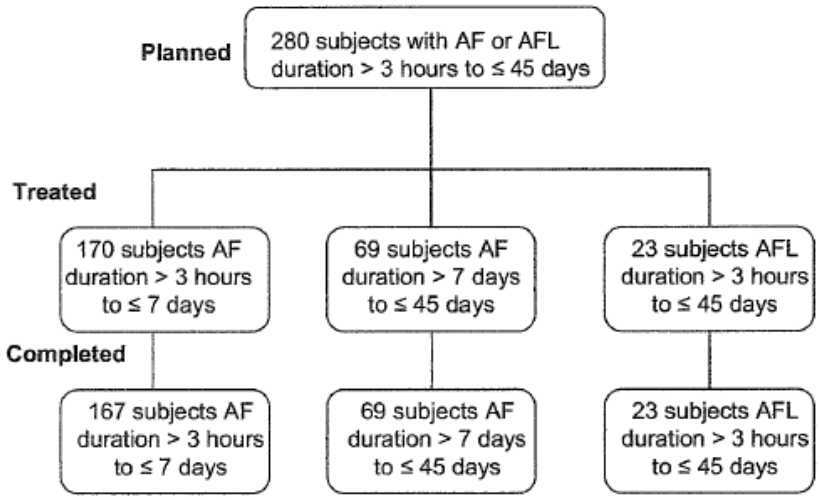
Results of pivotal study ACT-III

Patient disposition, baseline patient characteristics, treatment compliance

In study ACT-III, 280 subjects were planned for randomization: 200 subjects with short duration AF or AFL (>3 h and ≤ 7 days) and 80 subjects with long-duration AF or AFL (>7 days and < 45 days). Within each stratum, subjects were randomized in a 1:1 ratio to receive vernakalant or placebo. For the subject cohort with short duration AF or AFL, 77 subjects in each treatment group would provide 90% power (based on a two sided chi-square test with a 0.05 significance level) for detecting a 25% difference in the conversion rate between the two treatment groups (assuming a conversion rate of 25% in placebo and 50% in the vernakalant group). Considering a 5% spontaneous conversion rate prior to dosing, a 5% incidence of subjects with pacemakers, and 10 to15% of subjects with AFL, 100 subjects were planned for each treatment arm. The study also had 70% power to detect a significant difference in conversion rate between vernakalant and placebo in the subgroup of patients with long duration (>7 to <45 days) AFB or AFL (based on Fischer test at 5% significance level and assuming conversion rate of 5% in placebo and 30% in vernakalant group).

The study was conducted at 49 centres (in USA, Canada, Scandinavia and Latin America) from 27 June 2004 to 1 August 2005. The disposition of the subjects is described in Figure 3.

Figure 3: Disposition of subjects (ACT-III)



Treated: received any study drug
Completed Study: completed study through Day 30; derived from page 27 of CRF
n: total number of subject in each category

The FAS includes 265 of the 276 randomized subjects (96.0%). However, 3 of the subjects in the full analysis/safety set did not have confirmed AF or AFL: 1 randomized to placebo was not diagnosed with AF or AFL and 2 randomized to vernakalant had missing ECG data and the diagnosis could not be confirmed. These 3 subjects were included in the overall full analysis/safety set, but were excluded from the subgroups that are stratified by AF or AFL (Table 9). A total of 7 subjects (3 placebo, 4 vernakalant) in the full analysis set were excluded from the per protocol set prior to unblinding.

Table 9: Summary of analysis populations

Subject Status	Treatment Group		
	Placebo	RSD1235	Total
All Subjects †			
N	138	138	276
Full analysis set (safety set)	131 (94.9%)	134 (97.1%)	265 (96.0%)
Per protocol set	128 (92.8%)	130 (94.2%)	258 (93.5%)
Subjects with AF (Short- plus Long-Duration)			
N	121	119	240
Full analysis set (safety set)	121 (100.0%)	118 (99.2%)	239 (99.6%)
Per protocol set	118 (97.5%)	116 (97.5%)	234 (97.5%)
Subjects with Short-Duration AF			
N	84	86	170
Full analysis set (safety set)	84 (100.0%)	86 (100.0%)	170 (100.0%)
Per protocol set	81 (96.4%)	84 (97.7%)	165 (97.1%)
Subjects with Long-Duration AF			
N	37	33	70
Full analysis set (safety set)	37 (100.0%)	32 (97.0%)	69 (98.6%)
Per protocol set	37 (100.0%)	32 (97.0%)	69 (98.6%)
Subjects with AFL (Short- plus Long-Duration)			
N	9	14	23
Full analysis set (safety set)	9 (100.0%)	14 (100.0%)	23 (100.0%)
Per protocol set	9 (100.0%)	14 (100.0%)	23 (100.0%)

Subject base: all randomized subjects (includes 11 subjects who never received study drug)
Full analysis set/safety set: all randomized subjects who received any amount of study drug
Per protocol set: all subjects in the full analysis/safety set who had no significant protocol deviation
Short-duration: >3 hours and ≤ 7 days
Long-duration: >7 days and ≤ 45 days
† Three subjects in the "All Subjects" group (1 placebo, 2 RSD1235) did not have confirmed AF or AFL and are not included in the other subgroups.

The placebo and vernakalant treatment groups had similar baseline demographic and disease characteristics in the overall subject population and for the subgroups of subjects with AF, short duration AF**,** long duration AF and AFL. Continuous data on duration of AF was not collected in this study. The majority of subjects in both treatment groups had no history of CHF. The 26 subjects in the placebo group and 28 subjects in the vernakalant group with CHF had similar NYHA classifications. There were no significant differences between treatment groups for ejection fraction or chamber size. Subjects treated with vernakalant had lower baseline mean diastolic BP compared to subjects treated with placebo in the subgroup of subjects with short duration AF (75.1 versus 78.8 mmHg; p = 0.010). The proportion of subjects with AF or AFL symptoms was similar between treatment groups in the overall population and the subgroup of short duration AF. For the long duration AF subgroup, a greater proportion of vernakalant recipients had baseline shortness of breath compared to placebo recipients (13/32 [40.6%] versus 7/37 [18.9%]; p = 0.047). For subjects with AFL, a greater proportion of vernakalant recipients had baseline rapid heartbeats compared to placebo recipients (6/14 [42.9%] versus 0/9 [0%]; p = 0.046). The vernakalant and placebo treatment groups were similar in terms of background use of preselected antiarrhythmics in the overall population and all subgroups with the exception of significantly higher baseline use of class I antiarrhythmic medications in the vernakalant populations that included the target subgroup of subjects with short duration AF. The incidence of digoxin use was low but slightly greater for placebo recipients with short duration AF compared to vernakalant recipients. The use of general anaesthetics (propofol, alfentanil, fentanyl) was also higher in the placebo group, likely reflecting the more common use of electrical cardioversion in this group (91 placebo recipients had electrical cardioversion attempted within the first 24 h compared to 54 vernakalant recipients). The use of other concomitant medications was generally comparable between the two treatment groups.

In the overall population, the infusion for Dose 1 was completed for 99.2% (130/131) of subjects in the placebo group and 96.3% (129/134) of subjects in the vernakalant treatment group.[23] The infusion for Dose 2 was completed for all 128 subjects in the placebo group and all 91 subjects in the vernakalant group who began the second infusion.

Primary efficacy results

In subjects with short-duration AF, a greater proportion of subjects treated with vernakalant converted to sinus rhythm (for a minimum duration of one min) within 90 min of first exposure to the study drug compared to subjects treated with placebo (44/86 [51.2%] versus 3/84 [3.6%], diff= 47.6%, 95% CI: 36.3%, 58.9%, p<0.0001; odds ratio= 38.3, 95% CI: 9.2, 159.5).

Secondary efficacy results

Subjects with short duration AF who were treated with vernakalant experienced a shorter time from first study drug exposure to first conversion of AF to sinus rhythm (minimum duration of 1 min) within 24 h of first exposure to the study drug compared to subjects treated with placebo (p < 0.0001) (Table 10). A greater proportion of subjects with AF (duration of >3 h and < 45 days) who were treated with vernakalant experienced treatment induced AF termination (minimum duration of one min) within 90 min of first exposure to the study drug compared to subjects treated with placebo (47/118 [39.8%] versus 5/121 [4.1%]) (diff= 35.7%, 95% CI: 26.2%, 45.2%, p<0.0001; odds ratio= 20.6, 95% CI: 6.8, 62.4). Similar results in favour of vernakalant were observed in subjects with short duration AF or AFL (45/98 [45.9%] versus 3/92 [3.3%]) (diff=42.7%, 95% CI: 32.1%, 53.2%, p<0.0001; odds ratio=35.5, 95% CI: 8.2, 153.1) and in subjects with AF or

[23] Five (1 placebo, 4 vernakalant) of the 6 subjects who did not complete dose 1 had the infusion stopped due to predefined dose-stopping criteria. Dose 1 was prematurely discontinued for an additional subject in the vernakalant group because the subject converted to normal sinus rhythm

AFL (>3 hours and <45 days) (48/134 [35.8%] versus 5/131 [3.8%]) (diff=32.0%, 95% CI: 23.2%, 40.8%, p<0.0001; odds ratio=16.7, 95% CI: 5.7, 49.3).

Table 10: Time to conversion of AF to sinus rhythm within 24 hours – subjects with short duration AF

Treatment	N	Time (minutes) from First Study Drug Exposure to Conversion†				P-value‡
		25th Percentile	50th Percentile	75th Percentile	95% CI	
Placebo	84	705.0	>1440	>1440	>1440 to > 1440	< 0.0001
RSD1235	86	7.6	73.6	>1440	17.0 to 846.0	

Subject base: full analysis/safety set (all randomized subjects who received any amount of study drug)
Subjects who did not achieve conversion of AF or who were electrically cardioverted were censored at 24 hours or at the time of electrical conversion, as applicable.
CI = confidence interval of the median
† Method: Simon and Lee, Cancer Treatment Report 66:37-42, 1982
‡ P-value from log-rank; value is statistically significant at the P < 0.001 level

There was no statistically significant difference between the two treatment groups in the proportion of subjects with long duration AF (> 7 days and < 45 days) who had treatment induced AF termination (minimum duration of one min) within 90 min of first exposure to the study drug (vernakalant versus placebo: 9.4% versus 2.7%, p=0.3303). Only one of the 14 subjects with AFL (>3 h and < 45 days) treated with vernakalant experienced treatment-induced AFL termination (minimum duration of one min) within 90 min of first exposure to the study drug compared with none of the 9 subjects treated with placebo.

Exploratory efficacy results

Subjects with short duration AF who were treated with vernakalant experienced a shorter time from first study drug exposure to first conversion of AF to sinus rhythm (minimum duration of 1 min) within 90 min of first exposure to the study drug compared to subjects treated with placebo (p <0.0001) (Table 11). Of the 44 vernakalant treated subjects with short duration AF who converted to sinus rhythm within 90 min, only 1 subject did not have sinus rhythm at 2 h and another subject did not have sinus rhythm at the Day 7 follow up. Nine subjects had missing assessments (3 at 2 h, 2 at 4 h, 3 at 8 h and one at the Day 7 follow up) and were not counted for any subsequent assessments. All 3 placebo recipients who converted to sinus rhythm within 90 min maintained sinus rhythm through the Day 7 follow-up visit.

Table 11: Time to conversion of AF to sinus rhythm within 90 min – subjects with short duration AF

Treatment	N	Time (minutes) from First Study Drug Exposure to Conversion†				P-value‡
		25th Percentile	50th Percentile	75th Percentile	95% CI	
Placebo	84	>90	>90	>90	>90 to > 90	< 0.0001
RSD1235	86	7.6	73.6	>90	17.0 to 90	

Subject base: full analysis/safety set (all randomized subjects who received any amount of study drug)
Subjects who did not achieve conversion of AF or who were electrically cardioverted were censored at 24 hours or at the time of electrical conversion, as applicable.
CI = confidence interval of the median
† Method: Simon and Lee, Cancer Treatment Report 66:37-42, 1982
‡ P-value from log-rank

For subjects with short duration AF who received vernakalant treatment, 41.9% (36/86) of subjects converted to sinus rhythm within 90 min with the first dose only and 16.7% (8/48) of subjects converted after the second dose of vernakalant.

The number of subjects with any AF or AFL symptoms at 90 min was statistically significantly lesser in the vernakalant group compared to the placebo group, for the overall population, subjects with AF and subjects with short duration AF; however, there was no statistically significant difference between treatment groups at 24 h, 7 days or 30 days. Vernakalant recipients had a statistically significant lower incidence of palpitations, chest tightness/pains, rapid heartbeats and irregular heartbeat at 90 min compared to placebo recipients in the population of subjects with short-duration AF (Table 12). The incidence of palpitations, rapid heartbeats and irregular heartbeat was also lower for

vernakalant recipients compared to placebo recipients for all AF recipients and a lower incidence of rapid heartbeats and irregular pulse for all subjects. Vernakalant recipients with AFL had a higher incidence of rapid heart rate at baseline (6/14 [42.9%]) compared to placebo recipients (0/9; P = 0.046), but the incidence at 90 min was similar (2/9 [22.2%] placebo, 3/14 [21.4%] vernakalant).

Table 12: Statistically significant differences for AF or AFL symptoms

Symptom	Time Point	Number (%) of Subjects with Symptoms		P-value
		Placebo	RSD1235	
All Subjects				
		N = 131	N = 134	
Rapid heart beats	90 min	28 (21.4%)	14 (10.4%)	0.028
Irregular pulse	90 min	57 (43.5%)	32 (23.9%)	0.001
Subjects with AF (Short- plus Long-Duration)				
		N = 121	N = 118	
Palpitation	90 min	34 (28.1%)	19 (16.1%)	0.030
Rapid heart beats	90 min	26 (21.5%)	11 (9.3%)	0.012
Irregular pulse	90 min	55 (45.5%)	26 (22.0%)	<0.001
Subjects with Short-Duration AF				
		N = 84	N = 86	
Palpitations	90 min	31 (36.9%)	13 (15.1%)	0.002
Chest tightness/pains	90 min	5 (6.0%)	0	0.028
Rapid heart rate	90 min	23 (27.4%)	6 (7.0%)	<0.001
Irregular pulse	90 min	36 (42.9%)	16 (18.6%)	<0.001
Subjects with AFL (Short- plus Long-Duration)				
		N = 9	N = 14	
Rapid heart rate	Baseline	0	6 (42.9%)	0.046

Subject base: full analysis/safety set (all randomized subjects who received any amount of study drug)
P-value from Fisher's exact test

The median time to conversion from AF to sinus rhythm for the 44 vernakalant recipients with short duration AF who converted within 90 min of first study drug exposure was 8.0 min (range: 3 – 75 min) and the median for the 3 placebo recipients who converted was 34.0 min (range: 13 – 60 min).

Overall, a greater proportion of vernakalant recipients with short duration AF (44/86, 51.2%) converted to sinus rhythm within 90 min compared to placebo recipients (3/84, 3.6%). This 47.6% difference in treatment induced AF conversion to sinus rhythm was statistically significant ($p < 0.0001$). The median time to conversion in the vernakalant group was 8 min for subjects with short duration AF who converted within 90 min. *Post hoc* analysis showed that conversion to sinus rhythm was maintained by the majority of subjects with short duration AF who converted within 90 min; the life-table estimate of the percent of subjects remaining in sinus rhythm at Day 7 was 94.8%. Most (36/44) of the subjects who converted from short duration AF to sinus rhythm within 90 min of vernakalant treatment converted after the first dose. Subjects treated with vernakalant experienced a greater decrease in the number of AF or AFL symptoms compared to placebo recipients at 90 min ($p = 0.0330$) with a lower incidence of palpitations, chest tightness/pains, rapid heart rate and irregular heart beat.

Results of study ACT-II in post-cardiac surgery patients with AF/ AFL

Patient disposition, baseline patient characteristics, treatment compliance

In study ACT-II, 210 post-cardiac surgery subjects with AF (of >3 and <72 h duration) were enrolled into the study, with 140 subjects randomized to receive vernakalant and 70 subjects randomized to receive placebo. Assuming a placebo response rate of 35%, the proposed sample size would provide 90% power (based on a two-sided chi-square test with a 5% significance level) to detect a minimum difference between placebo and vernakalant of 23.5% (assuming response rate of 58.5% with vernakalant).

The study was conducted at 43 sites in Canada, Europe, Asia, South America, and the United States from 16 June 2004 to 22 February 2007. One of the major amendments to

the study protocol was that the exclusion criterion was removed to allow patients with prior history of atrial fibrillation and/or atrial flutter into the study. A total of 190 of the planned 210 subjects were randomized and 161 subjects received study drug. A total of 24 subjects spontaneously converted to sinus rhythm prior to receiving study drug and 5 subjects did not receive study drug for various reasons. Two subjects in the vernakalant treatment group were noted to have major protocol deviations (improper treatment administration and normal sinus rhythm at baseline) and were not included in the per protocol analysis set.

Demographic characteristics were similar in the placebo and vernakalant group and majority of subjects were White males with mean age of 68 years of age; a majority of subjects (93%) in both treatment groups were in AF at baseline and only 6-7% had AFL. Cardiovascular status within two weeks pre-surgery was similar in the two treatment groups. One subject in each group had a pacemaker and all but one subject in the placebo group were in sinus rhythm. No subjects in either group had evidence of second or third degree AV block. Approximately 67% of subjects in both treatment groups underwent CABG surgery alone; the incidence of only valvular surgery was higher in the vernakalant group (vernakalant versus placebo: 26.2% versus 18.5%) and that of patients undergoing both valvular and CABG was higher in the placebo group (7.5% versus 13%). There were no statistically significant differences between treatment groups in left atrial and left ventricular measurements. Approximately half of the subjects in both treatment groups had a normal ejection fraction and one-third of the subjects had left ventricular hypertrophy. The baseline use of rate control medications was similar in both treatment groups. Fewer patients were receiving rate and rhythm control medications at baseline, which was consistent with a patient population that was not experiencing persistent arrhythmia prior to cardiac surgery.

Two subjects in the placebo group did not receive the second infusion of the study drug. One patient converted to SR and another did not receive the second infusion for an unknown reason. In the vernakalant group, 38 subjects did not receive the second infusion of the study drug (34 subjects converted to SR, 1 subject converted to a junctional rhythm, and 3 subjects experienced adverse events during or following the first infusion and the second infusion was not administered).

Primary efficacy results

Overall, a statistically significant greater proportion of subjects in the vernakalant group (48/107, 44.9%) converted to sinus rhythm (for a minimum duration of 1 min) within 90 min of first exposure to the study drug compared to subjects in the placebo group (8/54, 14.8%) (diff= 30.0, 95% CI: 16.7, 43.4, p=0.0002; odds ratio=3.00, 95% CI: 1.53, 5.87). These results were supported by the per protocol analysis and the analysis in 'all randomized' subjects (Table 13).

Secondary efficacy results

The majority of subjects were in AF at baseline and statistically significant greater proportion of subjects in the vernakalant group (47/100, 47%) converted from AF to sinus rhythm (for a minimum duration of 1 min) within 90 min of first exposure to the study drug compared to subjects in the placebo group (7/50, 14%) (diff=33.0, 95% CI: 19.3, 46.7, p<0.0001; odds ratio= 3.25, 95% CI:1.61, 6.57). A total of 10 subjects were in AFL at baseline. One of four subjects in the placebo group (25.0%) converted to SR within 90 min. None of the six subjects in the vernakalant group converted to SR within 90 min of receiving the study drug. Subjects with AF or AFL who received vernakalant experienced a shorter time from first exposure to the study drug to conversion to SR (minimum duration of 1 min) within 90 min of first exposure to the study drug compared to subjects who received placebo (Table 14).

Table 13: Treatment induced conversion rates in all populations analysed

Population/ Subject Base	Subjects with Conversion		Treatment Difference (95% CI)†	P value‡	Relative Risk (95% CI)§
	Placebo	RSD1235			
Full Analysis Set	N=54 8 (14.8%)	N=107 48 (44.9%)	30.0 (16.7, 43.4)	0.0002	3.00 (1.53, 5.87)
Per Protocol Set	N=54 8 (14.8%)	N=105 47 (44.8%)	29.9 (16.5, 43.4)	0.0003	2.92 (1.50, 5.71)
All Randomized Set	N=63 15 (23.8%)	N=127 65 (51.2%)	27.4 (13.7, 41.0)	0.0005	2.10 (1.32, 3.35)
Full Analysis Set, data cutoff date March 31, 2006	N=46 6 (13.0%)	N=96 45 (46.9%)	33.8 (19.9, 47.8)	0.0001	3.54 (1.61, 7.79)

Conversion was determined by the CEC.
† (% Success in RSD1235 group) – (% success in placebo); missing values were considered not converted
‡ P value from Cochran-Mantel-Haenszel test, stratified by country
§ Relative risk in favor of conversion for RSD1235 versus placebo

Table 14: Time to conversion of AF/AFL to SR within 90 minutes

Treatment	N	Time (minutes) from First Study Drug Exposure to Conversion				P-value†
		25th Percentile	50th Percentile	75th Percentile	95% CI	
Placebo	54	>90	>90	>90	0 to infinity	<.001
RSD1235	107	13.8	>90	>90	41.60 to infinity	

Subject base: full analysis set (all randomized subjects who received any amount of study drug)
Product limit method. Subjects who did not achieve conversion of AF/AFL to SR for a minimum duration of 1 minute within 90 minutes or were electrically or pharmacologically (using therapies other than RSD1235) cardioverted were censored at 90 minutes or at the time of conversion, as applicable.
CI = confidence interval of the median
† P-value from log-rank.

Exploratory efficacy results

During the first 6 hours post dose, maintenance of treatment induced conversion to sinus rhythm was more common in vernakalant treated patients (82-94%) compared with placebo (62%); however, the proportion of patients still maintained in sinus rhythm at 24 hours and 7 days was similar in the vernakalant (57-59%) and placebo (50%) groups. For the 48 subjects with AF or AFL in the vernakalant group who converted to SR within 90 min, the median time to conversion was 12.3 min. Most (36/48, 75%) of the subjects who had treatment induced conversion within 90 minutes of receiving vernakalant converted after the first dose.

The number of subjects with at least one AF or AFL symptom at baseline in the vernakalant group (91.6%, 98/107) was similar to the placebo group (88.9%, 48/54). The presence of individual symptoms at baseline was also similar, with the exception of dizziness, which occurred in significantly (p=0.036) more patients in the vernakalant group ((13/107, 12.1%) compared with the placebo group (1/54, 1.9%). At Minute 90, fewer subjects in the vernakalant group (66.4%, 71/107) had at least one symptom compared with the placebo group (79.6%, 43/54), though the difference was not statistically significant (p=.099). At Minute 90, the number of subjects in the vernakalant group who experienced dizziness (5.6%, 6/107) had decreased, such that there was no statistically significant difference compared with placebo (1.9%, 1/54). Statistically significantly fewer subjects in the vernakalant group experienced rapid heartbeats, palpitations, and irregular pulse at Minute 90 compared with placebo subjects, consistent with the greater number of subjects in the vernakalant group that were in SR at Minute 90. There were no statistically significant differences between groups with respect to symptoms at 24 h**. It is important to note that at the 7 day and 30 day follow up visits, there was a trend suggesting higher incidence of symptoms in patients who had received vernakalant compared to placebo.**

Treatment-induced conversion rates were similar across the age groups of <65 years and ≥65 years as well as the grouping of subjects <75 years and ≥75 years. Treatment induced conversion rates were similar across gender. There was a greater treatment difference in those who received rate control (treatment diff was 50%) versus those who did not receive rate control medication (15%). In the subgroup of subjects who underwent CABG surgery, vernakalant treated patients showed statistically significant greater conversion rates compared with placebo (47.9% versus 13.5%, diff=34%, 95% CI: 18.4, 50.4, p=0.002); however, this was not observed in subgroup of patients that underwent valvular surgery (35.7% versus 20%, diff=15.7%, 95% CI: -14.8, 46.2, p=0.502). Treatment induced conversion rates of vernakalant versus placebo were not affected by ejection fraction, atrial dimension, ventricular dimension, or left ventricular hypertrophy.

Evaluator's comment

Vernakalant showed statistically significantly greater conversion to sinus rhythm within 90 min compared to placebo (45% versus 15%, p=0.0002); however this did not translate into a statistically significant improvement in AF symptoms at 90 min. *Post hoc* analysis showed that SR was more likely to be maintained in the first 6 hours post dose in the vernakalant group (82-94%) compared to placebo (62%) although there was no difference between vernakalant and placebo groups in maintenance of SR at 24 hours or 7 days.

Results of the amiodarone-controlled (AVRO) study

Patient disposition, baseline patient characteristics, treatment compliance

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

Of the subjects who were treated, 6 vernakalant subjects and 1 amiodarone subject discontinued the study, mostly due to AEs and a total of 225 subjects completed the study through the Day 30 follow up telephone call. Three subjects in each treatment group had major protocol deviations that could have affected the primary endpoint, and these subjects were excluded from the per-protocol population.[24]

Demographics were similar among the two treatment groups and the majority of subjects were White (95.7%) males (62.9%); mean age was 63 (range of 32 to 85) years and 15% of subjects were >75 years of age. Baseline characteristics and cardiovascular medical history were also well balanced among the two treatment groups. The majority of subjects (164/232, 70.7%) had experienced at least one previous AF episode, with 34.5% of subjects having >3 previous episodes. The median duration of the current AF episode was 17.7 hours, and 40.5% of subjects had AF duration of >24 hours. Approximately 20% (46/232) had a history of heart failure, with just over half of these subjects having NYHA Class II heart failure (25/46 subjects, 54.3%). There were no subjects with NYHA Class III heart failure enrolled in this study. There were 8.6% of vernakalant subjects and 13.8% of amiodarone subjects receiving rhythm control medications within 7 days prior to the first dose of the study drug. Rate control medications were being used by 64.2% of subjects prior to dosing, with beta blockers being the most common (59.9%); however, the use of beta blockers was numerically lower in the vernakalant group (54.3%) compared to the

[24] In the vernakalant group, 2 subjects were excluded due to dosing deviations for the second infusion and another subject was excluded because the volume of the first infusion was unknown. In the amiodarone group, 3 subjects were excluded because of receiving an antiarrhythmic agent within 24 hours prior to dosing, a randomization error, and unknown dosing information.

amiodarone group (65.5%). Medications used prior to the first dose of the study drug and continued after were generally similar between treatment groups and antithrombotic agents (149/232, 64.2%) were used most commonly in both groups.

Primary efficacy results

There was a statistically significantly (CMH, p<0.0001) greater proportion of subjects converting from AF to SR within the first 90 min in the vernakalant group (60/116, 51.7%) compared to amiodarone (6/116, 5.2%) (Table 15). Patients treated with vernakalant were 10 times more likely to convert to SR within 90 min as compared to subjects treated with amiodarone (OR= 10.0, 95% CI, 4.5 to 22.2). The results in the per-protocol population were consistent with the primary analysis (59/113, 52.2% versus 6/113, 5.3%, p<0.0001).

Table 15: Treatment induced conversion of AF to sinus rhythm within 90 min

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

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

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

c Relative risk in favor of conversion for vernakalant.

Secondary efficacy results

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

A statistically significantly (CMH p-value = 0.0012), greater proportion of subjects reported no AF symptoms at 90 min in the vernakalant group (62/116, 53.4%) compared to amiodarone (38/116, 32.8%) demonstrating that subjects treated with vernakalant were 1.63 times more likely to be free of their AF symptoms at 90 min compared to subjects treated with amiodarone (95% CI, 1.20 to 2.23). There was no evidence of heterogeneity across countries (Breslow-Day p-value = 0.2521).

Treatment with vernakalant resulted in a statistically significantly greater improvement in a subject's perception of their state of health at Hour 2 compared to amiodarone (mean adjusted change of 10.9 versus 5.6 points, p=0.0006).

Exploratory efficacy results

A significantly greater proportion of subjects in the vernakalant group converted to SR within the first 4 h post dose compared to the amiodarone group (54.4% versus 22.6%, adjusted log rank p-value <0.0001). In the vernakalant group, 25% of subjects converted to SR by Minute 11 and 50% converted by Minute 50, as compared to the amiodarone group in which <25% of subjects had converted to SR by 4 hours post dose. However, by Day 7, a non-significantly (p=0.9674) greater proportion of amiodarone treated patients (85.3%, 99/116) were free of AF symptoms compared to vernakalant treated patients (75.9%, 88/116).

The most frequently reported AF symptoms at entry were palpitations, irregular pulse, rapid heartbeat, fatigue, shortness of breath, dizziness and chest tightness/pain. The proportion of subjects reporting these symptoms at 90 min and at 7 days was reduced in both treatment groups and subjects were more likely to be free of symptoms at 90 min if they converted to SR.

In subjects receiving vernakalant who converted to SR within 90 min (N=60), sinus rhythm was maintained through 4 hours for 98.3% of subjects, and at Day 7, 91.7% of vernakalant subjects remained in SR without evidence of AF relapse.[25]

Evaluator's comments

A significantly greater proportion of vernakalant treated patients converted to SR within 90 min compared to amiodarone (52% versus 5%). However this should be interpreted with caution as amiodarone is a slower acting drug and it was administered for 120 min while the primary endpoint was within 90 min. This study showed that vernakalant IV was significantly more effective than amiodarone IV in providing rapid conversion to sinus rhythm within the first 90 min of initiating therapy in patients with AF duration (>3 hours to <48 hours).

Supportive studies

ACT-IV

The main objective of the Phase III, open label, multinational study 05-7-012 (ACT-IV) was to provide additional safety data in 236 patients with AF. In the short duration (>3 h to ≤ 7 days) AF group, the mean duration of AF was 35.4 hours. In the long duration (8 days to ≤ 45 days) group, the mean duration was 559.0 hours. The baseline demographics were similar in the short and long duration AF subgroups and the short duration AF group was generally representative of the target patient population. A majority of patients in both AF duration groups reported a history of AF (86.8% and 84.1% in the short and long duration AF groups, respectively); other common medical conditions were hypertension (44%), hyperlipidaemia (32%) and diabetes (13%). Over half of the patients were treated with beta blockers in the 7 day period prior to the start of the first vernakalant infusion; the proportion of patients who received a medication during this period was larger in the long duration AF group compared to the short duration AF group for all medications except calcium channel blockers and class I antiarrhythmics. The most common medications started prior to the study drug administration and continuing during the study were warfarin (28.1% and 58% in the short and long duration AF groups, respectively), metoprolol and diltiazem. Other medications administered to >10% of patients were

[25] The relapse of AF to hour 4 was defined as AF >30 seconds on Holter or AF on two 12-lead ECGs at least 30 seconds apart. The absence of AF relapse to Day 7 was calculated two ways: (1) based on continuous monitoring to hour 4 (as described previously) and the absence of AF on the Day 7 ECG; (2) based on continuous monitoring to hour 4 (as described previously), the absence of AF on the Day 7 ECG, and no AEs of AF/AFL up to Day 7. The absence of AF relapse to Day 30 was based on the absence of AEs of AF/AFL up to Day 30.

acetylsalicylic acid, enalapril and simvastatin**.** The infusion of Dose1 was completed for 98.3% (232/236) of patients. Four patients (2 in each AF duration group) had the infusion of Dose 1 prematurely discontinued for protocol defined dose stopping criteria. A total 85/167 (50.9%, 95% CI: 43.3, 58.5) patients with AF duration >3 h to ≤7 days converted to sinus rhythm within 90 min after the start of the first vernakalant infusion and the median time to conversion was 62.5 min (95% CI: 32.0 to 472.0) (Table 16).

Table 16: Descriptive statistics of time to first treatment induced conversion of AF to SR within 90 min

Parameter	AF Duration		
	>3 Hours - ≤ 7 Days	8 Days - ≤ 45 Days	>3 Hours - ≤ 45 Days
Time to Conversion (Minutes)			
N	85	8	93
Mean	18.6	37.5	20.2
SD	15.72	27.64	17.67
Minimum	3	3	3
Median	14.0	41.5	14.0
Maximum	87	79	87

Patient base: full analysis/safety set (all registered patients who received any amount of study drug)

Treatment-induced conversion from AF to sinus rhythm was determined by Holter monitor results and/or 12 lead ECG.

In the overall AF population, 93/236 (39.4%, 95% CI: 33.2, 45.6) of patients converted to sinus rhythm within 90 min after the start of the first vernakalant infusion, while only 8/69 (11.6%, 95% CI: 4, 19.1) patients with long duration AF converted to sinus rhythm within 90 min after the start of the first vernakalant infusion. In the 85 patients with AF duration > 3 h to ≤ 7 days who converted to sinus rhythm within 90 min after the first exposure to vernakalant, only 1 patient out of those with available data was not in sinus rhythm at 8 h and 24 h and 4 of 58 patients with available data were not in sinus rhythm at Day 7. No patients required electrical cardioversion within the first 90 min. However, electrical cardioversion was attempted on 96 patients within the first 24 h, (55/167, 32.9% in short duration AF and 41/69, 59.4% in long duration AF) and 81 were successfully converted. The rate of successful conversion was higher in the short duration AF subgroup (92.7%, 51/55) than in the long duration AF subgroup (73.2%, 30/41).

Scene 2 (1235-0703B)

A Phase II/III, multicentre, randomised, double blind, placebo controlled study involving 60 adult patients with atrial flutter (AFL). The study included patients with typical AFL based on the following criteria: AFL with a regular atrial rate of 220-320 bpm with a typical sawtooth pattern in leads II, III, and aVF. Most of the other inclusion and exclusion criteria were similar to the ones described for the pivotal Phase III studies. The two treatment groups showed similar baseline demographics and were similar in terms of duration of AFL clinical symptoms (214 hours in each group) and presence of pacemaker (13.3% and 10.3% in placebo and vernakalant groups, respectively). Diagnoses of atrial flutter for the purpose of inclusion in this study were made by the investigator at the site. A *post hoc* diagnosis of baseline rhythm was made by the CEC and showed that a slightly higher proportion of vernakalant subjects (34/39, 87.2%) had confirmed diagnoses of AFL at baseline compared to placebo subjects (11/15, 73.3%). The presenting AFL clinical symptoms were similar in character and occurrence rates in the two treatment groups at both screening and baseline assessment periods. The categories of drugs used and the incidence of use prior to and continued use during the study varied between the two treatment groups. The most frequently used concomitant medications overall were vitamin K antagonists (16/39, 41% vernakalant subjects; 11/15, 73.3% placebo subjects). The most frequently administered medications after the first infusion in both groups (53.3% placebo subjects and 51.3% vernakalant subjects) were in the "other general anaesthetics" category, which consisted of sedatives administered prior to electrical cardioversion.

All subjects in both treatment groups received the complete Dose 1. Thirty five of the 39 subjects in the vernakalant group who received Dose 1, were eligible to receive Dose 2. With the exception of a single vernakalant subject, all subjects in both groups that started to receive Dose 2 completed the dose.

Only one vernakalant patient (1/39, 2.6%) converted to sinus rhythm within 90 min and met the primary efficacy endpoint. However, it is important to note that even this patient was diagnosed as having AF by the CEC at the screening and all 3 baseline ECGs. No placebo subjects met this primary endpoint. Although vernakalant treated patients showed a shorter time to first treatment induced conversion of AFL to sinus rhythm compared to placebo treated patients, the difference was not statistically or clinically relevant (Table 17).

Table 17: Summary of time to first treatment induced conversion of AFL to SR

Treatment Groups	25th Percentile (Minutes) †	50th Percentile (Minutes) †	75th Percentile (Minutes) †	95% CI (Minutes)	P-value‡
Placebo (N = 15)	>1440	>1440	>1440	>1440 - >1440	0.449
RSD1235 (N = 39)	588.6	>1440	>1440	>1425 - >1440	

Subject base: all randomized subjects who received any amount of study drug (full analysis/safety set).
Conversion was defined as conversion of AFL to sinus rhythm for a minimum duration of one minute as determined/corroborated by the Clinical Events Committee from Holter data and/or 12-lead ECG data.
CI: Confidence Interval
† Method: Simon and Lee, Cancer Treatment Report 66:37-42, 1982.
‡ P-value from log-rank test.

A significantly reduced mean absolute ventricular response rate that occurred within 50 min of receiving the study drug was observed in vernakalant subjects (-8.2 bpm) compared with placebo subjects (-0.2 bpm) ($p<0.05$). There was no significant change from baseline in the incidence of AFL symptoms in either vernakalant or placebo groups. No subjects required electrical cardioversion within the first 90 min. Within the first 24 hours, cardioversion was attempted in similar proportions of subjects in both treatment groups (9/15, 60.0% placebo subjects; 21/39, 53.8% vernakalant subjects). Of these subjects, all (9/9) placebo subjects and 19/21 (90.5%) vernakalant subjects were successfully cardioverted. The median number of shocks was 1 for both treatment groups, while the median value of joules required for successful cardioversion varied (100 joules, placebo; 200 joules, vernakalant) between treatment groups.

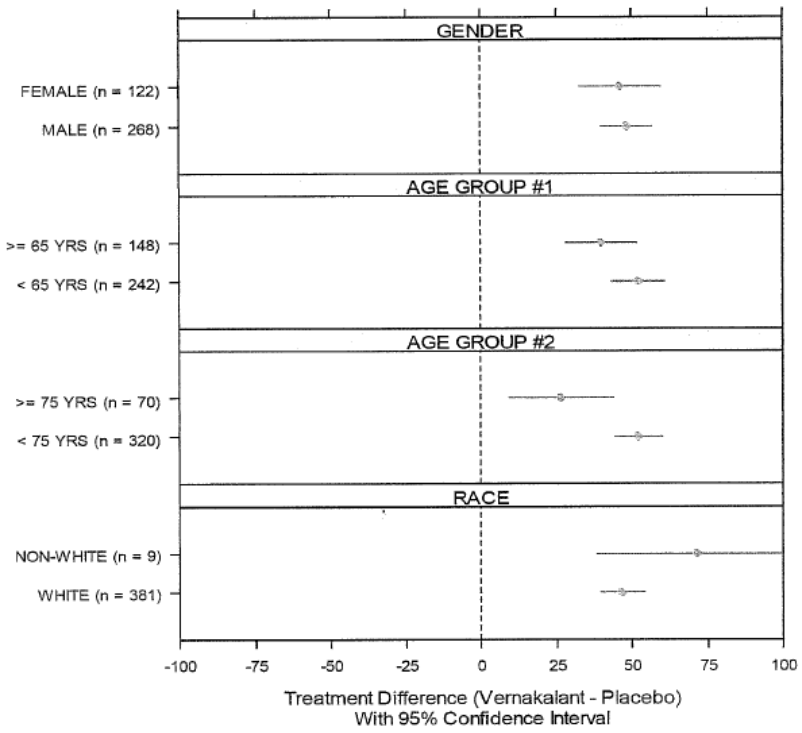
Clinical studies in special populations

Subpopulation analyses have been performed using pooled data from the ACT I/III pivotal studies. Efficacy comparisons are presented for subpopulations based on age (< 65, ≥ 65 and < 75, ≥ 75), sex, use of rate and rhythm control medications, and medical history; all subgroup analyses were only conducted for the proposed cohort of patients with short-duration AF.

Effect of sex, age, race and region

There was no difference in response to vernakalant injection based on sex. Conversion rates were significantly higher in the vernakalant group compared with placebo in both male and female patients (Figure 4). The treatment difference (vernakalant placebo) in the rate of conversion of AF to sinus rhythm for the short duration AF cohort was 46.6% in White patients and 71.4% in non-White patients, although this should be interpreted with caution due to the small number of non-White patients (n=9 in short duration cohort).

Figure 4: Treatment difference (vernakalant minus placebo) in conversion of AF to SR by sex, age and race in the short duration cohort



In age analyses for patients <75 years and ≥75 years, the treatment difference (vernakalant placebo) in the short duration cohort was 52.1% versus 26.4%, respectively (treatment by age group interaction p = 0.0538). Although conversion rates were significantly higher in the vernakalant group compared with placebo in both age groups, there was a definite trend suggesting reduced efficacy in patients aged >75 years.

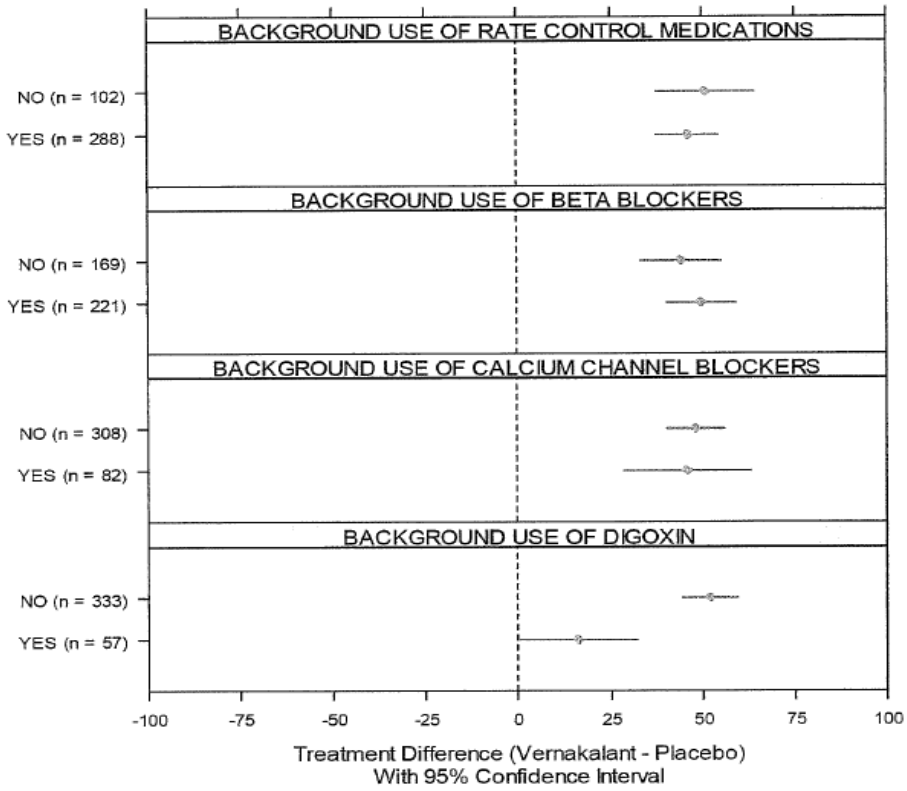
There were no significant differences in response to vernakalant injection by region; the treatment difference (vernakalant placebo) in the rate of conversion of AF to sinus rhythm in the short duration cohort was 43.0% in Europe versus 52.8% in non-European countries.

Effect of rate control medications

Rate control medications included beta blockers calcium channel blockers and digoxin.[26] The treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort for use versus non-use of rate control medications was 46% versus 50.9% (Figure 5). The treatment difference for use versus non-use of different classes of rate control medications was 49.8% versus 44.1% for beta blockers, 45.8% versus 48.0% for calcium channel blockers, and 16.3% versus 51.9% for digoxin. Conversion rates were significantly higher in the vernakalant group compared with placebo for all medication categories, with the exception of use of digoxin. There was a trend towards decreased efficacy in patients on concomitant digoxin treatment, although this trend was not statistically significant and was limited by small numbers of patients receiving digoxin.

[26] Specific medications in each category consisted of the following: Beta Blockers: acebutolol, atenolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, propranolol, nadolol, nebivolol, pindolol, betaxolol, tenoretic; Calcium Channel Blockers: (diltiazem, verapamil, udramil Digoxin: digoxin, digitalis.

Figure 5: Treatment induced conversion of AF to SR by use of rate control medication in the short duration cohort



Effect of rhythm control medications

Rhythm control medications consisted of Class I and Class III antiarrhythmics.[27] Background use was defined as taken within the last 7 days prior to the start of the first dose. There were no significant differences in response to vernakalant injection in patients taking rhythm control medications at baseline compared to those not taking rhythm control medications in the short-duration cohort or overall population (treatment difference for use versus non-use of rhythm control drugs was 43.1% versus 49%); the treatment difference for use versus non-use was 20.0% versus 50.7% for Class I antiarrhythmics and 55.8% versus 45.3% for Class III antiarrhythmics. Conversion rates were significantly higher in the vernakalant group compared with placebo for all medications categories. Although there was a trend towards decreased efficacy in patients with background use of Class I antiarrhythmics that were treated with vernakalant, the trend was not statistically significant (p-value for interaction = 0.9680 from a logistic regression model).

Effects of CYP2D6 inhibitors, CYP2D6 substrates, QT prolonging medications and CYP2D6 genotype

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. The treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort was 44.7% versus 48.1% for use versus non-use of CYP2D6 inhibitors, 42.0% versus 55.9% for use versus non-use of CYP2D6 substrates, and 44.0% versus 51.0% for use versus non-use of QT prolonging medications. Conversion rates were significantly higher in the vernakalant group

[27] Specific medications in each class were: Class I antiarrhythmics: procainamide, propafenone, disopyramide, flecainide, quinidine; Class III antiarrhythmics: amiodarone, ibutilide, dofetilide, sotalol.

compared with placebo for all categories. There were no significant differences in response to vernakalant injection by CYP2D6 genotype; the treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort was 41.8% in extensive metabolisers versus 33.3% in poor metabolisers.

Medical history

History of various medical conditions at baseline did not appear to alter the response to vernakalant injection, with the exception of congestive heart failure. The treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort for history versus no history of the medical condition was 26.9% versus 50.0% for CHF, 41.2% versus 52.1% for hypertension, 52.9% versus 47.0% for myocardial infarction, 48.1% versus 47.1% for ischaemic heart disease, 36.4% versus 48.5% for valvular heart disease, and 36.8% versus 52.0% for structural heart disease. Conversion rates were significantly higher in the vernakalant group compared with placebo for all of these conditions except a trend suggesting reduced efficacy in patients with history of CHF. However, interpretation of this was limited by very few patients with history of CHF compared to those without a history of CHF (42 versus 348). The ACT II study represents an enriched population in terms of underlying medical conditions, with all patients having a history of structural heart disease and 80.1% with a history of ischaemic heart disease. Efficacy in this patient population was similar to that in the other ACT studies.

LVEF, left atrial diastolic size

A *post hoc* analysis was performed to investigate the relationship between efficacy of vernakalant and left ventricular dysfunction. Patients from ACT II, ACT III and ACT IV in the short duration AF cohort with information on left ventricular ejection fraction (LVEF) function were included in this analysis. Ejection fraction 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 prespecified. The percentage of patients converting from AF to sinus rhythm was similar for patients with normal LVEF function and mild LVEF dysfunction.[28] Few patients had either moderate or severe LVEF dysfunction.

An additional *post hoc* analysis was performed to investigate the relationship between efficacy of vernakalant and left atrial size. Patients from ACT II, ACT III and ACT IV in the short-duration AF cohort with information on left atrial diastolic dimension (LADD) were included in this analysis. Data on LADD by echocardiography was provided by the local cardiologists that performed and read the studies. The efficacy of vernakalant in converting AF to sinus rhythm did not appear to be influenced by LADD less than 50 mm. Larger LADD were associated with diminished vernakalant efficacy.

Effect of renal and hepatic impairment

The difference (for patients treated with vernakalant compared with placebo) for the rate of conversion of AF to sinus rhythm in the short duration cohort was lower in patients with renal impairment (34.1%) compared to patients with normal renal function (55.5%). However, treatment difference was slightly lower in patients with abnormal hepatic function (36.8%) compared to patients with normal hepatic function (47.9%). Furthermore, patients with severe renal/hepatic impairment were excluded from all Phase III studies.

[28] Left ventricular function was classified based on ejection fraction obtained from noninvasive measures as reported by local cardiologists. An ejection fraction of ≥ 50% was classified as normal; 36% to 49%, mild dysfunction; 26% to 35%, moderate dysfunction; ≤ 25%, severe dysfunction.

Atrial flutter

The Scene 2 study (1235-0703B) failed to demonstrate efficacy of vernakalant injection in converting typical AFL to sinus rhythm. Subsequently the CEC determined that this patient was not in AFL at baseline but was in AF. ACT III included 23 patients (14 vernakalant; 9 placebo) with AFL of which only 1 vernakalant patient (0 placebo) converted from AFL to sinus rhythm after receiving study drug. Based on the results of these two studies, the sponsor was not pursuing an indication for conversion of AFL.

Analysis performed across trials (pooled analysis and metanalysis)

The Phase III pivotal studies, ACT I and ACT III were similar in design, patient characteristics. In a pooled analysis of the efficacy results from these 2 studies, vernakalant injection 3.0 mg/kg, followed by 2.0 mg/kg if needed, induced conversion from short duration AF to sinus rhythm within 90 min of first exposure to the study drug in a statistically significant and clinically meaningful greater proportion of patients compared with placebo (118/231, 51.1% versus 6/159, 4%) (Table 18). The median time to conversion was 10 min and 31.5 min in the vernakalant and placebo groups, respectively. 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% (n=132/231) of the primary AF population received a second dose (7 patients did not convert with the first dose and withdrew or were discontinued prior to the second dose). Of those vernakalant patients in the short duration AF cohort who did not convert to sinus rhythm after the first dose and thus received a second dose; only 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.

A *post hoc* analysis was also performed to determine the rate of conversion from AF to sinus rhythm for patients with AF duration of less than 48 h. This analysis was limited to the ACT I study because that is the only study for which continuous data on AF duration was collected. The rate of conversion of AF to sinus rhythm for patients with AF duration <48 h was 61.2% in the vernakalant group compared to 4.9% in the placebo group, a difference of 56.2% that was both statistically and clinically significant. Furthermore, this difference was greater than 47% treatment difference in all patients with short duration AF (<7 days).

Post hoc analysis of sinus rhythm maintenance following conversion was evaluated at 2, 4, and 8 h, 24 h/discharge and 7 days after the first infusion. For the 118 patients in the short duration AF cohort who converted to sinus rhythm within 90 min following vernakalant injection, the life table estimate for maintenance of sinus rhythm at 24 h was 97.2% and at 7 days was 93.0%.

An analysis was performed on the time to first conversion of AF to sinus rhythm within the first 24 h after initiation of the study treatment, with the time censored at the time of first pharmacological antiarrhythmic intervention or first attempt at electrical cardioversion. The median time to conversion was 1.3 h in the vernakalant group and >24 h in the placebo group. Approximately 30% of placebo patients had converted by Hour 24.

At 90 min after the first exposure to the study drug, the incidence of AF symptoms was significantly lower in the vernakalant group than the placebo group for both the short duration cohort (50.2% vernakalant versus 73.0% placebo) and the overall population (53.1% vernakalant versus 71.6% placebo) ($p<0.0001$ for both comparisons).

Table 18: Conversion of AF to SR by cohort and for the overall population – ACT I/III pooled pivotal studies

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)

Definitions: Conversion, atrial fibrillation to sinus rhythm for a minimum 1-minute duration within 90 minutes of first exposure to study drug.

Patient Population: All patients who received any amount of study medication.

Note that since this analysis focuses on conversion to sinus rhythm, the figures in this Table under Overall Population and Long Duration may differ from the data presented earlier (e.g., [Table 2 and Table 12]) which focus on termination of atrial fibrillation.

a Difference in percentage of successful conversions between vernakalant and placebo groups; missing values counted as failed conversions.

b Mantel-Haenszel odds ratio favouring conversion for vernakalant versus placebo.

c Cochran-Mantel-Haenszel test.

d Exploratory analysis.

e Fisher's exact test.

Evaluator's overall comments on clinical efficacy

Overall, efficacy was evaluated in 4 controlled, well conducted studies involving 783 patients with recent onset AF (< 7 days). Three were placebo controlled, double blind studies (ACT I, ACT II, ACT III) and one was an active controlled study (AVRO). The pivotal studies ACT I and ACT III included patients with atrial arrhythmia (AFB or AFL) with duration of >3 h to <45 days and only 390/601 patients had AF duration of <7 days; these studies permitted background use of rate or rhythm control medications, facilitated recruitment of patients with recurrent AF as well as new onset AF. Study ACT-II included 161 post cardiac surgery patients who developed sustained AF for 3 to 72 h. The AVRO study included 232 patients who had symptomatic AF of 3 to 48 h duration. Overall, the 4 controlled Phase III studies included patients who most likely had 'persistent' or

'paroxysmal' AF.[29,30] None of the studies enrolled patients with permanent atrial fibrillation.

Patients with significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis or reversible causes of AF were excluded from all Phase III studies. Furthermore, subjects with AMI and advanced CHF (2 of the main causes of AFB) were excluded in all 4 Phase III studies with the exception of AMI in the ACT-II study. Hence, the population studied is not representative of the target patient population for vernakalant injection and findings cannot be extrapolated to all patients with short term AFB as suggested in the proposed indication.

Supportive evidence was provided by the Phase IIa CRAFT study, SCENE-2 and the Phase III open label safety study ACT-IV. Efficacy was consistent across all studies (Figure 6). The CRAFT and ACT II studies enrolled patients with a duration of AF of 3 to 72 h. The data shown for ACT I, ACT III and ACT IV are for patients AF duration of 3 h to ≤ 7 days. The ACT IV study was an open-label, safety study, but efficacy was assessed and found to be similar to that observed in ACT I and ACT III**.**

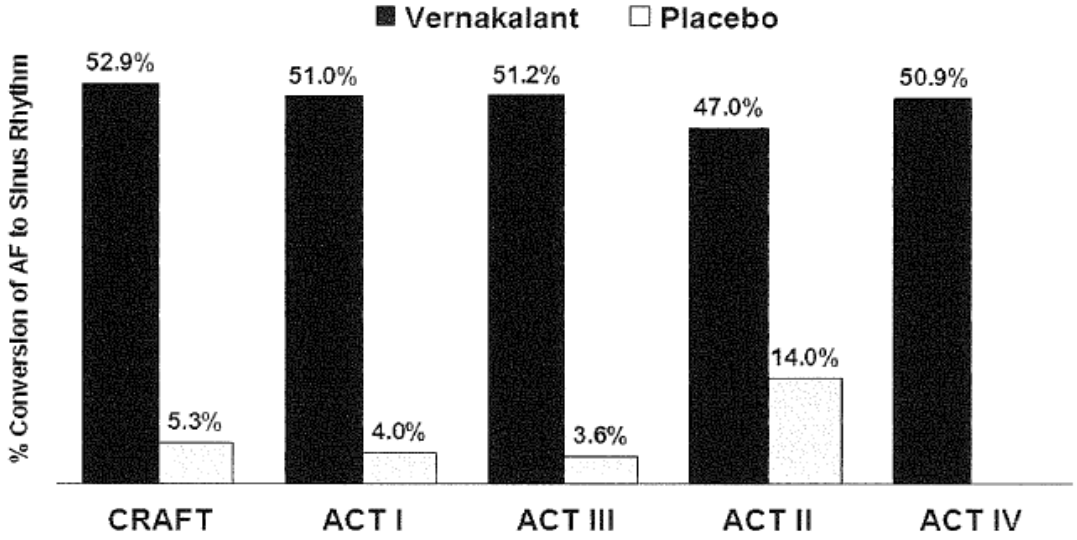
General efficacy conclusions for the proposed indication were derived from the primary AF population, consisting of those patients with recent onset AF (3 h to 7 days) in the randomised, placebo controlled ACT I and ACT III pivotal trials (N=390 total patients, consisting of 231 vernakalant treated and 159 placebo treated patients). Overall, conversion to SR within 90minutes post dose was statistically and clinically significantly greater in vernakalant treated patients compared with placebo (51% versus 4%, p<0.001). A majority (40%) of the patients converted to SR after the first vernakalant dose (3 mg/kg); conversion rate in patients receiving the second dose of vernakalant (2 mg/kg) was only 20%. [31]The median time to conversion to SR was only 10 minutes suggesting vernakalant acted rapidly.

[29] Persistent atrial fibrillation is characterized by an irregular rhythm that lasts for longer than 48 hours. This type of atrial fibrillation will not return to a normal sinus rhythm on its own, but will in response to certain types of treatment.

[30] Paroxysmal atrial fibrillation, the irregular rhythm occurs periodically. The human heart returns to the normal sinus rhythm on its own -- in a few minutes, hours, or days. People who have this type of atrial fibrillation may have episodes only a few times a year or every day. When these episodes begin and end is usually unpredictable, which can be very unsettling. About 1 in 4 people with paroxysmal atrial fibrillation eventually develop the permanent form of the condition.

[31] Sponsor comment: "The study was designed to demonstrate efficacy whether that be after 1 or 2 dose and not to compare efficacy between 1 and 2 doses."

Figure 6: Conversion rates of short duration AF across studies



CRAFT: dosing was 2 mg/kg + 3 mg/kg; data represents % in sinus rhythm at 1 hour post dosing. Atrial fibrillation duration >3 to 72 hours.

ACT I, III and IV: atrial fibrillation >3 hours to ≤ 7 days; ACT IV: a placebo group was not included in this open-label study; ACT II: atrial fibrillation post coronary artery bypass graft and/or valvular surgery; atrial fibrillation duration >3 to <72 hours.

Conclusions regarding efficacy in post cardiac surgery patients were deduced specifically from patients with AF (of 3 to 72 h duration) in the randomised, placebo controlled ACT II pivotal trial (N=107 vernakalant treated and 54 placebo treated patients). The specificity of the ACT II study design enabled efficacy (and safety) assessments of vernakalant injection in patients with new onset AF after cardiac surgery, a subset of the overall AF patient population not included in the ACT I, ACT III or AVRO studies. Atrial arrhythmias are common following cardiac surgery and are estimated to occur in 10% to 65% of patients, depending on definitions and methods of surveillance (Fuster et al, 2006).[15] In this study, a statistically significantly greater proportion of vernakalant treated patients showed conversion to SR (for a minimum duration of 1 min within 90 min) compared with placebo (45% versus 15%, p=0.0002). However, this did not translate into a statistically significant reduction in the incidence of AF symptoms at 90 minutes (vernakalant versus placebo: 66% versus 80%, p=0.099).

Vernakalant (3+2 mg/kg) injection had superior efficacy when compared directly to amiodarone (60 min infusion of 5 mg/kg followed by maintenance infusion of 50 mg over next 60 min) injection for the rapid conversion of recent onset AF (3 to 48 h duration) to sinus rhythm within 90 min (51.7% versus 5.2%, p <0.0001). These results should be interpreted with caution as the primary endpoint was the conversion rate within 90 min while patients randomised to amiodarone were still receiving the drug (amiodarone patients received infusion for up to 2 h) and amiodarone is known to be a slowly acting drug. However, this study did show that vernakalant ***was significantly more effective than amiodarone IV in providing rapid conversion to sinus rhythm within the first 90 min of initiating therapy in patients with AF duration <48 h.*** Additionally, vernakalant was associated with a higher rate of symptom relief and a great improvement in a subject's perception in their state of health compared to amiodarone.

The controlled Phase III studies were powered to detect statistically significant difference in primary endpoint of conversion to SR within 90 min post dose based on assumptions of estimated conversion rate of 25% in placebo patients versus 50% in vernakalant patients (in the AVRO study, the estimated conversion rates were 35% and 58% in the amiodarone and vernakalant groups, respectively). Furthermore, the actual conversion rates observed in the placebo/amiodarone groups were much lower that the estimated rates which may

have confounded interpretation of statistical significance of the huge treatment difference observed in these studies. This is especially important in light of the fact that effect of vernakalant on clinically relevant endpoints such as incidence of complications, morbidity and mortality were not evaluated.

All the Phase III studies showed statistically significant reduction in AF symptoms at 90 min post dose although blinding could have been compromised in almost 25% of the patients who received vernakalant due to specific AEs such as sneezing and dysgeusia which were experienced only by patients receiving vernakalant.

Maintenance of SR up to 24 h post dose was not evaluated as a pre-specified efficacy endpoint. Sinus rhythm maintenance following conversion was evaluated at 2, 4, and 8 h, 24 h/discharge and 7 days after the first infusion. For the 118 patients in the short duration AF cohort (in pivotal studies ACT-I and ACT-III) who converted to sinus rhythm within 90 min following vernakalant injection, the life table estimate for maintenance of sinus rhythm at 24 h was 97.2% and at 7 days was 93.0%. In study ACT-II in post cardiac surgery patients, SR was likely to be maintained in the first 6 hours post dose in the vernakalant group (82-94%) compared to placebo (62%), although there was no difference between the vernakalant and placebo groups by 24 h (and at 7 days). In the ACT-II study in post cardiac surgery patients, no subjects required electrical cardioversion within first 90 min and electrical cardioversion was attempted at any time point in the study for only 6 placebo and 5 vernakalant patients (all 5 vernakalant subjects were successfully cardioverted. In the AVRO study, 91.7% of the vernakalant patients who converted to SR within 90 min were maintained in SR at 7 days and did not show AF relapse. Within first 24 h, 30-37% of the vernakalant treated patients underwent electrical cardioversion (compared to 58% of placebo and 57% of amiodarone patients).

Efficacy of vernakalant appeared to be reduced in patients aged >75 years and in those with a history of CHF. The treatment difference in the rate of conversion of AF to sinus rhythm in the short duration cohort for history versus no history of the medical condition was 26.9% versus 50.0% for CHF, 41.2% versus 52.1% for hypertension, 52.9% versus 47.0% for myocardial infarction, 48.1% versus 47.1% for ischemic heart disease, 36.4% versus 48.5% for valvular heart disease, and 36.8% versus 52.0% for structural heart disease. Conversion rates were significantly higher in the vernakalant group compared with placebo for all rate/ rhythm control medication categories, with the exception of reduced response in patients using digoxin and Class I antiarrhythmics.

Of the 783 patients (randomised and treated) with short duration AF (< 7 days) in the 4 Phase III controlled studies, all the patients (n=393) in studies ACT-II and AVRO had AF duration of < 3 days (as it was the inclusion criteria in these studies). Of the 390 patients with short duration AF (< 7 days) in studies ACT-I and ACT-II, data on numbers of patients with AF duration < 3 days was not available. A *post hoc* analysis of efficacy of vernakalant in patients with AF duration <48 h (in study ACT-I) showed significantly greater conversion rates with vernakalant compared with placebo with treatment difference (vernakalant-placebo) of 56% which was greater than the 47% treatment difference observed in all patients with AF duration < 7 days. Continuous data on AF duration was not collected in study ACT-III. There was no evidence to confirm efficacy of vernakalant in patients with AF duration > 3 days but < 7 days due to lack of data.

Vernakalant was effective in converting recent onset AFB (especially AF duration < 3 days) to SR. However, conversion to and maintenance of SR for only a short period of time (at least one min within 90 min post dose as defined for the primary efficacy analysis of all Phase III studies) warrants neither the symptomatic improvement of AFB nor the prevention of its complications (such as cerebrovascular accident). The effect of vernakalant on morbidity and mortality was not evaluated in any of the Phase III studies. Furthermore, conversion rate was higher and more significant after the first dose of vernakalant with patients four times less likely to convert to SR after the second dose.

Safety

Introduction

The overall safety evaluation for vernakalant injection incorporates data from one Phase II, one Phase II/III study, 4 placebo or active controlled Phase III studies and a Phase III uncontrolled safety study (Table 2). Safety was evaluated based on adverse events, clinical laboratory profiles, vital signs, physical exam, 24 hour Holter monitoring, telemetry monitoring, and 12 lead ECGs. In the ACT- I and ACT-III pivotal studies, blood pressure measurements and 12 lead ECGs were performed every 5 min for the first 50 min (the period in which maximum vernakalant plasma concentrations would occur) and at 1.5, 2, 4, 8 and 24 h and were interpreted by the investigators for immediate clinical management. In the ACT- II pivotal study, blood pressure recordings and 12 lead ECGs were performed at 10, 25, 35 and 50 min and 1.5, 2, 4, 6 and 24 h. In Phase III studies, ECGs were also recorded at the time of conversion to sinus rhythm, at discharge/24 h and at the follow up visit on Day 7 (except in ACT II, which had follow up within 14 days).

Telemetry was performed continuously from baseline until a minimum of 2 h post dose. Holter monitoring was performed from at least 30 min prior to randomisation until 24 h post dose. All 12 lead ECG recordings were sent to a central cardiology laboratory for rhythm interpretation and safety assessment by a cardiologist and for interval measurement by an analyst. All reviews and analyses of ECG and Holter data were conducted by qualified personnel blinded to treatment assignment. The chairperson of the Data Safety Monitoring Board (DSMB) reviewed Holter alerts for ongoing safety monitoring. For the purposes of assessment of ventricular arrhythmia risk the analysis focussed on adverse events, there was cardiologist review of 12 lead ECG and Holter data. The Holter and 12 lead ECG data were analysed to identify the incidence of ventricular events, bradycardia and AFL. ECG data from the CRAFT study was not included in the integrated analysis of ECG parameters because the CRAFT study differed from the Phase III studies in that it had a different dosing period and used different vernakalant doses.

Patient exposure

Safety data was evaluated in 3 datasets:

(1) Pooled data from “all patients” with AF or AFL in Phase II (CRAFT, Scene 2) and III studies [ACT I, ACT II, ACT III, ACT IV], who received any amount of study medication (773 vernakalant and 335 placebo patients),

(2) Patients in ACT II are included in the "All Patients Pool" (above), but also presented separately in additional subanalyses. The "ACT II Pool" consists of all patients in the ACT II study of new onset AF or AFL subsequent to cardiac surgery, who received any amount of study medication (107 vernakalant and 54 placebo patients), and

(3) Safety results of amiodarone controlled study AVRO (116 vernakalant and 116 amiodarone patients).

In the ‘all patients’ safety pool, 507 of the 773 vernakalant treated patients received the maximum proposed dose of 5 mg/kg (3+2 mg/kg), while 241 patients received only the first dose of vernakalant (3mg/kg) (Table 19). In study ACT-II, 69/107 vernakalant treated patients received the maximum dose of 5 mg/kg, while 38 patients received only the first dose of vernakalant (3 mg/kg). For the pooled population of all patients in Phase II and III studies, the majority of patients were male (68%) and White (96%), with a mean age of 63 (range 22-94) years. Approximately half the study population was European. The majority of patients in ACT II were also male (75%) and White (94%), and tended to be older than the all-patients population, with a mean age of 68 years.

Table 19: 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**

Patient Population: Patients who received any amount of vernakalant.

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

Demographic and baseline characteristics were generally similar between treatment groups for both the 'all-patients' population and the ACT II population. The patients enrolled were generally representative of the patients seen in clinical practice, with frequent cardiovascular comorbidities, including hypertension and structural heart disease and frequent use of rate control medication. Patients with reversible causes of AF, obstructive heart disease, Class IV heart failure or heart failure requiring intravenous inotrope therapy were excluded from the clinical studies. In all, there were 142 vernakalant patients and 70 placebo patients with CHF. Of the 68 patients for whom NYHA classification was 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.

In the amiodarone controlled study AVRO, a majority of the patients were male (63%), White (96%) with mean age of 63 years (15% were >75 years) and median duration of current AF episode of 18 hours (35% had > 3 episodes of previous AF). The patients in this study had significant comorbidities including hypertension (72%), structural heart disease (35%) and NYHA class I or II heart failure (20%).

Adverse events

The analysis of adverse events was performed for 4 time periods: all post dose, 0-2 h post dose, 2-24 h post dose and 0-24 h post dose. The study design limited treatment with antiarrhythmic medications or electrical cardioversion within the 2 h following study drug administration. These treatments were not allowed during the 0 to 2 h post dose period unless the investigator concluded it was necessary to restore sinus rhythm quickly, such as in cases of electrical or haemodynamic instability. Subsequent to the 2 h post dose time point, patients who had not converted from AF to sinus rhythm could receive additional antiarrhythmic medications or undergo electrical cardioversion at the discretion of the investigator. Due to its short half-life (about 3 h in extensive metabolisers and 5.5 h in poor metabolisers), levels of vernakalant would be negligible by 24 h post dose. Thus the time frames for adverse event analysis were chosen in an effort to distinguish AEs associated with vernakalant injection from those associated with follow up treatments.

AEs in the 'all patients' safety pool

An overview of AEs in the 'all patients' and ACT-II safety pools and each post dose time period suggested that majority of the AEs in the vernakalant treated patients occurred in the first 2 h post dose**;** furthermore, the difference between vernakalant and placebo groups is not as big in the ACT-II study, which was in patients who had undergone cardiac surgery (Table 20). The most frequent system organ classes (SOCs) of AEs included *Nervous System Disorders* (35.3%vernakalant, 14.9% placebo), *Cardiac Disorders* (33.1% vernakalant, 29.9% placebo), and *Respiratory, Thoracic and Mediastinal Disorders* (28.7% vernakalant, 7.5% placebo). Over half of the events under *Cardiac Disorders* were relapse

of AF (17.5% vernakalant, 18.2% placebo). The differences between the vernakalant and placebo groups were predominantly due to the common events that tend to occur after vernakalant treatment, including dysgeusia, paraesthesia, cough, sneezing, feeling hot, infusion site pain, nausea and vomiting, pruritus and hyperhidrosis. The majority of AEs were mild or moderate in severity. The proportion of patients experiencing severe AEs in the first 24 hours after treatment was 5.8% in the vernakalant group and 3.3% in the placebo group.

Table 20: Overview of treatment emergent AEs by population and post dose time period

Population Event	Postdose Time Period	Number (%) of Patients: Placebo n	Placebo (%)	Vernakalant n	Vernakalant (%)	Appendix Table
All Patients						
N		335		773		
Any AE	0 to 2 hours	59	(17.6)	420	(54.3)	(2.7.4.3.1.2.2)
	2 to 24 hours	84	(25.1)	192	(24.8)	(2.7.4.3.1.2.3)
	0 to 24 hours	126	(37.6)	501	(64.8)	(2.7.4.3.1.2.4)
	All postdose	197	(58.8)	577	(74.6)	(2.7.4.3.1.2.1)
Any related AE	0 to 2 hours	24	(7.2)	378	(48.9)	(2.7.4.3.3.2.2)
	2 to 24 hours	4	(1.2)	30	(3.9)	(2.7.4.3.3.2.3)
	0 to 24 hours	27	(8.1)	389	(50.3)	(2.7.4.3.3.2.4)
	All postdose	31	(9.3)	398	(51.5)	(2.7.4.3.3.2.1)
ACT II						
N		54		107		
Any AE	0 to 2 hours	8	(14.8)	29	(27.1)	(2.7.4.3.1.3.2)
	2 to 24 hours	11	(20.4)	21	(19.6)	(2.7.4.3.1.3.3)
	0 to 24 hours	17	(31.5)	41	(38.3)	(2.7.4.3.1.3.4)
	All postdose	24	(44.4)	61	(57.0)	(2.7.4.3.1.3.1)
Any related AE	0 to 2 hours	0		22	(20.6)	(2.7.4.3.3.3.2)
	2 to 24 hours	0		4	(3.7)	(2.7.4.3.3.3.3)
	0 to 24 hours	0		25	(23.4)	(2.7.4.3.3.3.4)
	All postdose	0		27	(25.2)	(2.7.4.3.3.3.1)

In the "all patients' pool, common AEs associated with vernakalant treatment during the first 2 h post dose were dysgeusia (vernakalant versus placebo= 20.3% versus 2.4%), paraesthesia (8.2% versus 0%), sneezing (15% versus 0%), hypotension (4.7% s 0%), nausea (5.2% versus 0%) and bradycardia (2.6% versus 0%); the incidence of these AEs reduced during the 2-24 h post dose period with not much difference between the vernakalant and placebo groups (Table 21).

Table 21: Common treatment emergent AEs (≥1% and at higher incidence in vernakalant than placebo) in the first 24 h post dose – all patients

	0 to 2 Hours, N (%)		2 to 24 Hours, N (%)	
System Organ Class Preferred Term	Placebo (N=335)	Vernakalant (N=773)	Placebo (N=335)	Vernakalant (N=773)
CARDIAC DISORDERS				
Atrial flutter	1 (0.3)	10 (1.3)	1 (0.3)	5 (0.6)
Atrioventricular block first degree	1 (0.3)	3 (0.4)	0	5 (0.6)
Bradycardia	1 (0.3)	20 (2.6)	6 (1.8)	6 (0.8)
Sinus bradycardia	0	5 (0.6)	5 (1.5)	8 (1.0)
Ventricular extrasystoles	0	4 (0.5)	3 (0.9)	5 (0.6)
GASTROINTESTINAL DISORDERS				
Diarrhoea	1 (0.3)	6 (0.8)	2 (0.6)	4 (0.5)
Dry mouth	0	9 (1.2)	0	0
Nausea	0	40 (5.2)	4 (1.2)	10 (1.3)
Vomiting	0	10 (1.3)	1 (0.3)	2 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	2 (0.6)	10 (1.3)	4 (1.2)	16 (2.1)
Feeling hot	2 (0.6)	23 (3.0)	0	0
Infusion site pain	0	17 (2.2)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Back pain	0	1 (0.3)	1 (0.3)	7 (0.9)
NERVOUS SYSTEM DISORDERS				
Dizziness	6 (1.8)	27 (3.5)	3 (0.9)	6 (0.8)
Dysgeusia	8 (2.4)	157 (20.3)	0	2 (0.3)
Headache	8 (2.4)	10 (1.3)	3 (0.9)	21 (2.7)
Hypoaesthesia	0	5 (0.6)	0	3 (0.4)
Paraesthesia	3 (0.9)	63 (8.2)	1 (0.3)	2 (0.3)
Paraesthesia oral	1 (0.3)	18 (2.3)	0	1 (0.1)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Cough	2 (0.6)	33 (4.3)	2 (0.6)	1
Dyspnoea	0	7 (0.9)	2 (0.6)	5 (0.6)
Nasal discomfort	0	19 (2.5)	0	0
Sneezing	0	116 (15.0)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	1 (0.3)	25 (3.2)	1 (0.3)	4 (0.5)
Pruritus	0	28 (3.6)	0	1 (0.1)
VASCULAR DISORDERS				
Hypotension	3 (0.9)	36 (4.7)	9 (2.7)	9 (1.2)

Patient Population: All patients in [CRAFT, Scene 2, ACT I, ACT III, ACT IV, and ACT II].

Common AEs that occur after treatment with vernakalant injection have a predictable time of onset, occur peri-infusionally and are transient (Table 22). The incidence of treatment related AEs was higher in the vernakalant group (50.3%) than the placebo group (8.1%), with the majority of the difference accounted for by dysgeusia, sneezing and paraesthesia. Related AEs typically began during or shortly after the infusion and were transient. Infusion site pain, dysgeusia, sneezing, oral paraesthesia, cough, paraesthesia and nasal discomfort tended to begin during the first infusion and resolved within 15 min. Other

events, such as nausea and hyperhidrosis, tended to begin within the first 40 min after the start of treatment (Table 23).

Table 22: Median time to onset and median duration of treatment emergent AEs occurring in ≥5% of patients receiving vernakalant injection in the first 24 h post dose – all patients

Preferred Term	Vernakalant Incidence		Median Time To Onset	Median Duration
	n	(%)	minutes	minutes
Dysgeusia	158	(20.4)	7.0	11.0
Sneezing	116	(15.0)	8.0	5.0
Paraesthesia	65	(8.4)	9.0	8.0
Nausea	50	(6.5)	35.0	16.0
Hypotension	45	(5.8)	34.0	20.0

Subject Population: All patients in [CRAFT, Scene 2, ACT I, ACT III, ACT IV, and ACT II].

Table 23: Median time to onset and median duration of related treatment emergent AEs occurring in ≥1% of patients receiving vernakalant injection in the first 24 h post dose – all patients

Preferred Term	Vernakalant Incidence		Median Time To Onset	Median Duration
	n	(%)	minutes	Minutes
Dysgeusia	155	(20.1)	7.0	11.0
Sneezing	113	(14.6)	8.0	5.0
Paraesthesia	60	(7.8)	9.0	8.0
Nausea	37	(4.8)	33.0	15.0
Hypotension	31	(4.0)	17.0	13.0
Pruritus	27	(3.5)	12.0	11.0
Cough	26	(3.4)	8.0	8.0
Hyperhidrosis	25	(3.2)	22.0	30.0
Dizziness	20	(2.6)	13.5	26.5
Feeling hot	20	(2.6)	11.0	12.0
Nasal discomfort	19	(2.5)	9.0	10.0
Infusion site pain	17	(2.2)	2.0	9.0
Paraesthesia oral	17	(2.2)	8.5	9.5
Bradycardia	14	(1.8)	14.5	13.0
Headache	12	(1.6)	64.5	225.0
Vomiting	11	(1.4)	38.0	10.0
Dry mouth	9	(1.2)	23.0	34.5
Atrial flutter	8	(1.0)	25.0	750.5
Fatigue	8	(1.0)	89.5	792.0

Subject Population: All patients in [CRAFT, Scene 2, ACT I, ACT III, ACT IV, and ACT II].

AEs in ACT-II study

In study ACT-II, common AEs occurring in post cardiac surgery patients were also peri-infusional and transient (Table 24). Nausea was the most frequent AE occurring in post cardiac surgery patients (5.6% vernakalant, 3.7% placebo). There was a much lower incidence of dysgeusia, sneezing and paraesthesia in these patients than in ACT I/ACT III pooled population. The incidence of related AEs in the first 24 h post dose was 23.4% in the vernakalant group, with 2 additional patients experiencing related AEs in the remainder of the study. No related AE occurred in the placebo group (Table 25). The related AEs were generally mild to moderate in intensity.

Table 24: Common treatment emergent AEs (occurring in ≥1% and at a higher incidence in vernakalant than placebo) in the first 24 h post dose – ACT II

System Organ Class Preferred Term	0 to 2 Hours, N (%)		2 to 24 Hours, N (%)	
	Placebo (N = 54)	Vernakalant (N = 107)	Placebo (N = 54)	Vernakalant (N = 107)
CARDIAC DISORDERS				
Atrial flutter	0	2 (1.9)	0	2 (1.9)
Atrioventricular block first degree	0	1 (0.9)	0	2 (1.9)
Bundle branch block left	0	2 (1.9)	0	0
GASTROINTESTINAL DISORDERS				
Nausea	0	5 (4.7)	2 (3.7)	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Feeling hot	0	3 (2.8)	0	0
Peripheral oedema	0	1 (0.9)	0	1 (0.9)
NERVOUS SYSTEM DISORDERS				
Dysgeusia	0	2 (1.9)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dyspnoea	0	0	0	2 (1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	2 (1.9)	0	1 (0.9)
VASCULAR DISORDERS				
Flushing	0	2 (1.9)	0	0

Patient Population: All patients in [ACT II].

Table 25: Related treatment emergent AEs (occurring in >1 vernakalant patients and at a higher incidence than placebo) in the first 24 h post dose – ACT II

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	2 (1.9)	0	0
Atrioventricular block first degree	0	1 (0.9)	0	2 (1.9)
Bundle branch block left	0	2 (1.9)	0	0
GASTROINTESTINAL DISORDERS				
Nausea	0	3 (2.8)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Feeling hot	0	2 (1.9)	0	0
NERVOUS SYSTEM DISORDERS				
Dysgeusia	0	2 (1.9)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	2 (1.9)	0	0
VASCULAR DISORDERS				
Flushing	0	2 (1.9)	0	0

Patient Population: All patients in [ACT II].

AEs in amiodarone-controlled study

In the amiodarone controlled AVRO study, the incidence of treatment emergent AEs was higher for the vernakalant group compared to the amiodarone group within each time period. Treatment emergent AEs that occurred in 3 or more subjects within a treatment group within 24 h post dose included dysgeusia, cough, dizziness, nausea, atrial fibrillation, sneezing and hypertension. Most of these events occurred at a higher

incidence in the vernakalant group compared to the amiodarone group. The exception was dizziness, which occurred in 3 subjects in each group. Additional treatment emergent AEs that occurred in more than one subject in the amiodarone group within 24 h post dose included insomnia and prolonged activated partial thromboplastin time. In the vernakalant group, most of the common AEs occurred within 2 h post dose (with the exception of AF and dizziness); in the amiodarone group, most of the common AEs occurred between 2 to 24 h post dose. The majority of all post dose AEs were of mild or moderate severity. Severe AEs were reported in 4 subjects (3.4%) in the vernakalant group (increased INR; stomach discomfort; pulmonary embolism; chronic obstructive pulmonary disease [COPD] and pulmonary embolism) and 3 subjects (2.6%) in the amiodarone group (atrial fibrillation, cardiac arrest, and pneumothorax).

The majority of treatment emergent AEs that were considered to be related to the study drug within 24 h post dose occurred in the vernakalant group, with dysgeusia being the most common; other common related AEs that occurred within 24 h post dose in two or more subjects in the vernakalant group were sneezing, cough, bradycardia, nausea, paraesthesia, pharyngolaryngeal pain and throat irritation. With the exception of one event of bradycardia, all of these events occurred within the first two hpost dose. There were two subjects in the amiodarone group who had AEs that were considered to be related to the study drug within 24 h post dose: cardiac arrest occurring within two h post dose and increased blood bilirubin occurring within 2 to 24 h post dose. All of the related treatment emergent AEs were of mild or moderate severity, with the exception of the event of cardiac arrest in the amiodarone group. The majority of the related treatment emergent AEs occurring in >2 subjects within 24 h post dose began during or shortly after the infusion of the study drug and were generally transient (Table 26). There were 5 subjects in the study who had related AEs occurring between 24 h post dose and 7 days; 3 in the vernakalant group (one subject had increased ALT and AST, and two subjects had abnormal blood bilirubin and hyperbilirubinemia) and 2 in the amiodarone group (increased AST).

Table 26: Summary of related treatment emergent AEs by time period

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

AMIO: amiodarone injection; VERI: vernakalant injection.
Within a system organ class, subjects may have experienced more than one adverse event.

Special AEs of interest

Based on the safety profile of other antiarrhythmic agents and following review of the safety data for vernakalant, certain adverse events of interest were identified (ventricular arrhythmia, hypotension, bradycardia and AFL).

Ventricular arrhythmia

Analysis of ventricular arrhythmia events was based on AEs (using selected preferred terms), from 12 lead ECG recordings and from Holter monitoring.

The majority of the ventricular arrhythmia events seen in the vernakalant and placebo groups were asymptomatic non-sustained (average 3-4 beats) ventricular tachycardia. Ventricular ectopics were observed in many of these patients prior to dosing, suggesting a background incidence of this event in this population. The incidence of any ventricular arrhythmia event in the 0-2 h time period was similar in the placebo group (3.2%, 10/315) and the vernakalant group (3.9%, 29/737). Due to lack of comprehensive Holter data, CRAFT was excluded from this analysis, although ventricular arrhythmia events were not higher in vernakalant treated CRAFT patients (4/36) compared to placebo (5/20).

In the first 2 h following start of the study drug infusion, clinically meaningful ventricular arrhythmia (that is, reported as a serious adverse event or requiring discontinuation of

vernakalant) was reported in 0.6% (5/773) of patients receiving vernakalant and in 0% in the placebo group. Of these 5 patients in whom an SAE of ventricular arrhythmia was reported, 3 had a history of CHF. One of the remaining non-CHF patients experienced an SAE of ventricular fibrillation following a nonsynchronised electrical cardioversion attempt. One patient in study ACT III developed ventricular fibrillation resulting in death within the first 2 h after receiving vernakalant injection.[32] Between 2 and 24 h post dose there were no further clinically meaningful ventricular arrhythmia events in the vernakalant group and 2 events in the placebo group (2/335; 0.6%). There were four events of torsades de pointes, 3 of these events (2 in vernakalant injection, 1 in placebo) occurred more than 24 h following study drug administration; one event of torsades de pointes occurred within the first 24 hours after vernakalant injection administration and was captured on Holter (0.13%, 1/773).[33]

Hypotension

Hypotension events were reported from AE data and vital signs. The overall incidence of hypotensive events, using both the AE database and vital sign records as sources, was not significantly different during the first two h after dosing in vernakalant treated patients (7.6 % [56/737]) compared to placebo (5.1% [16/315]; percent risk difference of 2.5%, 95% CI -0.6 to 5.6). However, the incidence of AEs consistent with hypotension during the first two hours after dosing was significantly greater in those who received vernakalant (5.4% [40/737]) when compared to placebo (1.0% [3/315]; percent risk difference of 4.5%, 95% CI 2.5 to 6.4). Of note, there was no significant difference between vernakalant treated patients (6.1% [45/737]) and placebo treated (5.1% [16/315]) in hypotensive events from vital sign records (SBP < 90 mmHg) during the first two hours after dosing (percent risk difference of 1.0%, 95% CI -2.0 to 4.0). Change from baseline BP measurements was also marked by increased variability during the first 2 h after vernakalant treatment compared to placebo. As a result, outliers with a greater degree of hypotension post dose (< 80 mmHg), although rare, 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 (including SAEs leading to discontinuation), although uncommon, were reported more frequently among vernakalant treated patients than with placebo (9 vernakalant, 1.2%; 1 placebo, 0.3%). These SAEs generally occurred during or within 15 min of the end of a vernakalant infusion and resolved without sequelae. Hypotension tended to be transient and typically responded to discontinuation of vernakalant, infusion of saline, and/or Trendelenburg position and rarely required pharmacological intervention. The median duration of the hypotension was 20 min (ranged from 2 min to 2 h 16 min). Not all patients required treatment and only two patients received pharmacological support for blood pressure.

Despite the association of vernakalant with increased variability in BP changes from baseline, no AEs of hypertension or BP measurements of > 210 mmHg were observed in vernakalant treated patients during or within 2 h of infusion.

According to the logistic regression analysis performed across the entire Phase III population (of both placebo and vernakalant treated patients), 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, independent of drug treatment. Other factors correlating to an increased risk of hypotension (defined as an SBP measurement < 90 mmHg), although to a lesser extent than CHF and low starting SBP, were AFL and concomitant therapy with digoxin or

[32] Sponsor comment: "Patient with severe aortic stenosis and going ACS."

[33] Sponsor comment: "Immediately following ibutilide infusion."

furosemide. Additionally, an increased risk of hypotension was detected at vernakalant plasma levels of 4000 ng/mL [VERI-Pop-PK-PD]; the C_{max} following the second dose of vernakalant (2 mg/kg), 15 min after the 3 mg/kg dose, was 4.3 ug/mL, suggesting that patients requiring the second dose of vernakalant were more likely to experience hypotension.

In CHF patients, 22 of 137 treated with vernakalant (16.1%) experienced a hypotension associated event in the first 2 h post dose, compared to 3/64 placebo patients (4.7%; percent risk difference of 11.4, 95% CI 3.3 to 19.4). In the CHF subgroup the higher incidence of hypotension was driven by both differences in AE reporting (10.2% [14/137] vernakalant versus 0% placebo; percent risk difference of 10.2, 95% CI 5.1 to 15.3) as well as differences in vital signs (13.9% [19/137] vernakalant versus 4.7% [3/64] placebo; percent risk difference of 9.2, 95% CI 1.4 to 16.9). Hypotension was much less common in non-CHF patients; hypotension from vital signs was balanced between vernakalant and placebo treated non-CHF patients (4.3% [26/600] versus 5.2% [13/251], respectively; percent risk difference of -0.8, 95% CI -4.0 to 2.3), while the incidence of hypotension related AEs in non-CHF patients showed a difference between vernakalant and placebo (4.3% [26/600] versus 1.2% [3/251], respectively; percent risk difference of 3.1, 95% CI 1.0 to 5.3).

Bradycardia and other conduction disorders

Bradycardia events were reported from AE data and cardiologist review of 12 lead ECG/ Holter data.

The majority of the bradycardia events occurred between 0 and 2 h post dose were peri-infusional and resolved spontaneously. The incidence of bradycardia in the 0-2 h period (combining the AE database with the Holter and ECG database for heart rate < 40 bpm), was 3.8% (12/315) and 5.4% (40/737) for patients receiving placebo and vernakalant injection, respectively (diff=1.6, 95% CI -1.1 to 4.3). Of the patients who did not convert to sinus rhythm within the first 90 min post dose, the incidence of bradycardia in the first 2 h post dose was similar in placebo and vernakalant injection groups (4.0% [12/300] and 3.8% [18/469], respectively). However, the rate of bradycardia in patients who converted to SR within 90 min was higher in the vernakalant group (8.2%, 22/268) compared to placebo (0%) in the first 2 h post dose. In patients who did not convert within the first 90 min, but who subsequently underwent electrical cardioversion or other therapy after 2 h post dose, the rate of bradycardia events from 2-24 h post dose was 14.7% (44/300) in the placebo group and 7.7% (36/469) in the vernakalant group. The above results suggest that episodes of bradycardia were more likely to be associated with conversion to sinus rhythm. Clinically meaningful bradycardia (reported as a SAE or requiring discontinuation of vernakalant) was reported in 1.3% (10/773) of patients within the first 2 h after exposure to vernakalant and in 0% of 335 placebo patients. Four of the 10 episodes of clinically meaningful bradycardia during the first 2 h after initiation of vernakalant occurred at the time of termination of AF. Bradycardia generally responded to discontinuation of vernakalant and/or administration of atropine; two patients (one vernakalant and one placebo) required mechanical pacing. Between 2 and 24 h post dose, there were 3 additional clinically meaningful bradycardia events in the vernakalant group (0.4%, 3/773) and 2 events in the placebo group (0.6%, 2/335).

The incidence of cardiac conduction disorders was 2.5% (19/773) in the vernakalant group compared to 0.3% (1/335) in the placebo group. The events in vernakalant patients included first degree atrioventricular block (9 patients), complete atrioventricular block (4 patients), left bundle branch block left (4 patients), bundle branch block (1 patient), and right bundle branch block (1 patient). The incidence of complete atrioventricular block was low overall, occurring in 2 patients within 2 h of dosing, in 1 patient subsequent to electrical cardioversion, and in 2 patients at more than 24 h post dose. As with other bradyarrhythmia events, most of the events of complete heart block occurred at the time

of termination of AF; 3 events occurred upon termination of AF at 3 h 4 min, at 8 min and at 36 min post dose; 2 events of complete heart block occurred 4 days and 12 days post dose.

Atrial flutter

Within the first 2 h post dose, adjudicated cases of atrial flutter (from CEC assessment of 12 lead ECGs) were significantly more common after treatment with vernakalant (6.1% [45/737]) than with placebo (1.6% [5/315]; diff= 4.5%, 95% CI 2.3 to 6.7). The outcome of patients that developed atrial flutter on vernakalant was studied in the subgroup of vernakalant treated patients in the pooled ACT I/III population with AF at baseline (339 of the 737 Phase III patients). In the ACT I/III pooled population, 31 patients with only AF on pre-treatment ECGs developed atrial flutter within 90 min after receiving vernakalant (31/339, 9.1%). None of these AFL episodes was considered a serious adverse event. Of the 31 patients who developed atrial flutter, 10 (32.3%) converted to sinus rhythm within 90 min of treatment, 13 (41.9%) were electrically cardioverted to sinus rhythm within 24 h, 4 (12.9%) converted to sinus rhythm without additional antiarrhythmics, and 4 (12.9%) reverted to AF within 6 h and remained in AF at Hour 24. In the all-patients population, only one SAE of atrial flutter within the first 24 h post dose was reported. No patient with atrial flutter following treatment with vernakalant injection developed 1:1 atrioventricular conduction.

Deaths, Serious AEs

Across all studies for all follow up periods, 5 patients who received vernakalant injection died (3 patients in ACT I, 1 patient in ACT III, and 1 patient in ACT IV. Four of these deaths did not appear to be related to administration of vernakalant injection (one occurring on Day 2, one occurring on Day 8, and two occurring on Day 26). The fifth death, which was considered related to vernakalant injection, occurred in a patient who became hypotensive following administration of IV and oral metoprolol and again following administration of vernakalant injection. The hypotension led to ischaemia and a fatal ventricular arrhythmia. The patient was haemodynamically unstable with severe aortic stenosis and acute coronary syndrome and should have been excluded from the study, and should not have received the second injection of vernakalant based on the dose stopping criteria in the protocol.

In the AVRO study, there was 1 death in the vernakalant group which was due to COPD/ pulmonary embolism in a 68 year old male with many comorbidities[34]; there were no deaths in the amiodarone group.

There were no deaths in any of the placebo treated patients in the Phase II/ III studies or in any of the healthy volunteers who received vernakalant in the PK-PD studies.

In the 'all patients' safety pool, there was a trend towards a lower overall incidence of SAEs from the start of treatment to the 30 day follow up in the vernakalant group (90/773, 11.6%) compared to the placebo group (51/335, 15.2%) (diff= -3.6%, 95% CI -8.0% to 0.9%). However, SAEs were reported more frequently in the vernakalant group (19/773, 2.5%) than in the placebo group (2/235, 0.6%) within the first 2 h of dosing (percent risk difference 1.9%, 95% CI 0.5% to 3.2%). These events included 8 SAEs of hypotension in the vernakalant group (1.0% versus 0 in placebo; diff=1.0%, 95% CI 0.3% to 1.7%) and 11 of cardiac arrhythmia, including 5 of rate and rhythm disorders (0.6% versus 0 in placebo; diff=0.6%, 95% CI 0.1% to1.2%), 3 of supraventricular arrhythmias (0.4% versus 0 in placebo; diff=0.4%, 95% CI -0.1% to 0.8%), and 3 of ventricular arrhythmias and cardiac arrest (0.4% versus 0 in placebo; diff=0.4%, 95% CI -0.1% to 0.8%). Within the first 24 h post dose, the incidence of SAEs was similar in both groups (4.1% [32/773] vernakalant,

[34]Sponsor comment: "Death occurred on Day 24."

3.9% [13/335] placebo; diff= 0.3%, 95% CI -2.2% to 2.8%). The incidence of related SAEs was low overall, with a higher incidence in the vernakalant group (2.1%) than the placebo group (0.3%). Hypotension was the most frequent related SAE (8 vernakalant, 1.0%; 1 placebo, 0.3%) and the only one that occurred in the placebo group. Other related SAEs included bradycardia (3 patients, 0.4%), complete atrioventricular block (2 patients, 0.3%), and AFL, cardiogenic shock, sinus arrest, tachycardia, ventricular extrasystoles, ventricular fibrillation, pulmonary oedema, suffocation feeling, and aortic stenosis (occurring in 1 vernakalant patient each, 0.1%).

In the ACT-II study, the incidence of SAEs in the first 24 h post dose was low (1.9% vernakalant, 0% placebo). The only SAEs that occurred during this time were atrioventricular block complete and hypotension, both of which were related to treatment. The incidence of all post dose SAEs was similar between treatment groups (9.3% vernakalant, 11.1% placebo) and the only event that occurred in more than 1 vernakalant patient was haemothorax.

In the AVRO study, the incidence of SAEs (4.3% and 1.7% in vernakalant and amiodarone groups, respectively) and related SAEs (2.6% and 0.9%, respectively) within 24 h post dose was low but slightly higher in the vernakalant group. In both treatment groups, most of the SAEs that occurred were *Cardiac Disorders* and majority of them occurred in the first 2 h post dose (2.6% and 0.9%, respectively). The SAEs occurring within 24 h post dose that were considered by the investigator to be related to the study drug included angina pectoris, hypersensitivity, and ventricular tachycardia in the vernakalant group, and cardiac arrest in the amiodarone group.

Laboratory findings, vital signs

Laboratory changes

Lab parameters were evaluated in Safety Set which included results from studies ACT I, Scene 2, ACT III and ACT IV. Shifts to potentially clinically important high or low baseline chemistry values were small and similar for both placebo and vernakalant treatment groups at Hour 24 and follow up. Although CRAFT and ACT II were not included in this analysis because of differences in collection and processing procedures, no laboratory value outliers were observed with vernakalant treatment in either study. In the AVRO study, there were no clinically significant trends over time and no significant differences between vernakalant and amiodarone groups for any of the haematology, serum chemistry or urinanalysis lab parameters.

Effect on HR, ECG, cardioversion in 'all patients' safety pool

Baseline mean heart rate was similar in the placebo group (105.4 bpm) and the vernakalant group (103.7 bpm). Heart rate significantly decreased in vernakalant patients compared with placebo patients by Minute 5 (P=0.0021, ANCOVA) through Hour 4 (p<0.0001 through Hour 2, p=0.0026 at Hour 4, ANCOVA). The peak placebo subtracted difference of -15.0 bpm was recorded at Minute 90 and the reduction in HR was more obvious in vernakalant treated patients who had converted from AF to SR. In the population of all patients, 11 of 635 patients (1.7%) in the vernakalant group had a heart rate <40 bpm at any post dose ECG time point, compared to 4 patients (1.5%) in the placebo group. These shifts occurred throughout the assessment period and were not clustered around any particular time point.

Patients in the vernakalant group showed consistently greater increases in QRS interval compared with placebo; peak placebo subtracted increases in QRS interval from baseline of 7.7 ms (Minute 10) and 6.9 ms (Minute 35) were recorded. At Minute 90 and Hour 2, the placebo subtracted increases from baseline were 3.2 ms and 2.4 ms, respectively. Overall, 5.1% (34 / 704) patients in the vernakalant group with a QRS duration ≤140 ms at baseline shifted to a QRS duration >140 ms at any post dose time point. These shifts

occurred most frequently at the 10, 15 and 35 min time points. No placebo patients with QRS duration ≤140 ms at baseline had QRS duration >140 ms at any time point.

The baseline mean QTcB interval was similar in placebo patients (452.2 ms) and vernakalant patients (445.1 ms). The mean QTcB interval increased following administration of vernakalant and the change from baseline was statistically significant from Minute 5 to Minute 20 and then from Minute 35 to Minute 40. Peak placebo subtracted changes from baseline of +19.2 ms (Minute 10) and +11.7 ms (Minute 35) were recorded. Following these transient increases with vernakalant infusion, QTcB values resolved by 50 min post dose to the values seen at discharge in both treatment groups. Similar results were observed for change from baseline in QTcF interval. The peak proportion of vernakalant patients with QTcB or QTcF change from baseline ≥30 ms and ≥60 ms was observed at the end of the first infusion (Minute 10). From Hour 2 to follow up, there was no excess risk of QTcB or QTcF changes from baseline of ≥30 ms and ≥60 ms in the vernakalant group compared to the placebo groups. Shifts from baseline in QTcB interval and QTcF to >480 ms, >500 ms coincided with the end of the vernakalant infusions (and was greater than placebo). However, by Minute 50, the incidence of QTcF shifts to >480 and >500 ms were similar in vernakalant and placebo groups. The vernakalant group had no increased risk of QTcF shifts to >550 ms compared to the placebo group.

In order to further characterise what happens following conversion to sinus rhythm with both vernakalant and electrical cardioversion, the time to recovery of electrical systole postconversion (that is, the interval between the last QRS in AF and the first QRS of sinus rhythm) was compared between the different treatment groups in patients who were successfully converted to sinus rhythm. These data were prospectively collected during the conduct of ACT I and ACT III. The data was analysed by the Chair of the CEC, who was blinded to treatment group. Patients who converted to sinus rhythm within 2 h of vernakalant infusion resumed sinus rhythm after the last QRS in AF more quickly than placebo treated patients undergoing electrical cardioversion. Vernakalant did not appear to lengthen the pause following successful cardioversion with an electrical shock. Vernakalant did not suppress recovery of nodal function following termination of AF; a supraventricular QRS conducted from a sinus P wave was seen in twice as many patients converted with vernakalant infusion (70.9%) compared to placebo treated patients converted with an electrical shock (35.5%). The number of outliers showing sinus pauses ≥5 seconds was lower in the vernakalant group.

Electrical cardioversion for AF was not attempted within the first 90 min in the Phase II/III studies since this was the efficacy evaluation period. Within the first 24 h, 58.4% (184/315) of patients in the placebo group and 36.6% (270/737) of patients in the vernakalant group underwent electrical cardioversion. Vernakalant did not affect response to subsequent cardioversion. 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. The median number of shocks and the median number of joules required for successful cardioversion was the same in both treatment groups.

Effect on HR, ECG, cardioversion in the AVRO study

The mean heart rate decreased over time in both treatment groups; at 60 min post dose, the heart rate was reduced by 21.4 and 19.4 bpm in the vernakalant and amiodarone groups, respectively. At 60 min post dose, in subjects remaining in AF, the heart rate was reduced on average by 19.3 bpm in the amiodarone group, compared to 3.6 bpm in the vernakalant group. As expected, amiodarone showed a reduction in heart rate independent of conversion to SR. There were no subjects in either treatment group who had a heart rate <40 bpm at any post dose time point based on ECG interval data.

Vernakalant showed maximum mean increases in QRS interval of 7.4 ms, coinciding with the end of the second infusion, then decreasing over time. Amiodarone showed consistent increases of approximately 1-3 ms over time. Shifts in QRS duration from <140 ms to >140 ms at any post dose time point occurred in 4 vernakalant subjects and 4 amiodarone subjects. The majority of these subjects tended to stay above 140 ms for the duration of the study. There were no subjects in either treatment group who had a shift in QRS duration to >180 ms at any time point. In the vernakalant group, QTcB and QTcF were elevated at 10 min post dose and then decreased over time. In the amiodarone group, QTcB remained essentially unchanged while QTcF steadily increased over time. The incidence of shifts in QTcB to >450 and >480 ms was greater in the vernakalant group compared to the amiodarone group through 120 and 60 min post dose, respectively. Shifts in QTcB to >500 ms were consistently greater in the vernakalant group compared to the amiodarone group, although only a small number of subjects (<7 vernakalant subjects and <3 amiodarone subjects at any time) had a QTcB interval >500 ms. The incidence of shifts in QTcF to >450 ms was greater in the vernakalant group than in the amiodarone group through 60 min post dose; shifts in QTcF to >480 ms were sporadic in both groups. No subjects in either treatment group had a shift in QTcF to >500 ms or a shift in QTcB or QTcF to >550 ms. Vernakalant showed a relatively high incidence of change in QTcB or QTcF intervals of >30 ms and >60 ms from baseline during infusion periods, before decreasing rapidly post infusion, while amiodarone showed a slowly increasing number of shifts over time, with the incidence tending to be higher after 120 min post dose (QTcB) or after 35 min post dose (QTcF). Changes in QTcB or QTcF of >60 ms were observed in only a small number of subjects (<6 at any time).

Within the first 24 h, 30.2% of subjects in the vernakalant group and 56.9% of subjects in the amiodarone group underwent electrical cardioversion. Electrical cardioversion was successful in 91.4% of subjects in the vernakalant group and 95.5% of subjects in the amiodarone group. The median number of shocks and the median number of joules required for successful cardioversion was approximately the same in both treatment groups. Subjects who converted to SR within 2 h vernakalant infusion resumed SR after the last QRS in AF at a similar rate to subjects converting to SR on amiodarone. Vernakalant did not suppress recovery of nodal function following termination of AF; a supraventricular QRS conducted from a sinus P wave was seen in a similar number of subjects converted with vernakalant (81.0%) compared to amiodarone treated subjects (71.4%).

Safety in special populations

The incidence of adverse events of interest (ventricular arrhythmia, hypotension, bradycardia and AFL) in special patient groups and situations was evaluated by comparing the difference in event incidence between the vernakalant group and the placebo group in the 'all patients' safety pool. The AVRO clinical study report did not provide details on the effects of intrinsic and extrinsic factors on vernakalant safety.

Effects of intrinsic factors on vernakalant safety

Risk for ventricular arrhythmia, hypotension, bradycardia or AFL with vernakalant was not affected by age (< or >65years and < or >75 years), sex, history of hypertension and duration of AF. The number of non-White patients (30/773, 3.9%) and poor CYP2D6 metabolisers (2.2%, 17/773) was too small to allow a meaningful evaluation of safety by race/genotype.

Risk for bradycardia or AFL was similar in patients who had a history of congestive heart failure compared to those who did not. In patients with congestive heart failure who received vernakalant, there was an increased risk of hypotension and an increased risk of ventricular arrhythmia in the first 2 h post dose. These increased risks were not apparent

in the 2-24 h post dose period. Of the 10 vernakalant patients with CHF who had ventricular arrhythmia events in the first 2 h post dose, 3 patients had ventricular arrhythmia identified as an AE (the events were syncope, ventricular extrasystoles and ventricular fibrillation). Vernakalant was also associated with a slightly higher incidence of clinically meaningful events of hypotension and ventricular arrhythmia (defined as those involving serious adverse events or study drug discontinuation) in patients who had CHF compared with those who did not.

Risk for hypotension or AFL was similar in patients who had a history of valvular heart disease compared to those who did not. There was an increased risk of ventricular arrhythmia and a trend toward increased risk of bradycardia in the first 2 h post dose who received vernakalant who had a history of valvular heart disease. These differences were not apparent in the 2-24 h post dose period. Nine of 94 vernakalant patients (9.6%) with valvular heart disease experienced a ventricular arrhythmia event in the first 2 h post dose, compared to 0 of 49 placebo patients with valvular heart disease (diff= 9.6, 95% CI 3.6 to 15.5).

Vernakalant did not increase the risk for hypotension or bradycardia in patients who had a history of myocardial infarction compared to those who did not. However, patients with a history of myocardial infarction showed an increased risk of ventricular arrhythmia (vernakalant-placebo percent risk difference was 3.6 and 0.4 in patients with and without history of MI, respectively) and AFL (14.3 and 6.7, respectively).

Risk for bradycardia or AFL was similar in patients who had recent cardiac surgery (ACT-II study) compared to those who did not (studies ACT-I/III pool). There was an increased risk of ventricular arrhythmia in patients treated with vernakalant who had had cardiac surgery in the 0-2 h post dose period (percent risk difference was 3.7 and -0.7, respectively). There was also a trend toward increased risk of hypotension in patients who had had cardiac surgery and were treated with vernakalant (there were 6 cases of hypotension of which only 1 was an AE).

Risk of hypotension, bradycardia or AFL was similar in patients who had abnormal hepatic function compared to those with normal hepatic function. There was an increased risk of ventricular arrhythmia in the first 2 h post dose in vernakalant treated patients with abnormal hepatic function and moderate/ severe renal impairment.

Effects of extrinsic factors on vernakalant safety

Risk for ventricular arrhythmia, hypotension, bradycardia or AFL was similar in patients who were using background rate control medication compared to those who were not. There was an increased risk of hypotension in the first 2 h post dose in vernakalant treated patients who were using beta blockers (vernakalant versus placebo: 9.7% versus 3.9%) compared to those not taking beta blockers (4.8% versus 7.1%). Intake of calcium channel blockers or digoxin did not alter the risk of hypotension with vernakalant treatment. Risk for ventricular arrhythmia, hypotension, bradycardia or AFL was similar in patients who were using background rhythm control medications compared to those who were not. There was a trend toward increased risk of AFL during first 2 h post dose in vernakalant treated patients who were using Class I antiarrhythmics. Risk for ventricular arrhythmia, hypotension, bradycardia or AFL was similar in patients using CYP2D6 inhibitors or CYP2D6 substrates compared to those who were not. Risk for hypotension, bradycardia or AFL was similar in patients who were using QT-prolonging drugs compared to those who were not, while there was a trend for slightly increased incidence of ventricular arrhythmia in patients taking QT prolonging drugs.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with intravenous vernakalant. Vernakalant hydrochloride injection has been safely administered concomitantly with

other oral antiarrhythmic agents including the Class Ia antiarrhythmic procainamide, Class Ic agents including flecainide and propafenone and Class III agents including sotalol and amiodarone. There was a nonsignificant trend for increased risk of AFL with vernakalant in patients taking Class I antiarrhythmics. Vernakalant injection has been safely administered to patients taking rate control agents including digoxin, calcium channel blockers (diltiazem and verapamil), or beta-adrenergic blocking agents (metoprolol, atenolol, bisoprolol, carvedilol, nadolol and pindolol). In the first 2 h post dose there was an increased risk of hypotension in vernakalant treated patients taking beta blockers**.** Vernakalant is not highly bound to serum proteins and *in vitro* evidence suggests a low potential for protein binding related drug interactions. Population PK analysis demonstrated that concomitant use of CYP2D6 inhibitors did not influence the acute exposure (C_{max} and $AUC_{0\text{-}90min}$) of vernakalant. Vernakalant injection has been safely administered concomitantly with CYP2D6 substrates and medications known to inhibit CYP2D6.

Approximately 80% of patients in the All patients population were receiving concomitant anticoagulants, with no apparent safety concerns. Approximately 50% of patients treated with vernakalant injection have been on background oral anticoagulants. Vernakalant injection use was not associated with an increased risk of bleeding or thromboembolic complications in patients taking vitamin K antagonist oral anticoagulants.

Discontinuations due to AEs

Across all studies, 13 patients (10 vernakalant, 3 placebo) were withdrawn from the study. Reasons for withdrawal were adverse events (5 patients), lost to follow up (3 patients), and other (5 patients). Other reasons included lack of study drug (2 patients), inability to obtain intravenous access, prolonged QT interval and withdrawal of consent.

The study drug was permanently or temporarily discontinued due to an adverse event for 28 vernakalant patients (3.6%) and 1 placebo patient (0.3%). There were 11 patients who discontinued the study drug due to 14 SAEs, including hypotension (7 events), bradycardia (2 events), and tachycardia, ventricular extrasystoles, AFL, complete atrioventricular block, and suffocation feeling (1 event each). Non-serious AEs that led to withdrawal and occurred in more than 1 vernakalant patient included bradycardia (3 patients), nausea (2 patients), bundle branch block left (2 patients), and ECG QRS complex prolonged (2 patients).

In the AVRO study, the incidence of discontinuations due to AEs was low overall (3/116, 2.9% in vernakalant and 1/116, 0.9% in amiodarone group) and all treatment emergent AEs that led to discontinuation of the study drug were considered to be serious and related to the study drug (angina, ventricular tachycardia and hypersensitivity in vernakalant group and cardiac arrest in amiodarone group). In both treatment groups, these AEs began within 40 min after the start of the first infusion of the study drug and resolved within 5 min, with the exception of the SAE of hypersensitivity, for which the symptoms resolved after 28 min.

Evaluator's overall comments on clinical safety

In all Phase II and III studies (except AVRO), 773 patients received vernakalant (of whom 507 received the maximum proposed dose of 5 mg/kg). The majority of the AEs in vernakalant treated patients occurred in the first 2 h post dose and the most common AEs were dysgeusia, paraesthesia, sneezing, hypotension, nausea and bradycardia. A majority of these AEs were mild to moderate.

In the 0-2 h time period, the incidence of any ventricular arrhythmia event was similar in the vernakalant and placebo group (3.9% versus 3.2%) but the incidence of clinically relevant ventricular arrhythmia (SAE or discontinuation) was higher in the vernakalant

group (0.6%, 5/773) compared to placebo (0%). The risk of ventricular arrhythmia was increased in patients with history of CHF, AMI, cardiac surgery, abnormal hepatic function and moderate/ severe renal impairment.

Hypotension occurred either during infusion or early after the end of the infusion and was usually corrected by standard supportive measures. The incidence of clinically meaningful hypotension (SAEs or discontinuations) during first 2 h post dose was higher in vernakalant group compared with placebo (0.8% versus 0% in non-CHF patients). However, the risk of hypotension was increased in patients with history of CHF, low baseline SBP and vernakalant plasma levels of 4000 ng/mL (associated with the maximum 5 mg/kg dose).

The majority of the bradycardia events (4-5% in vernakalant and placebo groups) occurred between 0 and 2 h post dose, were peri-infusional and resolved spontaneously. Four of the 10 clinically serious events of bradycardia (SAEs or discontinuations) occurred at the time of termination of AF and the other events responded to discontinuation of vernakalant and/or administration of atropine; there were 2 cases of complete AV block.

Patients with AF receiving vernakalant had a higher incidence of converting to atrial flutter within first 2 h post dose compared with placebo (10% versus 2.5%); a majority of these patients continued to revert to sinus rhythm on continuation of recommended vernakalant dose. Furthermore, no patients with atrial flutter following vernakalant treatment developed 1:1 atrioventricular conduction. There was a trend toward increased risk of AFL during first 2 h post dose in vernakalant patients who were using Class I antiarrhythmics.

Age, sex, history of hypertension or duration of AF did not appear to affect the safety of vernakalant (in terms of common AEs of bradycardia, hypotension, ventricular arrhythmias and AFL). Vernakalant was associated with a slightly higher incidence of clinically meaningful events of hypotension and ventricular arrhythmia (defined as those involving SAEs or study drug discontinuation) in patients who had CHF compared with those who did not. Of the 5 patients with a SAE of ventricular arrhythmia, 3 had a history of CHF. Patients with a history of myocardial infarction and those with abnormal hepatic function and moderate/ severe renal impairment also showed an increased risk of ventricular arrhythmia. There was an increased risk of hypotension in the first 2 h post dose in vernakalant treated patients who were using beta blockers (vernakalant versus placebo: 9.7% versus 3.9%) compared to those not taking beta blockers (4.8% versus 7.1%).

There were 6 deaths in vernakalant treated patients and no deaths were reported in placebo/ amiodarone patients. Four of the deaths in vernakalant patients were not related to administration of vernakalant injection (occurred 2 to 26 days after injection); of the 2 other deaths, one was due to hypotension in a patient coadministered oral and IV metoprolol (leading to ischaemia and ventricular fibrillation) and another was due to COPD/ pulmonary embolism in a patient with other comorbidities. The incidence of SAEs was higher in vernakalant treated patients compared to placebo in the first 2 h post dose (2.5% versus 0.6%), including 8 SAEs of hypotension and 11 SAEs of cardiac arrhythmias (supraventricular/ ventricular arrhythmia/ cardiac arrest); however, the incidence of SAEs was similar in the first 24 h post dose (4.1% versus 3.9%). The incidence of discontinuations due to AEs in vernakalant treated patients was low (3-4% compared to <1% in placebo/ amiodarone groups) and the most common causes of discontinuations were hypotension and bradycardia.

Patients treated with vernakalant showed significant reduction in HR and also showed consistently greater increases in QRS interval with 5% (34/704) patients shifting from baseline of <140ms to QRS duration of >140ms at any post dose time point (most common at 10, 15 and 35 min post dose). Within the first 24 h (ECV was not attempted in first 90

min post dose), 57-58% of placebo/amiodarone and 30-37% of vernakalant patients underwent electrical cardioversion and vernakalant did not appear to affect response to subsequent cardioversion. There were no other significant effects on other laboratory parameters.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

The TGA's questions have been listed followed by a summary of the sponsor's response (in *italics*); this is followed by the evaluator's comments, if necessary, in normal font.

Question 1

Please justify:

a. A dosage regimen in patients with hepatic and renal impairment above 2 mg/kg.

b. Why the use of vernakalant in patients with severe hepatic and renal impairment should not be contraindicated.

Sponsor's response

The sponsors stated that results from the Phase I renal impairment study (VERO-106-REN) suggested that renal function status had no clinically significant effect on acute exposure, half-life or clearance of vernakalant. Results from the Phase I hepatic impairment study (VERO-107-HEP) demonstrated no significant difference in acute exposure of vernakalant in patients with hepatic impairment. The lack of change in vernakalant exposure with varying degrees of hepatic impairment, suggests that no difference in the nature, incidence or severity of adverse events is to be expected in patients with hepatic impairment.

In Study VERO-106-REN, the clearance of vernakalant was lower in all renal impairment groups compared with the normal renal function group, with the lowest clearance values in the moderate and severe renal impairment groups. In study VERO-107-HEP, clearance was slower in patients with severe hepatic impairment and the geometric mean values of AUC and $t_{1/2}$ were also higher compared to the normal hepatic function group. Furthermore, the wide 90% CI make interpretation of results in both studies difficult.

The dose used in the hepatic and renal impairment studies (2 mg/kg) was lower than the (maximum) dose intended for use in AF patients (3 mg/kg and 2 mg/kg), since the primary aim of these studies was to evaluate the effects of hepatic or renal impairment on PK parameters of vernakalant, thereby identifying patients at risk and evaluating the need for dose adjustment. In previous intravenous ascending dose studies in the clinical development program, vernakalant demonstrated linear PK at doses up to 5 mg/kg. Consequently, it is reasonable to extrapolate results from lower doses. Since the volunteer patients with hepatic or renal impairment would derive no benefit from exposure to vernakalant, and effects on PK parameters could be adequately assessed following a 2 mg/kg dose, it was felt that higher exposures were not required. Further, a single infusion would allow for a clearer interpretation of the effects on PK parameters without the confounding effects of a double infusion.

In order to address this issue of wide 90% CI, the sponsors provided results from Phase II/3 patient population using POP PK analyses to determine if renal and hepatic impairment affect vernakalant exposure across a larger patient population. Overall, results from this POP PK analysis demonstrated that serum creatinine (in addition to CYP2D6 metaboliser status and age) is indeed a covariate that influences vernakalant clearance. However, although patients with high serum creatinine may have higher maximum plasma vernakalant

concentrations, a sensitivity analysis indicated that the differences in C_{max} and AUC due to high serum creatinine are small (VERI-Pop-PK). The sponsors concluded that dose adjustment on the basis of renal function (or the other covariates) is not deemed necessary.

To characterize PK at clinical doses as a function of hepatic function, a post hoc analysis of patients with normal versus impaired hepatic function within the primary safety population was also conducted using POP PK analyses. An analysis of variance (ANOVA) of hepatically impaired patients [N=36 (1 dose); N=82 (2 doses)] versus patients with normal liver function [N=134 (1 dose); N=281 (2 doses)] was performed for C_{max} and $AUC_{0\text{-}120min}$ to estimate the geometric mean ratio [hepatically impaired/normal liver function] and corresponding confidence interval for each regime This analysis suggests a modest increase of 9-25% for C_{max} and 15-20% for $AUC_{0\text{-}120min}$ in AF/AFL patients with hepatic impairment who received either 1 or 2 doses, compared to AF/AFL patients with normal liver function. These minor and temporary elevations in acute exposure are not considered clinically meaningful.

Mild to moderate renal/ hepatic impairment does not appear to have clinically significant effect on vernakalant PKs. The sponsor's justification for not using the proposed dose of vernakalant in the PK studies is acceptable and data on the proposed doses in patients with mild/ moderate hepatic/ renal impairment is also available from the Pop-PK analysis using data from Phase II/III studies. Hence, vernakalant at proposed doses may be used with caution in patients with mild/ moderate renal/ hepatic impairment. However, use of vernakalant in patients with severe renal/ hepatic impairment should be in 'contraindications' or 'used with extreme caution' due to the fact that patients with severe renal and hepatic impairment were excluded from the Phase II/III studies and evidence from the PK studies suggested that vernakalant exposure may be increased in patients with severe renal/ hepatic impairment.

Question 2

For the pivotal efficacy trials, please provide a brief summary of where the patients were recruited from.

Clinical trial participants from ACT I were recruited from 19 sites in Denmark, 6 sites in Sweden, 13 sites in Canada, and 6 sites in the United States. The ACT II patients were recruited from 43 sites in Canada, Europe, Asia, South America and the United States (8 sites in Canada, 4 sites in Denmark, 4 sites in Italy, 5 sites in Poland, 7 sites in India, 5 sites in Argentina, and 10 sites in the United States). Patients In ACT III were recruited from 6 sites in Argentina, 1 site in Chile, 9 sites in Canada, 5 sites in Sweden, 13 sites in Denmark, 1 site in Mexico, and 14 sites in the United States. In AVRO, patients were recruited from 4 sites in Australia, 8 sites in Canada, 12 sites in Czech Republic, 5 sites in Denmark, 4 sites in Estonia, 1 site in Finland, 4 sites in France, 18 sites in Germany, 1 site in Latvia, 3 sites in Lithuania, 7 sites in the Netherlands, 12 sites in Poland, 4 sites in Serbia, 8 sites in Slovakia, 3 sites in Sweden, and 8 sites in Ukraine.

Question 3

Please provide a brief summary of the appropriateness of amiodarone as a comparator. Are there any other drugs which could have been used as a comparator?

Amiodarone was chosen as a comparator in the AVRO Study based on its widespread use in the treatment of AF across the EU and its relative safety in a broad AF population. The sponsor justified use of amiodarone based on its relative safety and ability to use it a wider population of AF patients with structural heart disease unlike other Class I antiarrhythmics; amiodarone has been shown to be safe in patients with ischaemic heart disease, hypertension, congestive heart failure (CHF), and previous myocardial infarction.

Flecainide was not used as it is contraindicated in patients with left ventricular dysfunction, heart failure, and patients with a history of myocardial infarction, and should be used with caution in patients with post-cardiac surgery AF.

Ibutilide was not used as it is mainly effective in conversion of atrial flutter and not atrial fibrillation and also because it is associated with a high risk of ventricular arrhythmias.

Amiodarone appears to be an appropriate comparator. However, amiodarone is much slower acting drug and requires an initial infusion of 60 min (followed by maintenance infusion over next 60 min); hence interpretation of the primary efficacy endpoint in the AVRO study (conversion to sinus rhythm within 90 min) is limited. However, efficacy of vernakalant over amiodarone in terms of primary endpoint was supported by higher rate of symptom relief and overall health. Hence, the sponsor's response is acceptable.

Question 4

Please provide the following information:

a. The objectives of the proposed clinical trial in patients with recent onset atrial fibrillation but without a history of heart failure.

b. A brief summary of the trial, including its design, the trial hypothesis, the relevant statistical considerations and power and the numbers of patients enrolled and randomised.

c. Are there any intentions to conduct a study in patients with conditions known to induce atrial fibrillation including recent AMI and advanced CHF?

(a) The sponsor is not part, nor has oversight about the conduct of ACT V. ACT V is conducted by Astellas Pharma Global Development, another licensee of Cardiome, that has the marketing rights in the United States, Canada and Mexico.

The primary objectives of the study are to evaluate the safety and efficacy of vernakalant injection in patients with recent onset symptomatic AF (more than 3 h but less than 7 days), and no evidence or history of CHF. Further, the study will evaluate the influence of CYP2D6 genotype status on the PK and PD of vernakalant (and its metabolites). Additionally, the study allows for an exploratory analysis of safety and healthcare resource utilisation between vernakalant and ECV.

(b) This is a randomised, double blind, placebo controlled, parallel group study in which approximately 470 patients will be randomised in a 2:1 ratio to vernakalant and placebo to provide a total of 450 treated patients (300 on vernakalant and 150 on placebo) assuming a 5% dropout rate between randomisation and administration of the study drug. This sample size of 300 vernakalant treated patients was selected to provide the one-sided 95% upper confidence limit for the rate of the primary safety variable (Composite of occurrences of hypotension, ventricular arrhythmias and death verified by the Clinical Events Committee occurring within 2 h after start of treatment) is <1% if no events were observed in patients treated with vernakalant. The one-sided 95% upper confidence limit with no events among 300 patients is given by the Rule of Three. i.e., 3/300 = 0.01.

Using a two-sided chi-square test with a significance level of 0.05, this sample size would provide more than 98% power to detect a treatment difference of 35% in the primary efficacy endpoint of conversion of AF to sinus rhythm (SR) between the two treatment groups, assuming the placebo conversion rate is 10%. To date, a total of 270 patients have been enrolled and randomised.

(c) The sponsor has no current plans to conduct studies in patients with conditions known to induce AF, such as recent acute myocardial infarction (AMI) and advanced heart failure (HF), however this may become a focus of further life cycle development.

Although the sponsors have provided some details of the study protocol, it is not clear why this study was conducted in patients with no history of CHF; vernakalant is not contraindicated in patients with CHF (except Stage III or IV CHF in the revised PI) and AF is quite common in patients with CHF.

Question 5

It is not clear why the sponsors reversed the regimen used in the dose finding CRAFT study (2+3 mg/kg) to the current proposed regimen (3+2 mg/kg) in the Phase III studies. No specific reason was provided for this switch. Please explain the reasons for this switch in the dosage regimen.

The sequence of 2 mg/kg and 3 mg/kg doses used in CRAFT was reversed for the Phase III studies, based on the assumption that more patients would convert on the first dose if the higher dose was given first. Therefore the dose regimen selected for the Phase III studies was 3 mg/kg infused over 10 min followed by a 15 min observation period and, if no conversion to sinus rhythm was seen, a second dose of 2 mg/kg infused over 10 min was administered. A 15 min observation period was selected to ensure completion of the alpha distribution phase prior to adding the second dose.

Doses for CRAFT, in turn, were chosen on the basis of efficacy studies in the canine AF models in which the ED_{50} was approximately 1 mg/kg (over 5 min), and the maximum dose studied in Phase I (5 mg/kg). In Phase 1, mild neurosensory side effects and mild ECG changes (PR, QRS and QT lengthening) were seen at doses of 4 and 5 mg/kg. Hence, doses lower than 4 mg/kg were investigated in CRAFT.

Question 6

Please explain in detail how the findings can be extrapolated to all patients with short term atrial fibrillation, that is, of no more than 7 days' duration.

The sponsor acknowledged that the findings cannot be extrapolated to all patients with short term AF. Specifically, the data on post cardiac surgery patients are derived from ACT II, which was conducted in patients of ≤3 days duration. Therefore, the sponsor proposed to change the indicated population as follows:

- *For non-surgery patients: atrial fibrillation ≤7 days duration*
- *For post-cardiac surgery patients: atrial fibrillation ≤3 days duration*

The prescribing information will be revised accordingly.

Question 8 (Question 7 was of an administrative nature)

In the 4 Phase III controlled studies, of the 783 patients representative of the target patient population of recent onset AF (< 7 days duration), 393 patients from studies ACT II and AVRO had inclusion criteria that specified AF duration of < 3 days. Of the 390 patients with AF duration < 7 days in pivotal studies ACT I and ACT II, details on the exact number of patients with AF duration < 3 days were not provided. The sponsor is requested to provide details of the exact numbers of patients in ACT I and ACT II whose atrial fibrillation was of less than 3 days duration. Post hoc analysis (in study ACT I only) seemed to suggest that patients with AF duration < 48 h had better conversion rates compared to those with AF duration > 48 h.

The subgroup of 290 patients with AF duration quantified and AF lasting > 3 to < 48 h in the ACT I and IV studies, included 229 given vernakalant (103 in ACT I and 126 in ACT IV) and 61 given placebo (in ACT I).

In the AF ≤ 48 h group from ACT I and IV (where AF duration was recorded), the conversion rates were:

a. *ACT I: 61.2% (95% CI = 51.8% to 70.6%)*

b. *ACT IV: 57.9% (95% CI = 49.3% to 66.6%)*

The subgroup of 324 patients with AF duration quantified and AF lasting > 3 to < 72 h in the ACT I and IV studies, included 256 given vernakalant (116 in ACT I and 140 in ACT IV) and 68 given placebo (in ACT I).

In the AF < 72 hour group from ACT I and IV (where AF duration was recorded), the conversion rates were:

a. *ACT I: 58.6% (95% CI = 49.7% to 67.6%)*

b. *ACT IV: 53.6% (95% CI = 45.3% to 61.8%)*

In ACT II, AF duration was not established by the hour, so it is not possible to provide the number of patients with AF <48 h, but there were 100 patients treated with vernakalant with AF duration <72 h and 47.0% converted to SR. In AVRO, all 116 patients treated with vernakalant had AF duration <48 h and 51.7% converted to SR.

Although the number of patients with AF duration >3 and <7 days appears to be limited, efficacy in subgroup of patients with AF duration <3 days appears to be similar to that observed in the proposed short duration AF (<7days) population. The sponsor's response is acceptable.

Question 9

The sponsor was requested to:

a. Explain why there was no similar *post hoc* analysis of the results from study ACT-II.

b. Submit a *post hoc* analysis from the above from ACT-II.

c. Submit a *post hoc* analysis from the above pooled results of ACT-I and ACT-II.

All patients enrolled in ACT II had AF duration ≤ 72 h but parsing out the data into finer detail (≤ 48 h) was not possible as the exact date and time of AF onset was not collected. As such a post hoc analysis for AF <= 48 h was not conducted for ACT II.

The response was acceptable because the revised proposed indication specifies that use in post cardiac surgery patients is limited to patients with AF duration < 3 days.

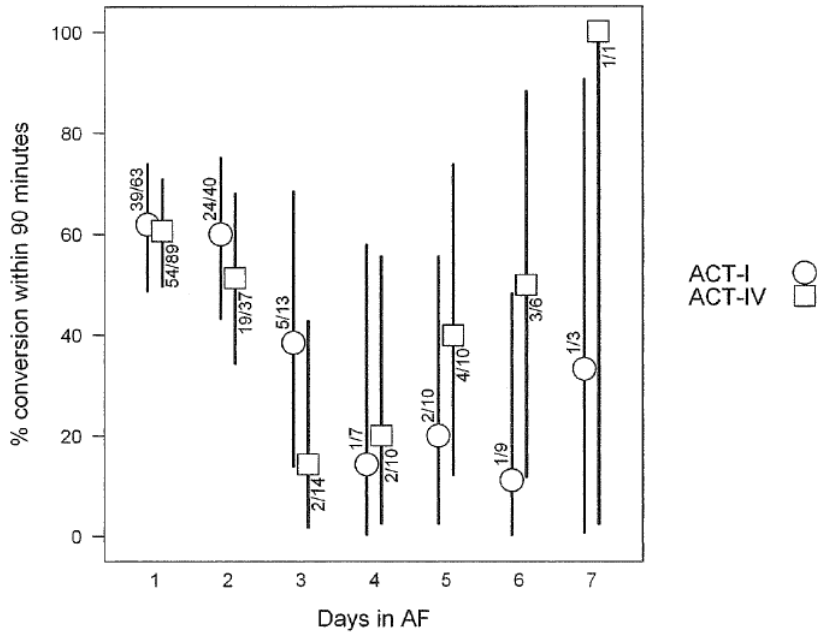
Question 10

Continuous data on AF duration was not collected in study ACT-III. There was no evidence to confirm efficacy of vernakalant in patients with AF duration > 3 days but ≤ 7 days due to lack of data. Please explain this deficiency.

The sponsor acknowledged that the evaluator was correct. In ACT III the population was divided into patients with AF ≤ 7 days or AF > 7 days and ≤ 45 days. No additional data was collected to allow analysis of efficacy based on AF duration in daily bins.

The sponsor emphasised however that the conversion rates across ACT I, III and IV in the recent onset AF group (AF < 7 days) would suggest the conversion rate in ACT III patients with AF > 72 h would not be that dissimilar to that observed in the ACT I and ACT IV AF > 72 h group (Figure 7). Further, the analysis of risk/benefit of cardioversion methods and decision on treatment of paroxysmal AF based on duration either ≤ 7 days or > 7 days is consistent with the most recent joint ACC/AHA/ESC guidelines (2006).

Figure 7: Treatment induced conversion from AF to SR versus the duration of AF by study



Question 11

Furthermore, the proposed indication does not specify that efficacy in post cardiac surgery patients has only been evaluated for recent onset AF of < 3 days duration. Please justify why the proposed indication should not reflect this deficiency.

The sponsor acknowledges that the data on post cardiac surgery patients (derived from ACT II) was conducted in patients of ≤ 3 days duration. Therefore, as noted above, the sponsor proposed to change to indicated population as follows:

- *For non-surgery patients: atrial fibrillation ≤ 7 days duration*
- *For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration*

Question 12

The controlled Phase III studies were powered to detect a statistically significant difference in the primary endpoint of conversion to SR within 90 min post dose based on assumptions of an estimated conversion rate of 25% in placebo patients versus 50% in vernakalant patients (in the AVRO study, the estimated conversion rates were 35% and 58% in the amiodarone and vernakalant groups, respectively). However, the references on which these assumptions were based were not provided in the study protocols. Please provide these references.

The assumptions for a conversion rate of 25% in placebo patients with AF ≤7 days were estimated using a range of results from a number of published manuscripts. These included Kochiadakis et al. (1998) -placebo rate of 28% at 1 hour; Vardas (2000) - placebo rate of 25% at 1 hour, Capucci et al (1992)- placebo rate of 29% at 3 hours, and Donovan et al (1995) - placebo rate of 22% at 2 hours.[18,19,20,21] *The vernakalant rate for the controlled Phase III studies was based on the results of the Phase IIa CRAFT study. In the AVRO study, the estimated conversion rates were in fact 25% and 45% in the amiodarone and vernakalant groups, respectively. The manuscript from Martinez Marcos (2000) was the basis for estimating amiodarone conversion rates, while the vernakalant rate was estimated using subgroup analyses of patients with AF ≤48 hours from the ACT I study.*[22]

Question 13

Furthermore, the actual conversion rates observed in the placebo/amiodarone groups were much lower than the estimated rates which may have confounded interpretation of the statistical significance of the huge treatment difference observed in these studies.

This is especially important in light of the fact that the effects of vernakalant on clinically relevant endpoints such as incidence of complications, morbidity and mortality were not evaluated. Please provide a detailed justification of the impact of these issues on the statistical validity of the clinical trial data.

The sponsor agreed that the observed conversion rates in the placebo/ amiodarone groups were lower than anticipated, however this would not confound the interpretation of the statistical significance. The intrinsic differences between the reference studies (used in the power calculations) and the confirmatory Phase III studies conducted in the vernakalant development program prevent one from making cross-study comparisons. The statistical validity of the Phase III confirmatory studies in question can be assessed by interrogation of both the design and conduct of these confirmatory trials to ensure bias did not confound the results. To minimize bias, all of these confirmatory trials were designed and conducted as double-blind, randomized, and controlled (placebo or active) clinical trials. Furthermore, sensitivity analyses confirmed the robustness of the results suggesting no influence of bias. The unexpected difference between actual and anticipated conversion rates would not be expected to affect the validity of the safety conclusions drawn from the program. However, we recognize the inherent limitations in the precision with which an effect on rare safety events can be determined from a reasonably sized clinical development program. For this reason, a post-authorization safety study, SPECTRUM, has been designed. This study will augment the available safety data.

Question 14

There were noted to be 2 cases of ventricular fibrillation (one fatal). Please explain in full whether either or both of these adverse events thought to be in any way causally related vernakalant?

A related serious adverse event of ventricular fibrillation occurred in the ACT III study. This patient developed ventricular fibrillation resulting in death within the first 2 h after receiving vernakalant injection. The patient was a 64 year old white male with a history of critical aortic stenosis. He was admitted with chest pain, atrial fibrillation with a rapid ventricular rate of 158 bpm, ST segment elevation, troponin elevation and screening blood pressure was 97/59, 101/76 and 105/71 mmHg. He was treated with intravenous and oral metoprolol and his blood pressure fell to 90/70 mm Hg, requiring fluid resuscitation to improve blood pressure. He became hypotensive (75/42 mmHg) following a first infusion of vernakalant injection and required further fluid resuscitation. A second vernakalant infusion was administered again resulting in hypotension (65/41 mmHg). A serious adverse event of ventricular fibrillation developed 12 minutes after completion of the second infusion of vernakalant injection, and resuscitation was unsuccessful. The patient's aortic stenosis was also recorded as a serious adverse event. The investigator assessed the severity of both events to be severe and possibly related to the study drug. The patient's clinical presentation of acute coronary syndrome should have excluded him from the study based on the protocol exclusion criteria. In addition, the patient's repeated episodes of hypotension should have led to cessation of dosing, based on the dose-stopping criteria for blood pressure <85 mmHg and intolerable side effects.

An unrelated serious adverse event of ventricular fibrillation also occurred in the Phase II CRAFT study. This patient developed ventricular fibrillation following a nonsynchronised electrical shock delivered during attempted electrical cardioversion. The patient, a 24 year old female, presented to emergency in AF with a rapid ventricular response. The patient

received vernakalant injection 0.5 mg/kg followed by 1 mg/kg without conversion to sinus rhythm. One hour and 54 minutes following the start of the first infusion of vernakalant injection, electrical cardioversion was attempted. A delay of approximately 10 seconds occurred before the current release, and with slight paddle movement, a nonsynchronised cardioversion shock was delivered with ensuing ventricular fibrillation noted on the cardiac monitor. Immediate defibrillation resulted in conversion to normal sinus rhythm. First degree burns at the paddle sites were the only sequelae and the patient was discharged the following day. The investigator determined the event was unlikely to be related to the study drug and resulted primarily due to the delivery of a nonsynchronised electrical shock during attempted cardioversion as the result of a loose cardiac monitor lead. This is a case of nonsynchronised cardioversion due to a technical malfunction which is known to happen rarely.

Of the two cases of ventricular fibrillation, the non-fatal one did not appear to be related to vernakalant treatment. However, in the opinion of the evaluator, the fatal episode of VF was definitely related to vernakalant therapy. It was accepted that the patient with the fatal VF should not have been given vernakalant in the first place and then definitely should not have been given the second dose following the hypotensive episode. But it was alarming that the fatality still occurred in a highly monitored environment. Patients with recent onset AF are likely to have significant cardiac comorbid conditions. The sponsor has revised the PI to address the concerns regarding the safety of vernakalant in the proposed patient population (see sponsor's response to Question 19 below).

Question 15

The safety data indicated a death to pulmonary embolus. Please advise:

a. Was this event in any way thought to be causally related to vernakalant?

b. Was there any evidence of deep venous thrombosis?

c. What is known about the effects of vernakalant on the various coagulation factors?

d. Is vernakalant known to have any pro-thrombotic effect or tendency?

a) The patient was a 64 year old White male with a history of atrial fibrillation and virosis, was enrolled in the ACT IV open label study and received 2 doses of vernakalant. He did not convert to sinus rhythm. He was subsequently electrically cardioverted to sinus rhythm.

An SAE of pulmonary embolism began 2 days after receiving the study drug. The patient had reported experiencing symptoms of viral airway infection one week prior to enrolment in the study. A chest x-ray completed the day of the event did not reveal any infiltrates but did reveal a questionable lymph node in the right hilus. A CT scan of the thorax was done and a pulmonary embolism was discovered on the left side. The patient was not experiencing any dyspnoea but was started on anticoagulation the same day. The investigator assessed the severity of this event to be moderate and not related to the study drug. The patient completed the study.

The death due to pulmonary embolism was in a vernakalant treated patient in the AVRO study. The patient in the ACT IV study died due to GI haemorrhage. Please clarify.

b) According to the report received from the investigator, there were no clinical signs suspicious for the presence of deep vein thrombosis.

c) While a direct effect of vernakalant on coagulation factors has not been studied, preclinical data from the rat 28 day IV toxicology study and the dog 28 day IV toxicology study showed that there is no effect on APTT or PT at any of the vernakalant doses tested (10, 20 and 40 mg/kg/day in the rat and 5, 10, and 20 mg/kg/day in the dog), suggesting that vernakalant does not affect the coagulation cascade. The lack of effect on parameters of

coagulation is supported by the absence of significant differences in PT and PTT between the active and placebo groups in the clinical program.

d) There are no non-serious thrombotic events reported in the program. Serious events in the IV program were listed. It was not possible to draw definitive conclusions from the small number of events reported, but there does not appear to be an overall tendency toward an increase in thrombotic events. Further information will be derived from the postmarketing safety study (SPECTRUM), anticipated to launch in Europe in 2011.

The data provided by the sponsor seem to suggest that vernakalant does not have any pro-thrombotic effects but this would need to be confirmed in a larger number of patients (the post-marketing SPECTRUM study being conducted in EU could provide some information on this).

Question 16

The safety data indicated there were adverse events of third degree AV block. Please provide information on the proportion of such events thought in any way to be causally related to vernakalant.

There were 2 (0.2%, 2/889) patients who experienced third degree AV block as an adverse event within the first 24 hours after exposure to vernakalant. One patient was a post cardiac surgery patient (ACT II) with pre-existing right bundle branch block and left anterior hemiblock who experienced a serious adverse event of third degree AV block at the time of termination of AF during the first infusion of vernakalant. This event was resolved after 8 to 9 minutes of pacing by epicardial wire and was characterised by the investigator to be definitely related to the study drug. The second patient (ACT I) experienced a serious adverse event of third degree AV block approximately 3 hours after vernakalant infusion and immediately following an attempted electrical cardioversion. Following the heart block the patient received two doses of intravenous atropine and intravenous isoprenaline, the patient's heart rate increased and she converted to sinus rhythm. The investigator characterised the event as possibly related to vernakalant.

Both cases of third degree block were definitely or possibly related to vernakalant treatment suggesting that this AE is also a risk associated with vernakalant.

Question 17

There were noted to be adverse events of hypotension. Please provide information on the proportion of all such events thought in any way to be causally related to vernakalant.

The incidence of hypotension in the vernakalant group in the Phase II-III studies within 0-2 hours post dose was (4.7%, 36/773) of which 4.0% (31/773) were assessed as drug related by the investigator; incidence of hypotension in placebo patients was (0.9%, 3/335), of which 0.3% (1/335) were considered drug related . Within 2-24 hours post dose, the incidence of hypotension events in the vernakalant group was (1.2%, 9/773; none were considered drug related) compared to 2.7% (0.3% drug related) in placebo group.

Clinically meaningful hypotension (reported as a serious adverse event or requiring discontinuation of treatment) was reported in 1.2% (9/773) of patients within the first 2 hours after exposure to vernakalant and in 0% of placebo patients. Of the 9 hypotension associated SAEs reported in the first 24 hours post dose in vernakalant treated patients, 4 were reported in CHF patients (2.9%, or 4/139 Phase III patients), and 5 (0.8%, or 5/598) patients without CHF.

In AVRO, no vernakalant patients (0.0%, 0/116) and one amiodarone patient (0.9%, 1/116) had a hypotension event within 0-2 hours post dose. Within 2-4 hours post dose, one vernakalant patient (0.9%, 1/116) and one amiodarone patient (0.9%, 1/116) had a

hypotension event. The one hypotension event recorded in the vernakalant group (patient 305-1006- 004) was a 70-year-old black male with a history of hypertension and was considered unlikely to be related to the study drug.

Since both vernakalant and amiodarone may cause hypotension, investigators were advised in the AVRO protocol that patients were to be adequately hydrated and haemodynamically optimized prior to receiving treatment. In addition, the minimum SBP was raised from 90 to 100 mmHg. These changes may have played a role in decreasing the incidence of hypotension events in AVRO.

Hypotension events with vernakalant were peri-infusional; responded to Trendelenburg position and/or fluids in all but two patients (noted above, patients 012 11655121 and 305-1006-004) who received vasopressors. Risk can be anticipated and managed in proposed clinical setting.

The risks of hypotension associated with vernakalant treatment have been addressed in the revised PI.

Question 18

Please advise why the contraindications for vernakalant should not reflect the full spectrum of these exclusions. If the sponsor does not agree with the contraindication of these conditions, the sponsor is requested to justify why there should not be appropriate, relevant precautionary statements clarifying these issues in the PI.

As is common in clinical trials, most of the exclusions listed were intended to avoid the effects of intercurrent illness confounding the safety data set, rather than due to any a priori concern that patients with the conditions excluded were at higher risk of adverse events with vernakalant. The sponsor maintained that in most cases it is sufficient to note the absence of evidence in these populations, rather than contraindicating these conditions in the PI. However, the sponsors acknowledged that patients with some of the listed conditions do have an increased potential for adverse reactions to vernakalant.

Exclusion for advanced heart failure

The sponsor agreed that sufficient safety information is not available to justify use in advanced heart failure. Subsequently, the following language will be added to the "Contraindications" section: "Patients with severe heart failure [corresponding to NYHA IV or unstable NYHA III.]"

Exclusion for advanced hepatic failure

The safety population provides substantial experience in patients with hepatic impairment, with 20% of patients having some degree of impairment. The incidence of most AEs was similar between patients with normal and abnormal hepatic function. There was a slight excess of ventricular arrhythmia from 0 to 2 hours in patients with hepatic impairment but all of these events were mild, with most consisting of brief runs of monomorphic tachycardia. None of the events were classified as serious, and none resulted in discontinuation. Therefore, the sponsor concluded that no specific contraindication is required in hepatic impairment. Given the lack of data in advanced hepatic failure, the sponsor agreed that it is reasonable to caution against use in this population, as is done in the current PI. However, given the reassuring data from the general population with hepatic impairment, the sponsor did not believe this should rise to the level of a contraindication.

Severe renal disease

The Phase I study, VERO-106-REN, demonstrated that there is no clinically meaningful difference in exposure after administration of vernakalant injection in patients with mild, moderate, or severe renal impairment. Therefore, the sponsor maintained that a contraindication in this population is unwarranted.

Severe pulmonary disease

Vernakalant does not have any known pulmonary effects. Minimal, clinically insignificant decreases in both mean respiratory rate and mean oxygen saturation were seen in both vernakalant and placebo groups. Therefore, based on the available evidence, there is no basis for concern in patients with severe pulmonary disease.

Patients with secondary causes of atrial fibrillation

There is limited published information on the efficacy of antiarrhythmics in patients with secondary causes of atrial fibrillation (except for postoperative.) Generally, appropriate treatment of secondary atrial fibrillation is reversal of the underlying cause and antiarrhythmics therapy is usually unsuccessful and therefore this is not addressed in the PI.

Patients who have failed DC cardioversion

There is limited information on the efficacy of pharmacological therapy directly following DC cardioversion, and conducting a trial in this patient group would be logistically very difficult. Because there is no biologically plausible reason to expect this group to be at increased risk for adverse events following vernakalant infusion, the sponsor maintained that a contraindication is unwarranted.

The response to most of the conditions was acceptable with the exception of severe hepatic and renal impairment due to increased risk of ventricular arrhythmias in patients with renal/ hepatic impairment and also other reasons discussed in evaluator's comments to Question 1 of this section.

Questions 19 - 22

These questions related specifically to the proposed PI and are therefore beyond the scope of this AusPAR.

Question 23

A recent case report was received from the sponsor regarding a report of cardiogenic shock in a male patient given a single dose of vernakalant as part of the ACT V clinical trial. As a result of this report, the FDA has placed a clinical hold on the trial. Please:

a. provide information from your clinical trial database on the number of cases of shock, including cardiogenic shock or related events from persons exposed to vernakalant and any analyses of causality, including dose response, frequency, and comparison rate with placebo or active medicine.

b. provide a full and detailed explanation of any investigations being undertaken as a result of this adverse event finding.

c. comment on how this finding impacts on the risk/benefit profile for vernakalant.

d. comment on how this finding will affect the Safety Specification of the Risk Management Plan.

e. provide information on the reasons for the FDA's action to halt the ACT V trial.

(a) From the previous Phase II-III studies, there was one vernakalant treated patient (1/889; 0.1%) and no placebo patients (0; 0%) with a serious adverse event of cardiogenic shock reported. This case was described in detail. Other serious and related hypotension events were discussed in Question 17.

Now there are 2 reports of serious cardiogenic shock in vernakalant treated patients (considered to be related to study treatment) compared to none in placebo patients.

(b) The sponsor has reviewed the case, in conjunction with available clinical experts, including the Data Safety Monitoring Board (DSMB) and the Clinical Events Committee (CEC). The case was described in detail. Overall, review of the patient's medical history and presenting characteristics, drug administration, additional investigations including echocardiogram and a coronary angiogram did not reveal a clear aetiology for the initial adverse events that occurred in this patient upon infusion of vernakalant, nor is there a clear explanation for the occurrence of two additional discrete episodes of pulseless electrical activity (PEA) several days later. No additional investigations are planned at this time.

The evaluator provided a more detailed description of this case with a timeline. The evaluator concluded that the timelines support possible causality of vernakalant to the SAE of cardiogenic shock, which in turn was most likely responsible for the complications and eventual death of the patient.

(c) The sponsor described the revised PI.

(d) The sponsor was currently working with the business partner company responsible for the ACT V clinical trial, to obtain additional clinical detail about the study case report of cardiogenic shock. The sponsor continues to review the risk management strategy for vernakalant and upon completion of the company's review of the emerging data and evaluation of the possible cause(s) of the reported events, the sponsor will determine if any changes to the current strategy are needed and seek the Agency's concurrence with the strategy.

e) As noted above, the event of cardiogenic shock occurred in the ACT V clinical trial which is being conducted by Astellas Pharma, US. The FDA agrees with the sponsor's assessment that the event was likely drug related and has put the study on hold pending submission of a more detailed description of the case and any changes to the protocol needed to the minimize patient risk. Astellas has conducted a detailed investigation of the case at the investigational site and is evaluating the protocol to determine if any changes are required to mitigate any risk to patients.

Did the ACT 5 study protocol follow the precautions inserted in the revised PI highlighting risk of hypotension, populations at risk, management and prompt discontinuation and other supportive measures for occurrence of clinically meaningful hypotension. This is especially important because if the patient developed this fatal SAE despite the precautions, it would represent a serious safety concern. The attachment provided by the sponsors does not provide details of the ACT 5 study protocol.

The sponsors have not commented on nor mentioned the fact that the patient died following the above SAE.

Clinical summary and conclusions

Clinical aspects

Clinical pharmacology

Vernakalant injection has a short pharmacokinetic half-life which results in a rapid onset and offset of action. It has a low potential for proarrhythmic activity, rapid onset of action, transient adverse effects and low plasma protein binding. Nonclinical studies have also demonstrated limited potential for drug-drug interactions between vernakalant and other drugs typically administered to the intended patient population, although no drug interaction studies were conducted with the proposed IV formulation of vernakalant. Vernakalant is relatively selective for the atria over ventricles due to its combination of atrial preferential electrophysiological actions and the unique electrophysiological characteristics of fibrillating atria. These properties differentiate vernakalant from Class I

and Class III antiarrhythmic agents and the data supporting relative atrial selectivity suggest that vernakalant represents an advance over existing agents in this respect for the conversion of AF to sinus rhythm. The selective effect on atrial tissue coupled with the late INa block suggests vernakalant may have a lower risk of proarrhythmia than drugs which predominantly affect ventricular tissue through block of potassium channels (for example, Class III agents such as ibutilide or dofetilide) and sodium channels (for example, Class I agents such as flecainide).

Clinical efficacy

The efficacy of vernakalant was evaluated in 783 patients with recent onset AF (duration < 7 days) which included patients with comorbidities including structural heart disease. Patients with significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis or reversible causes of AF were excluded from all Phase III studies. Furthermore, subjects with AMI and advanced CHF (two of the main causes of AFB) were excluded in all four Phase III studies with the exception of AMI in the ACT-II study. Hence, the population studied is not representative of the target patient population for vernakalant injection and findings cannot be extrapolated to all patients with short term AFB as suggested in the proposed indication.

Overall, conversion to SR within 90 minutes postdose was statistically and clinically significantly greater in vernakalant treated patients compared with placebo (51% versus 4%, p<0.001). A majority (40%) of the patients converted to SR after the first vernakalant dose (3mg/kg); conversion rate in patients receiving the second dose of vernakalant (2mg/kg) was only 20%. The median time to conversion to SR was only 10 minutes suggesting vernakalant acted rapidly.

The specificity of the ACT II study design enabled efficacy (and safety) assessments of vernakalant injection in patients with new onset AF after cardiac surgery, a subset of the overall AF patient population not included in the ACT I, ACT III or AVRO studies. Atrial arrhythmias are common following cardiac surgery and are estimated to occur in 10% to 65% of patients, depending on definitions and methods of surveillance (Fuster et al, 2006).[15] In this study, a statistically significantly greater proportion of vernakalant treated patients showed conversion to SR (for a minimum duration of 1 min within 90 min) compared with placebo (45% versus 15%, p=0.0002). The incidence of AF symptoms in postcardiac surgery patients treated with vernakalant was nonsignificantly lesser than placebo (66% versus 80%, p=0.099); however, there was a trend suggesting more symptoms in vernakalant treated subjects at the 7 day and 30 day follow-up visits.

Vernakalant (3+2 mg/kg) injection had superior efficacy when compared directly to amiodarone (60 min infusion of 5 mg/kg followed by maintenance infusion of 50 mg over next 60 min) injection for the rapid conversion of recent onset AF (3 to 48 h duration) to sinus rhythm within 90 min (51.7% versus 5.2%, p <0.0001). These results should be interpreted with caution as the primary endpoint was the conversion rate within 90 minutes while patients randomised to amiodarone were still receiving the drug (amiodarone patients received infusion for up to 2 hours) and amiodarone is known to be a slowly acting drug. However, the AVRO study did demonstrate that vernakalant **was significantly more effective than amiodarone IV in providing rapid conversion to sinus rhythm within the first 90 minutes of initiating therapy.**

All the Phase III studies (except ACT-II in post-cardiac surgery patients) showed statistically significant reduction in AF symptoms at 90 minutes postdose although blinding could have been compromised in almost 25% of the patients who received vernakalant due to specific AEs such as sneezing and dysgeusia which were experienced only by patients receiving vernakalant.

Maintenance of SR was only evaluated as an exploratory efficacy endpoint. In studies ACT-I and ACT-III, the life table estimate for maintenance of SR at 24 hours and 7 days was

97% and 93%, respectively. However, in postcardiac surgery patients, the maintenance of SR at 24 hours and 7 days was only 57-58%. In the AVRO study, 92% of patients who converted to SR within 90 minutes were maintained in SR at 7 days.

There was a trend suggesting reduced efficacy of vernakalant in patients > 75 years, those with history of CHF, valvular heart disease and structural heart disease. Vernakalant was effective in converting short term AFB to SR. However, conversion to and maintenance of SR for only a short period of time (at least one min within 90 min postdose as defined for the primary efficacy analysis of all Phase III studies) warrants neither the symptomatic improvement of AFB nor the prevention of its complications (such as cerebrovascular accident). The effect of vernakalant on morbidity and mortality was not evaluated in any of the Phase III studies although it is suggested by the CHMP guidelines. Furthermore, conversion rate was higher and more significant after the first dose of vernakalant with patients four times less likely to convert to SR after the second dose.

Clinical safety

In all Phase II and III studies (except AVRO), 773 patients received vernakalant (of whom 507 received the maximum proposed dose of 5 mg/kg). The majority of the AEs in vernakalant treated patients occurred in the first 2 hours postdose and the most common AEs were dysgeusia, paraesthesia, sneezing, hypotension, nausea and bradycardia. The majority of these AEs were mild to moderate.

The incidence of clinically relevant ventricular arrhythmia (SAE or discontinuation) was higher in the vernakalant group (0.6%, 5/773) compared to placebo (0%). The risk of ventricular arrhythmia was increased in patients with history of CHF, AMI, cardiac surgery, abnormal hepatic function and moderate/severe renal impairment. Hypotension occurred either during infusion or early after the end of the infusion and was usually corrected by standard supportive measures. The incidence of clinically meaningful hypotension (SAEs or discontinuations) during first 2 hours postdose was higher in vernakalant group compared with placebo (0.8% versus 0% in non-CHF patients). However, the risk of hypotension was increased in patients with history of CHF, low baseline SBP and vernakalant plasma levels of 4000ng/mL (associated with the maximum 5 mg/kg dose). A majority of the bradycardia events (4-5% in vernakalant and placebo groups) occurred between 0 and 2 hours postdose, were peri-infusional and resolved spontaneously. Four of the 10 clinically serious events of bradycardia (SAEs or discontinuations) occurred at the time of termination of AF and the other events responded to discontinuation of vernakalant and/or administration of atropine; there were 2 cases of complete AV block. Patients with AF receiving vernakalant had a higher incidence of converting to atrial flutter within first 2 hours postdose compared with placebo (10% versus 2.5%); a majority of these patients continued to revert to sinus rhythm on continuation of recommended vernakalant dose. Furthermore, no patients with atrial flutter following vernakalant treatment developed 1:1 atrioventricular conduction. There was a trend toward increased risk of AFL during first 2 hours postdose in vernakalant patients who were using Class I antiarrhythmics.

Age, sex, history of hypertension or duration of AF did not appear to affect the safety of vernakalant (in terms of common AEs of bradycardia, hypotension, ventricular arrhythmias and AFL). Vernakalant was associated with a slightly higher incidence of clinically meaningful events of hypotension and ventricular arrhythmia (defined as those involving SAEs or study drug discontinuation) in patients who had CHF compared with those who did not. Of the 5 patients with a SAE of ventricular arrhythmia, 3 had a history of CHF. There was an increased risk of hypotension in the first 2 hours post dose in vernakalant treated patients who were using beta-blockers (vernakalant versus placebo: 9.7% versus 3.9%) compared to those not taking beta-blockers (4.8% versus 7.1%).

There were 6 deaths in vernakalant treated patients and no deaths were reported in placebo/amiodarone patients. Four of the deaths in vernakalant patients were not related to administration of vernakalant injection (occurred 2 to 26 days after injection); of the 2 other deaths, one was due to hypotension in a patient coadministered oral and IV metoprolol (leading to ischaemia and ventricular fibrillation) and another was due to COPD/pulmonary embolism in a patient with other comorbidities. The incidence of SAEs was higher in vernakalant treated patients compared to placebo in the first 2 hours postdose (2.5% versus 0.6%), including 8 SAEs of hypotension and 11 SAEs of cardiac arrhythmias (supraventricular/ ventricular arrhythmia/ cardiac arrest); however, the incidence of SAEs was similar in the first 24 hours postdose (4.1% versus 3.9%). The incidence of discontinuations due to AEs in vernakalant treated patients was slightly higher (3-4% compared to <1% in placebo/ amiodarone groups) and the most common causes of discontinuations were hypotension and bradycardia.

Patients treated with vernakalant showed significant reduction in HR and also showed consistently greater increases in QRS interval with 5% (34/704) patients shifting from baseline of <140 ms to QRS duration of >140 ms at any postdose time point (most common at 10, 15 and 35 min postdose). There were no significant effects on other laboratory parameters. Within the first 24 hours (ECV was not attempted in first 90 min postdose), 57-58% of placebo/amiodarone and 30-37% of vernakalant patients underwent electrical cardioversion and vernakalant did not appear to affect response to subsequent cardioversion.

Long-term safety beyond 30 days follow-up was not evaluated as it was a short-acting drug.

Benefit risk assessment

Benefits

Vernakalant injection has a short pharmacokinetic half-life which results in a rapid onset and offset of action. It has a low potential for proarrhythmic activity, rapid onset of action, transient adverse effects and low plasma protein binding. Nonclinical studies have also demonstrated limited potential for drug-drug interactions between vernakalant and other drugs typically administered to the intended patient population, although no drug interaction studies were conducted with the proposed IV formulation of vernakalant. Vernakalant is relatively selective for the atria over ventricles due to its combination of atrial preferential electrophysiological actions and the unique electrophysiological characteristics of fibrillating atria. These properties differentiate vernakalant from Class I and Class III antiarrhythmic agents and the data supporting relative atrial selectivity suggest that vernakalant represents an advance over existing agents in this respect for the conversion of AF to sinus rhythm. The selective effect on atrial tissue coupled with the late INa block suggests vernakalant may have a lower risk of proarrhythmia than drugs which predominantly affect ventricular tissue through block of potassium channels (Class III agents such as ibutilide or dofetilide) and sodium channels (Class I agents such as flecainide).

Overall, efficacy was evaluated in 4 controlled, well conducted studies involving 783 patients with recent onset AF (< 7 days). The design of these studies complied with the TGA-adopted EU guidelines with the exception of the fact that effects on morbidity and mortality were not evaluated. Vernakalant was shown to be effective in converting AF of a recent onset (duration 3 h to < 7 days) for at least one minute (within 90 min postdose), thus meeting the primary efficacy endpoint of the program. All the Phase III studies showed statistically significant greater conversion to sinus rhythm compared to placebo and the active comparator, amiodarone. The median time to conversion to SR was only 10 minutes suggesting that vernakalant acts rapidly.

The most commonly used agent, amiodarone, is contraindicated in the presence of Class Ia and Class III antiarrhythmics and is not recommended to be combined with beta-blockers or calcium channels blockers with rate control properties (for example, diltiazem and verapamil). Furthermore, amiodarone has a delayed onset of activity and can require infusions of up to 24 hours, as it may take several hours or longer for successful cardioversion [Chevalier et al., 2003; Cordarone X PI, 2010].[35,36] Considering the slow onset of action of amiodarone, vernakalant would provide an important therapeutic option for rapid conversion to SR.

The specificity of the ACT II study design enabled efficacy (and safety) assessments of vernakalant injection in patients with new onset AF after cardiac surgery, a subset of the overall AF patient population not included in the ACT I, ACT III and AVRO studies.

Vernakalant also showed significant reduction in AF symptoms at 90 minutes postdose although blinding could have been compromised in almost 25% of the patients who received vernakalant due to specific AEs such as sneezing and dysgeusia which were experienced only by patients receiving vernakalant. A *post hoc* analysis showed that 93-97% of vernakalant patients who had converted within 90 minutes maintained SR at 24 hours and 7 days, although the maintenance rate was much lower in post-cardiac surgery patients treated with vernakalant (57-58%).

Another important benefit of pharmacological conversion is to provide an alternative to electrical cardioversion and its associated risks [Guedon-Moreau et al., 2007], including risks associated with sedation and anaesthesia [Burton et al., 2004].[37,38]

More patients in the placebo group (58.4%, 184/315) underwent electrical cardioversion compared to the vernakalant group (36.6%, 270/737) within the first 24 hours. Although a third of the patients treated with vernakalant still needed electrical cardioversion, vernakalant did not affect response to subsequent cardioversion.

Risks

Conversion to sinus rhythm regularises ventricular rate, improves cardiac function, cardiac output, exercise capacity, improves symptoms and improves haemodynamics (Fuster et al., 2006).[15] However, invasive haemodynamic testing was not done for vernakalant.

Conversion to and maintenance of SR for only a short period of time (at least one min within 90 min postdose as defined for the primary efficacy analysis of all Phase III studies) by vernakalant warrants neither the symptomatic improvement of AF nor the prevention of its complications (such as cerebrovascular accident). The effect of vernakalant on morbidity and mortality was not evaluated in any of the Phase III studies.

Furthermore, conversion rate was higher and more significant after the first dose of vernakalant with patients four times less likely to convert to SR after the second dose. The risk of hypotension was increased at vernakalant plasma levels associated with the maximum 5 mg/kg dose. Hence, the benefit risk profile of the second dose of vernakalant does not appear to be favourable.

[35] Chevalier P, Durand-Dubief A, Burri H *et al.* Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2003; 41: 255–262.

[36] Sanofi-Aventis. Cordarone X Product Information, 2010. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05573-3.

[37] Guédon-Moreau L, Gayet JL, Galinier M, *et al.* Incidence of early adverse events surrounding direct current cardioversion of persistent atrial fibrillation. A cohort study of practices. Thérapie 2007; 62: 45-48.

[38] Burton JH, Vinson DR, Drummond K *et al.* Electrical cardioversion of emergency department patients with atrial fibrillation. Ann Emerg Med 2004; 44: 20-30.

There was a trend suggesting reduced efficacy in patients with a history of CHF, valvular heart disease, structural heart disease and renal/hepatic impairment. Furthermore, subjects with advanced heart failure which is also a common cause of AF were excluded from all studies.

The incidence of SAEs was higher in vernakalant treated patients compared to placebo in the first 2 hours postdose (2.5% versus 0.6%), including 8 SAEs of hypotension and 11 SAEs of cardiac arrhythmias (supraventricular/ventricular arrhythmia/cardiac arrest). The incidence of discontinuations due to AEs in vernakalant treated patients was slightly higher (3-4% compared to <1% in placebo/amiodarone groups) and the most common causes of discontinuations were hypotension and bradycardia.

The effect of vernakalant on complications of AF (for example, thromboembolism) or morbidity/mortality were not evaluated in the clinical studies. There were no deaths in the placebo/amiodarone group compared to 6 deaths in the vernakalant treated patients. Four of these deaths were not likely to be related to administration of vernakalant injection due to the fact that they occurred 2 days to 26 days after the administration of the short-acting vernakalant injection. However, 2 deaths occurred within 2 hours of starting the vernakalant infusion in a highly monitored environment and were due to ventricular fibrillation and pulmonary embolism in patients with other comorbidities.[39] Hence, the cardiac risks associated with vernakalant infusion need to be explored further as patients with recent onset AF are likely to have significant comorbidities. Other adverse events that further diminish the benefit risk profile of vernakalant include third degree AV block, life threatening bradycardia and hypotension. The report of the serious adverse event of cardiogenic shock which led to termination of the ACT-V study by the FDA has raised additional safety concerns. The ACT-V study was specifically conducted in patients without history of CHF. However, this patient developed serious cardiogenic shock which led to other complications and in eventual death 3 weeks after administration of vernakalant.

Balance

Atrial fibrillation is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function [Fuster et al., 2006].[15] 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].[40] The lifetime risk to develop AF at 55 years of age has been estimated at 23.8% in men and 22.2% in women [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].[41,42,43] AF can cause discomfort and is associated with a number of symptoms, such as palpitations, chest pain, dyspnoea, fatigue and light-headedness [Fuster et al., 2006].[15] AF can also lead to stroke,

[39] Sponsor comment: "There was an event of pulmonary embolism reported within 24 hours but it did not result in death. The patient with a pulmonary embolism died 24 days later."

[40] Heeringa J, van der Kuip DAM, Hofman A *et al.* Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006; 27: 949-953.

[41] Mariscalco G, Engström KG. Atrial fibrillation after cardiac surgery: risk factors and their temporal relationship in prophylactic drug strategy decision. Int J Cardiol 2008; 129: 354-62.

[42] Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001; 135: 1061-1073.

[43] Mathew JP, Fontes ML, Tudor IC *et al.* A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004; 291: 1720-1729.

congestive heart failure, and an overall increase in morbidity and mortality [Fuster et al., 2006; Heeringa *et al.*, 2006; Stewart *et al.*, 2002].[15,40,44]

Atrial fibrillation can be treated by either rate control (allow AF to continue but control the ventricular response rate by slowing conduction through AV node with calcium channel blockers, beta-blockers and/or digoxin) or by rhythm control therapies (convert to sinus rhythm with non-pharmacological and/or pharmacological therapies and attempt to maintain sinus rhythm with maintenance medications) or a combination of rate and rhythm control therapy.

Currently available antiarrhythmic drugs for the treatment of atrial fibrillation are limited in their efficacy and have potential for adverse effects, including torsades de pointes. With the ageing of the population, the incidence of atrial fibrillation will double in frequency over the next 15 years. Vernakalant endeavours to fulfil the requirement for more effective and safer antiarrhythmic drugs for the treatment of atrial fibrillation.

Vernakalant provided rapid conversion to sinus rhythm (within 10 minutes of infusion). It was significantly more effective than placebo or amiodarone for the proposed indication in a selective population of patients with recent onset AF (< 7 days). Unlike amiodarone, vernakalant could be given with rate control drugs such as calcium channel blockers or beta-blockers. Vernakalant may reduce the need for electrical cardioversion with its associated risks within the first 24 hours and does not affect the response to subsequent cardioversion.

Based on the diminished response observed with the second dose of vernakalant compared to that of the first dose and the increased risk of AEs such as hypotension associated with maximum vernakalant dose of 5 mg/kg, vernakalant may be useful in a single dose formulation for a population similar to that studied in the vernakalant clinical program (contraindications in patients with obstructive heart disease, advanced CHF, other reversible causes of AF); however, efficacy/safety of a single dose (3 mg/kg) vernakalant was not evaluated in this submission.

Although vernakalant did improve AF symptoms, blinding in the studies could have been compromised in almost 25% of the patients who received vernakalant due to specific AEs such as sneezing and dysgeusia which were experienced only by patients receiving vernakalant. Another major limitation of the submission was that the effects on morbidity and mortality were not evaluated in any of the vernakalant studies.

Conversion from AF to sinus rhythm is associated with risks which are independent of whether electrical or pharmacological means are employed (for example, thromboembolism). Although vernakalant is atrial specific and less likely to cause ventricular arrhythmias, there were two cases of ventricular fibrillation in vernakalant treated patients, one of which was fatal in a highly monitored environment. The level of exposure to this drug is limited and there is no assurance that other cases of ventricular fibrillation will not occur when exposure to vernakalant increases and subjects with significant structural heart disease are exposed. There was another death in a vernakalant treated patient due to pulmonary embolism.[45] Other adverse events that further diminish the benefit-to risk-profile of vernakalant include third degree AV block, life threatening bradycardia and hypotension.

[44] Stewart S, Hart CL, Hole DJ *et al.* A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113: 359–364.

[45] Sponsor comment: "This event was assessed as not related to the study drug."

Conclusions

Based on the submitted data, the benefit risk profile of vernakalant (2 doses, 3 mg/kg followed by 2 mg/kg) is not favourable for the proposed indication of 'rapid conversion of recent onset atrial fibrillation (< 7 days duration) to sinus rhythm."

V. Pharmacovigilance findings

Risk management plan

Safety specification

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the Office of Product Review (OPR). The summary of the ongoing safety concerns as specified by the sponsor is shown in Table 27.

The clinical evaluator noted that the safety specification was generally accurate with the exception of the following issues:

- Patients with significant valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis or reversible causes of AF were excluded from all Phase III studies. Furthermore, subjects with AMI and advanced CHF (2 of the main causes of AF) were excluded in all 4 Phase III studies with the exception of AMI in the ACT-II study. Hence, the findings cannot be extrapolated to all patients with short term AFB as suggested in the proposed indication.
- Exposure in special populations: the proposed dose of vernakalant was not evaluated in patients with hepatic/renal impairment and patients with severe renal/hepatic impairment were excluded from the pivotal clinical studies.

Table 27: Ongoing safety concerns

Important identified risks	Hypotension Bradycardia Ventricular arrhythmia in patients with history / evidence of CHF
Important potential risks	Ventricular arrhythmia in patients without CHF Atrial flutter Overdose / Medication error
Important missing information	Patients with heart failure NYHA class III and IV Diseases / Conditions not studied in clinical trials: • Patients with prolonged QT (uncorrected > 440 msec) • Patients with severe bradycardia, sinus node dysfunction, or second and third degree heart block (without pacemaker) • Patients with clinically meaningful valvular stenosis • Patients with hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis Off label use, to include: • Patients with severe aortic stenosis, or systolic blood pressure < 100 mm Hg • Patients with recent myocardial infarction or acute coronary syndrome • Patients treated for arrhythmias other than atrial fibrillation Use of intravenous antiarrhythmic drugs (class I and class III) within 4-24 hours prior to vernakalant administration Use of intravenous antiarrhythmic drugs (class I and class III) in the first 4 hours after vernakalant administration Use of oral antiarrhythmic therapy (class I and class III) Patients with pacemakers Hepatic impairment Use in pregnant or lactating women Paediatric use

Pharmacovigilance plan

The sponsor stated that routine pharmacovigilance activities are proposed to monitor all the specified ongoing safety concerns.[46]

[46] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Furthermore, in view of the recognised limitations of spontaneous reporting, the sponsor proposed to arrange for organised, prospective data collection and pre-specified analysis through a post authorisation registry study to further monitor all the specified ongoing safety concerns, except for the important missing information: 'Use in pregnant or lactating women' and 'Paediatric use'. This multicentre registry study will be launched in multiple EU countries to collect data about normal conditions of use and dosing and to characterise reporting frequencies for medically significant adverse drug reactions. 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 the drug. The design of this registry will be consistent with the principles of a post authorisation safety study as described in Volume 9A of The Rules Governing Medicinal Products in the European Union, Guidelines on Pharmacovigilance for Medicinal Products for Human Use.

The primary research objectives of the registry are to describe patients receiving vernakalant injection in the context of the product label for the appropriate use and dosing of the product, and to better estimate the incidence of medically significant health outcomes of interest (HOIs). Collection of information on appropriate dosing/administration and patient selection for vernakalant injection will provide an assessment of physician behaviour in the context of the product label.

The OPR reviewer had no objection in principle to the sponsor implementing an additional post authorisation safety study (PASS) to further monitor all the specified ongoing safety concerns, except for the important missing information: 'Use in pregnant or lactating women' and 'Paediatric use'.

The draft protocol for this PASS and the proposed reporting milestones appeared reasonable, except for the apparent discrepancy between the study definition of significant hypotension being symptomatic hypotension with systolic BP < 90 mmHg and the ongoing safety concern limit in regard to the important identified risk: 'Hypotension' and the important missing information: 'Off-label use' being systolic BP < 100 mmHg. The OPR reviewer noted that the sponsor should amend the former accordingly. In addition a final protocol for this study should be provided to the TGA for review once it becomes available.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for the important potential risks: 'Ventricular arrhythmia in patients without CHF' and 'Atrial flutter'; and the important missing information: 'Patients with pacemakers', 'Use in pregnant or lactating women' and 'Paediatric use'.[47]

Additional risk minimisation activities have also been proposed for all the remaining ongoing safety concerns. Detailed healthcare professional education materials (the content of which will be finalised when the European Summary of Product Characteristics is approved) will attempt to minimise the risk of vernakalant associated undesirable effects in the intended population and specific subpopulations, inappropriate patient selection and inappropriate use of vernakalant. A draft information card was provided and will form the basis of this proposed education program. These materials will be pre-tested for comprehension and understanding by healthcare providers, prior to distribution. The healthcare professional (HCP) education materials, including the HCP Information Card, will be agreed with the national authorities prior to distribution of these materials in each EU Member State, in order to allow adaptation of the materials to

[47] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

national legislative and/or health system constraints. The sponsor will use methods to distribute the healthcare professional materials that may include providing the materials with the shipped product, and inclusion of the content of the educational material in national online tools accessible to health care providers.

The OPR reviewer noted that the sponsor should definitively state whether the proposed additional risk minimisation activities will be conducted in Australia in accordance with Australian specific registration details. Final Australian HCP education materials, including the HCP Information Card, should be submitted to the TGA for review and evidence that these HCP education materials have been pre-tested for comprehension and understanding by health care providers should also be provided.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft Product Information document be revised but this consideration is beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator recommended approval with respect to chemistry and manufacturing control.

Details of the submission were presented to the PSC in November 2010. The PSC considered that if more than one manufacturing site was ever to be proposed, then the sponsor should provide, at that time, further data relating to sterility, batch analysis and stability for each site.

In addition, the PSC "considered that while the chosen structural population PK model was appropriate, the covariate (and final) model may not be. This is due to the fact that the stepwise inclusion and deletion process appears not to have been employed despite the claim that it was. This may have led to the conclusion that weight was not important and the selection of a rather very large gender effect (it is very hard to justify a 50% difference in V_d between males and females with similar body weights). Furthermore, the conclusion that weight was not important is at odds with the sponsor's proposal of doses in units of mg/kg. The PSC agreed that this should be brought to the attention of the Delegate and the ACPM".

The Delegate requested that the sponsor respond to this comment of the PSC.

Nonclinical

There were no nonclinical objections to the registration of vernakalant for the rapid conversion of recent onset atrial fibrillation to sinus rhythm.

In vitro and *in vivo* studies indicated that vernakalant acted as a cardiac sodium and potassium channel blocker with demonstrable anti-arrhythmic activity. It may be expected to show a degree of atrial specificity based on inhibition of I_{KUr} and I_{KACh} and possibly via frequency and voltage dependent inhibition of the sodium channel Nav 1.5 (hH1).

Safety pharmacological studies with IV administration were generally adequate. Repeated dose toxicity studies were conducted in rats and dogs. Vernakalant elicited dose limiting CNS activity, including convulsions, uncoordinated gait and tremors. Also elicited were

respiratory effects with a transient increase in tidal volume as well as some cardiovascular changes. Although experimental conditions varied between studies, blood pressure, heart rate and contractility were reduced by vernakalant. Potential interactions with platelets were not investigated. High dose drug exposures based on C_{max} were about six times the expected human value in the case of rats and about two times the expected human value in the case of dogs. Those based on cumulative AUC over the 2-4 week study periods were above 20 times the expected human value for both species.

Following single IV administration, plasma vernakalant clearance was relatively high in the experimental species examined, with associated short $t_{1/2}$ values (approx. 2-3 L/h/kg for clearance and 3 h for $t_{1/2}$ in dogs).

Vernakalant was shown to be a substrate for p-glycoprotein in an *in vitro* assay. *In vitro* studies with human preparations showed that vernakalant was metabolised mainly via CYP2D6 with the formation of 4-O-demethylated vernakalant and to a small extent the corresponding 3-O-demethylated derivative. Low levels of glucuronidation of the 4-O-demethy derivative were also demonstrable.

A positive result was obtained in one genotoxicity assay (chromosomal aberrations *in vitro*). The nonclinical evaluator commented that while it would have been prudent to have conducted another confirmatory assay, the weight of evidence suggests that vernakalant does not pose an overall genotoxic risk given its proposed single use.

Increased post-implantation loss and fetal variations and malformations were seen in rats and rabbits with twice daily oral dosing during organogenesis, at respective exposures of 1.7 and 3 times the maximum recommended clinical exposure. The clinical relevance of these findings was, according to the nonclinical evaluator, somewhat diminished by the generally high exposure margins achieved with twice daily oral dosing in animals compared with the proposed single/intermittent clinical use of vernakalant. However, as also noted by the nonclinical evaluator, the degree of concern would need to be reconsidered should the indicated patient population be expanded in the future to include more frequent and/or increased dosing with this product.

Clinical

Clinical evaluation

The clinical evaluator recommended that, based on the submitted data, the benefit risk profile of vernakalant was not favourable for the proposed indication. While the drug demonstrated efficacy in the rapid conversion of atrial fibrillation to sinus rhythm, there were significant safety concerns which were felt to outweigh its efficacy benefit. Although vernakalant is atrial specific, there were two cases of VF in vernakalant treated patients and one of these was fatal. The clinical evaluator was of the opinion that, because of the limited level of exposure to the drug, there is no assurance that other cases of VF will not occur when greater numbers of subjects are exposed once the drug is approved, including subjects with significant structural and other heart disease. There was another death in a vernakalant treated patient due to pulmonary embolism.[45] Other AEs that further diminished the benefit risk profile of the drug were third degree AV block, life threatening bradycardia and hypotension.

Pharmacology

Vernakalant has the following properties:

- It is extensively and rapidly distributed in the body with V_d of approx. 2 L/kg
- The free fraction in human serum is 53-63% at a concentration range of 1-5 µg/mL

- C_{max} and AUC is dose proportional between 0.5 and 5 mg/kg
- It is extensively and rapidly metabolized. High levels of vernakalant itself and of its metabolites are measured in urine within 2 hours after dosing
- In CYP2D6 EMs, vernakalant was mainly metabolized by CYP2D6 mediated O-demethylation followed by glucuronidation. In CYP2D6 PMs, direct glucuronidation of vernakalant is a more important metabolic pathway.

Pharmacokinetics in the target population was similar to that in healthy subjects with a dose proportional increase in $AUC_{0\text{-}90min.}$ Overall no dosing adjustments were necessary according to CYP2D6 genotype

With respect to the effect of age, sex, race and renal/hepatic impairment:

- Age, sex and race did not have a significant effect on vernakalant pharmacokinetics following IV infusion.
- Although the mean CL_R of vernakalant was decreased in all renal impairment groups, the C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ of vernakalant and its main metabolite RSD1385 for the subjects with mild, moderate and severe renal impairment were similar to those for the subjects with normal renal function.
- Similarly, elimination rate somewhat slower in patients with severe hepatic impairment compared with the other groups (mild/moderate impairment, normal) but vernakalant exposure by C_{max} and AUC was similar in all groups.
- However, because of wide 90% CIs in both the renal and hepatic impairment studies, no conclusive evidence for lack of effect of renal/hepatic impairment on vernakalant PK.
- In both the studies in subjects with renal/hepatic impairment, only a dose of 2 mg/kg studied, not the proposed dose of 3 + 2 mg/kg; patients with severe renal/hepatic impairment excluded from the Phase III studies.

No formal clinical drug-drug interaction studies were conducted. In the population PK analysis, β-blockers and the four most commonly used concomitant medications (warfarin, metoprolol, furosemide and digoxin) were not significant covariates of acute exposure to vernakalant ($AUC_{0\text{-}90min}$ and C_{max}). *In vitro* evidence suggests a lack of competition/interaction for binding sites with warfarin, propranolol, acebutolol, diltiazem, verapamil or quinidine

Vernakalant has been administered with concomitant medications known to inhibit CYP2D6 in several patients to date, with no significant AEs observed and vernakalant has been safely administered to subjects receiving concomitant warfarin.

Using invasive electrophysiological testing, it was shown that vernakalant prolonged AERP in a dose-dependent manner. At the doses studied, 2 and 4 mg/kg, vernakalant had no significant effects on ventricular refractoriness or repolarisation and it tended to slow conduction in ventricular tissue at the higher dose level. The proposed maximum dose of 5 mg/kg was not studied. Invasive haemodynamic testing was not done for vernakalant.

Efficacy

The efficacy of vernakalant injection was evaluated in 3 placebo controlled clinical studies. These 3 randomised, double blind studies included two pivotal Phase III studies, ACT I and ACT III, in which the cohort of short duration AF patients constituted the primary efficacy population and one pivotal Phase III study, ACT II, which expanded the efficacy profile to include post-cardiac surgery patients. There was one Phase III active controlled (IV vernakalant versus IV amiodarone) study (AVRO), which evaluated the efficacy of vernakalant in patients with AF of 3 to 48 hours duration.

Supportive safety and/or efficacy data was available from another three studies. The first was a Phase II study in patients with AF, the Cardiome Recent onset Atrial Fibrillation Trial [CRAFT]. The second was a Phase III open label safety study in patients with AF [ACT IV] which included some efficacy assessments and the third was another Phase III study [Scene 2] which assessed the efficacy and safety of IV vernakalant in the conversion of atrial flutter (AFL) to sinus rhythm.

Dose response studies

1235-1001 [CRAFT] was a Phase IIa, randomized, double blind, placebo controlled, step up dose, three arm parallel design study. The percentage of patients whose AF was terminated, for at least one minute, during infusion or in the 30 minute follow up period was significantly greater in the 2-3 mg/kg vernakalant group compared to placebo (11/18, 61.1% versus 1/19, 5.3%, p = 0.0003). There was no such statistically significant result when the lower step up regimen (0.5-1.0 mg/kg) was compared with placebo (Table 3).

As noted by the clinical evaluator, it was not clear why the regimen used in the CRAFT study, 2 + 3 mg/kg, was reversed in the Phase III studies (3 + 2 mg/kg). The sponsor has responded (see List of Questions below).

Pivotal studies

The clinical efficacy of vernakalant in the treatment of patients with AF was evaluated in three randomized, double blind, placebo controlled studies [ACT I, ACT II and ACT III] and in an active controlled study versus IV amiodarone [AVRO]. Their study designs were similar and in general accord with the relevant TGA-adopted EU guideline, although it should be noted that this particular guideline has not been revised since November 1995.[8]

The guideline gives very little specific advice about endpoints, even primary endpoints. The primary efficacy endpoint for the all the Phase III pivotal trials in this submission was the proportion of patients with AF of > 3 hours but ≤ 7 days duration who had treatment induced conversion to sinus rhythm for a minimum duration of one minute within 90 minutes of first exposure to the study drug. Thus a subject whose AF was abolished for at least a minute but for less than 2 minutes or one hour, for example, would have achieved the primary efficacy outcome. However, from the standpoint of actual clinical utility, maintenance of effect is of more interest. However, this was only studied in the context of exploratory endpoints.

Pivotal study, ACT I (1235-0703)

Primary efficacy endpoint

In subjects with short duration AF, a statistically and clinically significantly (p < 0.0001) greater proportion of vernakalant recipients (75/145, 51.7%), compared with placebo recipients (3/75, 4.0%), converted to sinus rhythm within 90 minutes and met the primary efficacy endpoint (treatment difference, vernakalant – placebo = 47.7% with 95% CI [38.5%, 57%] and odds ratio = 24.0 with 95% CI [6.9, 83.6)]. The PP analysis showed similar results (51.4% versus 4.2%, treatment difference = 47.2% with 95% CI [37.8%, 56.6%], p < 0.0001 and odds ratio = 22.6 with 95% CI [6.4, 79.7].

Key secondary efficacy endpoints

In subjects with short duration AF, compared with placebo recipients, vernakalant treated patients experienced a statistically and clinically significantly (p < 0.0001) shorter time from first study drug exposure to first conversion of AF to sinus rhythm lasting at least one minute and within 24 hours of first exposure to study drug (Table 6) with similar results in the overall population (Table 7). Patients with long duration AF did not show any difference in the time to termination of AF between treatment groups.

Exploratory endpoints

There were a number of exploratory efficacy endpoints which were supportive of the principal results. From a real world, practical, clinical perspective, of particular interest is how long the anti-arrhythmic effect lasted. There was a *post hoc* analysis which calculated what were termed "*life table estimates*" which declared 97.0% maintenance of sinus rhythm at 24 hours and 92.0% maintenance at 7 days in subjects with short duration AF treated with vernakalant. This was compared with 66.7% maintenance for the 3 subjects in the placebo group. The sponsor was asked to clarify precisely what is meant by a life table estimate. Does it mean, for example, that 92.0% of the 75 subjects in the short duration group who converted to sinus rhythm after treatment with vernakalant (that is, 69 subjects) were all clinically examined at 7 days and found to be still in sinus rhythm? If not, what are the exact percentages of subjects successfully treated with vernakalant who were still found, by clinical examination, to be in sinus rhythm at 24 hours and at 7 days?

Pivotal study, ACT III, 04-7-010

Primary efficacy endpoint

In subjects with short duration AF, a greater proportion of subjects treated with vernakalant converted to sinus rhythm within 90 minutes of first exposure to the study drug compared with placebo-treated subjects (44/86, 51.2% versus 3/84, 3.6%, treatment difference vernakalant – placebo = 47.6% with 95% CI [36.3%, 58.9%], $p < 0.0001$ and odds ratio = 38.3 with 95% CI [9.2, 159.5].

Key secondary efficacy endpoints

Subjects with short-duration AF who were treated with vernakalant when compared with those who were treated with placebo, experienced a shorter time from first study drug exposure to first conversion of AF to sinus rhythm within 24 hours of first exposure to study drug (Table 10). Other secondary endpoints were generally supportive of the primary outcome. However, as with the previous study, ACT I, it should be noted that in those with long duration AF, there was no statistically significant difference between the two treatment groups in the proportion of subjects who had treatment induced AF termination within 90 minutes of first exposure to study drug (vernakalant versus placebo: 9.4% versus 2.7%, $p = 0.3303$). Also, only one of the 14 subjects with AFL (> 3 hours and < 45 days) treated with vernakalant experienced treatment induced AFL termination for at least one minute within 90 minutes of first exposure to study drug compared with none of the 9 subjects treated with placebo.

Exploratory endpoints

There were a number of exploratory endpoints which were also generally supportive of the primary outcome. Again the most important of these from a practical, clinical perspective would have to be the proportions of subjects in each treatment group still in sinus rhythm after a period of follow up. Of the 44 subjects who converted to sinus rhythm after treatment with vernakalant in the short duration AF group, 35 (79.5%) and 33 (75.0%) patients were still in sinus rhythm at 24 hours and 7 days, respectively.

Pivotal study ACT II, 1235-0104

Primary efficacy endpoint

A statistically significantly greater proportion of subjects in the vernakalant group (48/107, 44.9%) converted to sinus rhythm for at least one minute within 90 minutes of first exposure to the study drug compared to subjects in the placebo group (8/54, 14.8%). The treatment difference, vernakalant minus placebo was equal to 30% (95% CI [16.7%, 43.4%], $p = 0.0002$ and odds ratio = 3.00 with 95% CI [1.53, 5.87] (table 13). These results were supported by both the per protocol and the all randomized subjects analyses.

Key secondary efficacy endpoints

These were generally supportive of the primary outcome. However, for the total of 10 subjects in atrial flutter at baseline, one of the four in the placebo group converted to sinus rhythm within 90 minutes while none of the six subjects in the vernakalant group did so.

Exploratory endpoints

Two of the exploratory efficacy analyses are noteworthy. The proportions of patients still maintained in sinus rhythm at 24 hours and at 7 days were similar in the vernakalant (57-59%) and placebo (50%) groups. It should be noted that the 50% in the placebo group refers to 50% of a total of only 8 subjects who converted to sinus rhythm within 90 minutes. In other words, 4 out of 8 subjects in the placebo group maintained sinus rhythm at both 24 hours and 7 days. By contrast, 59.5% of 48 subjects (29) who responded to vernakalant within 90 minutes were still in sinus rhythm at 24 hours with the corresponding figures at 7 days being 56.9% of 48 subjects (27 subjects). These figures are once again the life table estimates. The Delegate requested the sponsor to give the actual percentages of subjects in each of the treatment groups who were found, by clinical examination, to be still in sinus rhythm at 24 hours and at 7 days.

The second of the noteworthy exploratory analyses concerns the comparative symptom analysis in each of the treatment groups. While there were statistically significantly fewer subjects in the vernakalant group who experienced rapid heartbeats, palpitations and irregular pulse at 90 minutes compared with those in the placebo group, there were no statistically significant differences between treatment groups with respect to symptoms at 24 hours. Furthermore, at both the 7 day and 30 day follow up visits, there was a trend to a higher incidence of symptoms in patients who had received vernakalant compared with those who had received placebo. It is debatable how much weight can be attached to the reporting of symptoms at a greater time from the treatment and without knowing whether the symptoms were being reported in responders or nonresponders. The sponsor was requested to re-do these analyses, this time stratified by responder versus non-responder.

Pivotal study AVRO, VERI-305-AMIO

Primary efficacy endpoint

There was a statistically significantly ($p < 0.0001$) greater proportion of subjects converting from AF to sinus rhythm within the first 90 minutes in the vernakalant group (6/116, 51.7%) compared to amiodarone (6/116, 5.2%) (Table15). Patients treated with vernakalant were 10 times more likely to convert to sinus rhythm within 90 minutes as compared to subjects treated with amiodarone (OR = 10.0, 95% CI [4.5, 22.2]. The results in the per protocol population were consistent with those from the primary analysis (59/113, 52.2% versus 6/113, 5.3%, $p < 0.0001$). As noted by the clinical evaluator, amiodarone is a slower acting drug and was given as an infusion over 120 minutes, that is for a full 30 minutes beyond the time point at which the primary efficacy endpoint was measured.

Key secondary efficacy endpoints

These were generally supportive of the primary outcome. Treatment with vernakalant resulted in a statistically significantly faster conversion rate from AF to sinus rhythm within the first 90 minutes compared to amiodarone. In the vernakalant group, 25% of subjects had converted by 11 minutes and 50% by 50 minutes postdose compared to the amiodarone group where only 5% had converted by 90 minutes. A statistically significantly ($p = 0.0012$) greater proportion of subjects reported no AF symptoms at 90 minutes in the vernakalant group (62/116, 53.4%) compared to amiodarone (38/116, 32.8%). It is interesting that the latter two percentage rates are much closer than those for the primary efficacy parameter which was for actual AF conversion. This may have

something to do with the differing modes of action of the two drugs, as well as their differing rates of action.

Exploratory endpoints

There are results here that hint at the fact that, from the perspective of showing the comparator amiodarone in its best possible light, this was a deeply flawed and biased study. The clinical evaluator noted that there was a significantly greater proportion of subjects in the vernakalant group who converted to sinus rhythm within the first 4 hours post-dose compared to the amiodarone group (54.4% versus 22.6%, adjusted log rank p-value < 0.0001). Comparative conversion rates at 90 minutes were 51.7% versus 5.2%. Thus between the time points of 90 minutes and 4 hours, there was a shift from 51.7% to 54.4% (that is, almost no shift) for the vernakalant treated group compared with a shift from 5.2% to 22.6% (that is, over a 4 fold increase) for the amiodarone treated group. The Delegate could find no further reports of the raw conversion rates for each treatment group beyond the time point of 4 hours. Also the clinical evaluator noted that by Day 7, a non-significantly greater proportion of amiodarone treated patients (85.3%, 99/116) were free of AF symptoms compared to vernakalant treated patients (75.9%, 88/116). Further insight into the unfairness of the comparison between the two agents is given in a table which compares the proportions of patients who converted within 90 minutes and maintained sinus rhythm up to the time points of 4 hours, 7 days and 30 days. Here the comparison with amiodarone is based always on the 6 amiodarone treated patients who responded within 90 minutes. However, it is known that many more responded soon afterwards. The Delegate requested that the sponsor, in its pre-ACPM response, show the numbers and rates in each treatment group who converted to sinus rhythm at any time up to 24 hours and then the corresponding numbers and rates for those who were found to be still in sinus rhythm at 7 days.

Supportive studies

Study 05-7-012, ACT IV

The main objective of the Phase III, open label study 05-7-012, ACT IV was to provide additional safety data in 236 patients. Efficacy was assessed and found to be similar to that reported in each of the pivotal studies, ACT I and ACT III.

Study 1235-0703B, Scene 2

Scene 2 was a Phase II/III, multicentre, randomised, double blind, placebo controlled study involving 60 adult patients with atrial flutter (AFL). Only one vernakalant patient (1/39, 2.6%) converted to sinus rhythm within 90 minutes and met the primary efficacy endpoint. Even this patient was diagnosed as having AF. No placebo subjects met the primary endpoint.

Efficacy in special populations

There was no difference in response to vernakalant injection according to sex. Analysis by age comparing those < 75 years with those ≥75 years showed a trend to reduced efficacy with increased age with conversion rates of 52.1% in the younger age group and 26.4% in the older age group.

Conversion rates were significantly higher in the vernakalant group compared with placebo for all categories of concomitant rate control medication, with the exception of digoxin. With concomitant digoxin, there was a suggestion of decreased efficacy but there were only small numbers of patients on digoxin.

Conversion rates were higher in the vernakalant group compared with placebo for all categories of concomitant rhythm control medications.

There were no significant differences in response to vernakalant injection in patients taking concomitant CYP2D6 inhibitors, CYP2D6 substrates or QT prolonging medications.

Nor were there any significant differences in response to vernakalant injection by CYP2D6 genotype.

History of various medical conditions at baseline did not appear to alter response to vernakalant injection, with the exception of a prior history of congestive cardiac failure. The rates of conversion of AF to sinus rhythm in the cohort with short duration AF were 26.9% for those with a history of congestive cardiac failure versus 50.0% without any such history.

The rates of conversion to sinus rhythm in the short-duration cohort were lower in patients with renal impairment (34.1%) compared with patients with normal renal function (55.5%). The contrast was not as marked with respect to hepatic impairment where the rates of conversion to sinus rhythm were 36.8% in patients with abnormal hepatic function and 47.9% in those with normal hepatic function. Patients with severe renal or hepatic impairment were excluded from all Phase III studies.

Atrial flutter

The Scene 2 study (1235-0703B) failed to demonstrate efficacy of vernakalant injection in the conversion of typical atrial flutter to sinus rhythm.

Analysis performed across clinical trials

The Phase III pivotal studies, ACT I and ACT III were similar in design and patient characteristics. In a pooled analysis of the efficacy results from these 2 studies, vernakalant injection 3.0 mg/kg, followed by 2.0 mg/kg if required, induced conversion from short-duration AF to sinus rhythm within 90 minutes of first exposure to study drug in a statistically and clinically significantly greater proportion of patients compared with placebo (118/231, 51.1% versus 6/159, 4%).

Safety

The overall safety evaluation for vernakalant injection incorporated data from one Phase II, one Phase II/III study, four placebo or active controlled Phase III studies and a Phase III uncontrolled safety study. Safety data was evaluated in 3 datasets:

- Pooled data from the "All Patients" set with AF or AFL in Phase II (CRAFT, Scene 2) and Phase III studies [ACT I, ACT II, ACT III and ACT IV] who received any amount of study medication (773 vernakalant and 335 placebo patients)
- Patients in ACT II, the post-cardiac surgery study, were included in the "All Patients Pool" above but were also presented separately in various sub-analyses. This "ACT II Pool" consisted of all patients in the ACT II study of new onset AF or AFL subsequent to cardiac surgery, who received any amount of study medication (107 vernakalant and 54 placebo)
- Patients in the amiodarone controlled study, AVRO (116 vernakalant and 116 amiodarone)

The majority of the AEs in vernakalant treated patients occurred in the first 2 hours postdose. The most frequent classes of AEs included *Nervous System Disorders* (35.3% vernakalant versus 29,9% placebo) and *Respiratory, Thoracic and Mediastinal Disorders* (28.7% vernakalant versus 7.5% placebo). Over half the events under *Cardiac Disorders* were relapse of AF (17.5% vernakalant versus 18.2% placebo). The most common AEs were dysgeusia, paraesthesia, sneezing, hypotension, nausea and bradycardia. The majority of these AEs were mild to moderate in severity.

In the "All Patients Pool", common AEs associated with vernakalant treatment during the first 2 hours postdose were, in decreasing order of frequency in the vernakalant group: dysgeusia (vernakalant 20.3% versus placebo 2.4%), sneezing (15% versus 0%), paraesthesiae (8.2% versus 0.9%), nausea (5.2% versus 0%), hypotension (4.7% versus

0%), cough (4.3% versus 0.6%), pruritus (3.6% versus 0%),dizziness (3.5% versus 1.8%), hyperhidrosis (3.2% versus 0.3%), feeling hot (3.0% versus 0.6%), bradycardia (2.6% versus 0%), nasal discomfort (2.5% versus 0%), paraesthesiae oral (2.3% versus 0.3%), infusion site pain (2.2% versus 0%), atrial flutter (1.3% versus 0.3%), vomiting (1.3% versus 0%) and dry mouth (1.2% versus 0%). Also of note were ventricular extrasystoles (vernakalant 4/773, 0.5% versus 0/335 on placebo, 0%). Interestingly, the incidence of headache in the first 2 hours postdose was higher in the placebo group (vernakalant 1.3% versus placebo 2.4%). The incidences of these AEs during the following 22 hour period between the 2 hour and 24 hour postdose time points largely equalized with no or only minor differences between the two treatment groups. In that second time period, the exceptions included the following AEs of importance which were now more common in the placebo group: bradycardia (vernakalant 0.8% versus placebo 1.8%), sinus bradycardia (vernakalant 1.0% versus placebo 1.5%), ventricular extrasystoles (vernakalant 0.6% versus placebo 0.9%) and hypotension (vernakalant 1.2% versus placebo 2.7%). In that second time period, atrial flutter was still more common in the vernakalant group, albeit now with a halved incidence compared with the first 2 hours (vernakalant 0.6% versus placebo 0.3%). Also in that second time period, headache became more common in the vernakalant group (vernakalant 2.7% versus placebo 0.9%). The sponsor was asked to clarify whether the event of paraesthesiae includes paraesthesiae oral (the latter listed separately) and whether bradycardia includes sinus bradycardia (also listed separately).

In Study ACT II, common AEs occurring in postcardiac surgery patients were also peri-infusional and transient, although there was a much lower incidence of dysgeusia, sneezing and paraesthesiae in these patients compared with the patients in the pooled ACT I/ACT III population. In the amiodarone controlled AVRO study, the incidence of treatment emergent AEs was higher in the vernakalant group compared with the amiodarone group.

Common AEs that occur after treatment with vernakalant injection have a reasonably predictable time of onset, occur peri-infusionally and are transient.

In the "All Patients Pool", the incidence of SAEs was higher in vernakalant treated patients compared to placebo in the first 2 hours postdose (19/773, 2.5% versus 2/335, 0.6%), including 8 SAEs of hypotension in the vernakalant group (1.0% versus 0%) and 11 SAEs of cardiac arrhythmias (supraventricular/ ventricular arrhythmia/ cardiac arrest) in the vernakalant group (1.4% versus 0%). These 11 SAEs of cardiac arrhythmia included 3 of ventricular arrhythmias and/or cardiac arrest. However, the incidence of SAEs was similar in the first 24 hours postdose (4.1% versus 3.9%). The incidence of related AEs was low overall, with a higher incidence in the vernakalant group (2.1%) than in the placebo group (0.3%). Hypotension was the most frequent related SAE (vernakalant 8/773, 1.0% versus placebo 1/335, 0.3%) and the only one that occurred in the placebo group. Other related SAEs included bradycardia (3 patients, 0.4%), complete AV block (2 patients, 0.3%) and AFL, cardiogenic shock, sinus arrest, tachycardia, ventricular extrasystoles, ventricular fibrillation, pulmonary oedema, suffocation feeling and aortic stenosis (occurring in 1 vernakalant patient each, 0.1%). In the ACT II study, the incidence of SAEs in the first 24 hours postdose was low (1.9% vernakalant versus 0% placebo). The only SAEs that occurred during this time were complete AV block and hypotension, both of which were related to treatment. In the AVRO study, the comparative incidences in the vernakalant and amiodarone groups were as follows: SAEs, 4.3% and 1.7%, respectively and related SAEs, 2.6% and 0.9%, respectively. The SAEs occurring within the first 24 hours postdose that were considered by the investigator to be related to the study drug included angina pectoris, hypersensitivity and ventricular tachycardia in the vernakalant group and cardiac arrest in the amiodarone group. The AE of cardiac arrest in the amiodarone group did not appear to have been fatal. The incidence of discontinuations due to AEs in vernakalant treated patients was low (3-4% compared to

<1% in placebo/ amiodarone groups) and the most common causes of discontinuations were hypotension and bradycardia.

There were 6 deaths in vernakalant treated patients and no deaths were reported in placebo/ amiodarone patients. Four of the deaths in vernakalant patients were not related to administration of vernakalant injection (occurred 2 to 26 days after injection). Of the 2 other deaths, one was due to hypotension in a patient coadministered oral and IV metoprolol (leading to ischaemia and ventricular fibrillation). This patient was haemodynamically unstable with severe aortic stenosis and acute coronary syndrome and should have been excluded from the study. Furthermore, he should not have received the second injection of vernakalant based on the dose-stopping criteria in the study protocol. The other was death was due to COPD/ pulmonary embolism in a patient with other comorbidities.

Adverse events of special interest

The majority of the ventricular arrhythmia events seen in the vernakalant and placebo groups were asymptomatic, non-sustained (average of 3-4 beats) ventricular tachycardia. In the 0-2 hour time period, the incidence of any ventricular arrhythmia event was similar in the vernakalant and placebo group (3.9% versus 3.2%) but the incidence of clinically relevant ventricular arrhythmia (SAE or discontinuation) was higher in the vernakalant group (0.6%, 5/773) compared to placebo (0%). The risk of ventricular arrhythmia was increased in patients with history of CHF, AMI, cardiac surgery, abnormal hepatic function and moderate/ severe renal impairment. For example, of the 5 patients in whom an SAE of ventricular arrhythmia was reported, 3 had a history of congestive heart failure. Between 2 and 24 hours postdose, there were no further clinically meaningful ventricular arrhythmia events in the vernakalant group compared with 2 events in the placebo group. There were 4 events of torsades de pointes of which 3 (2 vernakalant, 1 placebo) occurred more than 24 hours following study drug administration. There was one event of torsades de pointes which occurred within the first 24 hours after vernakalant administration. This was a 9-beat run of a ventricular arrhythmia captured on Holter monitor 2 hours and 20 minutes after the commencement of vernakalant injection and therefore about 2 hours after cessation of the latter but immediately following an infusion of ibutilide. The sponsor was asked to comment on why the latter patient was given an antiarrhythmic medication so soon after the injection of vernakalant.

Hypotension occurred either during infusion or early after the end of the infusion and was usually corrected by standard supportive measures. SAEs of hypotension (including SAEs leading to discontinuation), although uncommon, were reported more frequently among vernakalant treated patients than among placebo treated patients (9 vernakalant, 1.2% versus 1 placebo, 0.3%). However, the risk of hypotension was increased in patients with history of CHF, low baseline SBP and vernakalant plasma levels of 4000 ng/mL (associated with the maximum 5 mg/kg dose). In congestive heart failure patients, 22 of 137 treated with vernakalant (16.1%) experienced a hypotensive episode in the first 2 hours postdose compared to 3 of 64 placebo treated patients (4.7%). Hypotension was much less common in non-CHF patients.

The majority of the bradycardia events (vernakalant 5.4% versus placebo 3.8%) occurred between 0 and 2 hr postdose, were peri-infusional and resolved spontaneously. Episodes of bradycardia were more likely to be associated with conversion to sinus rhythm. Four of the 10 clinically serious events of bradycardia (SAEs or discontinuations) occurred at the time of termination of AF and the other events responded to discontinuation of vernakalant and/or administration of atropine. The incidence of complete AV block was low overall, occurring in 2 patients within 2 hours of dosing and at the time of termination of the AF, in 1 patient subsequent to electrical cardioversion and again at the time of termination of the AF and finally in 2 patients at more than 24 hours post-dose (4 days and 12 days postdose).

Within the first 2 hours postdose, adjudicated cases of atrial flutter (from CEC assessment of 12 lead ECGs) were significantly more common after treatment with vernakalant (6.1%, 45/737) than after placebo (1.6%, 5/315). Of 31 patients who had only AF on pre-treatment ECGs and who developed atrial flutter after receiving vernakalant, 10 converted to sinus rhythm within 90 minutes of treatment, 13 were electrically cardioverted to sinus rhythm within 24 hours, 4 converted to sinus rhythm without additional antiarrhythmics and 4 reverted to AF within 6 hours and remained in AF at Hour 24. Furthermore, no patients with atrial flutter following vernakalant treatment developed 1:1 atrioventricular conduction. There was a trend toward increased risk of AFL during first 2 hours postdose in vernakalant patients who were using Class I antiarrhythmics.

Age, sex, history of hypertension or duration of AF did not appear to affect the safety of vernakalant (in terms of common AEs of bradycardia, hypotension, ventricular arrhythmias and AFL). Vernakalant was associated with a slightly higher incidence of clinically meaningful events of hypotension and ventricular arrhythmia (defined as those involving SAEs or study drug discontinuation) in patients who had CHF compared with those who did not. Of the 5 patients with a SAE of ventricular arrhythmia, 3 had a history of CHF. Patients with a history of myocardial infarction and those with abnormal hepatic function and moderate/ severe renal impairment also showed an increased risk of ventricular arrhythmia. There was an increased risk of hypotension in the first 2 hours post dose in vernakalant-treated patients who were using beta-blockers (vernakalant versus placebo: 9.7% versus 3.9%) compared to those not taking beta-blockers (4.8% versus 7.1%).

Patients treated with vernakalant showed significant reduction in HR and also showed consistently greater increases in QRS interval with 5% (34/704) patients shifting from baseline of <140 msec to QRS duration of >140 msec at any postdose time point (most common at 10, 15 and 35 minutes postdose). Within the first 24 hours (ECV was not attempted in first 90 minutes postdose), 57-58% of placebo/ amiodarone and 30-37% of vernakalant patients underwent electrical cardioversion and vernakalant did not appear to affect response to subsequent cardioversion. There were no other significant effects on other laboratory parameters.

Postmarketing experience

At the time the clinical evaluation report was commenced, vernakalant had only just been approved in the EU. In the latter jurisdiction, marketing authorisation was granted on 1 September 2010. There should be by now a body of postmarketing experience data available. The sponsor was requested to supply, with its pre-ACPM response, whatever post-marketing data is available together with a summary of this data in its response.

List of questions

The clinical evaluator asked a number of questions of the sponsor and the sponsor responded. This discussion is summarised in this AusPAR. Later in the evaluation process the sponsor provided an additional response to certain other comments made in the clinical evaluation report. As noted previously, questions of an administrative nature or concerning the proposed PI are not addressed in this AusPAR. Questions which have been satisfactorily addressed are not discussed further. The following is a summary of the issues raised:

Question 1

The sponsor was asked to justify a dosage regimen above 2 mg/kg in patients with hepatic/renal impairment and to justify why the use of vernakalant should not be contraindicated in patients with severe hepatic/renal impairment. Since the volunteer patients with hepatic or renal impairment in the PK studies would have derived no benefit from exposure to the drug and because of the previously demonstrated linear PK up to

doses of 5 mg/kg, it was felt that higher exposures were not required. The clinical evaluator judged this justification adequate and the Delegate agreed. However, the Delegate also agreed with the evaluator that use of vernakalant in patients with severe hepatic/renal impairment should be contraindicated. As noted by the evaluator, there are 2 reasons, the exclusion of patients with severe hepatic/renal impairment from the Phase II/III studies and the evidence from the PK studies of likely increased exposure in patients with this degree of hepatic/renal impairment.

Question 4

The sponsor provided what details it could of the study which has been halted, that is, the study in patients with recent onset AF but without any evidence of congestive heart failure. To date, a total of 270 patients out of a projected 470 (randomised 2:1 vernakalant: placebo) have been enrolled and randomised. The evaluator stated that it is still not clear why this study was conducted with no history of CHF. However, this study was done at the request of the US FDA. Given, the higher rates of AEs like hypotension associated with CHF patients, it would be worth gaining some insight into whether vernakalant is safer to use or even more effective in patients without CHF. The sponsor was requested to comment on this issue in its pre-ACPM response.

Question 8

The sponsor was asked to comment on an observation by the evaluator that patients with AF duration of < 48 hours seemed to have better conversion rates than those whose AF duration was > 48 hours. It appears that data on AF duration was collected/recorded only in ACT I and IV. Given that AF duration was used to define who could enter the trial, the delegate found it difficult to understand how such data was not collected for ACT III. In ACT II, the postcardiac surgery study, it is comprehensible in that the subjects were known not be in AF prior to surgery and the time of surgery is known. The sponsor was requested to clarify. The sponsor's answer to the stratification observation, that is, AF duration < and > 48 hours is simply not clear. What have been provided are the comparative rates for < 48 hours and < 72 hours. Not only do these 2 groups overlap but they do not include the subjects whose AF duration was ≥ 72 hours and < 7 days. The evaluator stated that a *post hoc* analysis was also performed to determine the rate of conversion from AF to sinus rhythm for patients with AF duration of less than 48 hours. As noted above, this analysis was limited to ACT I and IV, the only studies in which data on AF duration was collected/recorded. The rate of conversion of AF to sinus rhythm for patients with AF duration < 48 hours was 61.2% in the vernakalant group compared to 4.9% in the placebo group. Therefore there must be data to calculate the rate of AF conversion for patients with AF duration > 48 hours. Insight is provided by the answer to Question 10. The sponsor provided a graph which plots the % conversion within 90 minutes versus the number of days of AF duration. The success rate drops fairly dramatically where the AF duration has been longer than 3 days. Using this figure, for ACT I, the rates of conversion for subjects with AF duration ≤ 2 days is (39+24)/63+40) = 63/103 = 61.2% as previously reported and for subjects with AF duration ≤ 3 days, the rate is 68/116 = 58.6%. However, for those whose AF duration was ≥ 4 days, the rate is (1+2+1+1)/(7+10+9+3) = 5/29 = 17.2%. The sponsor was requested to confirm these findings.

Question 13

The Delegate agreed with the sponsor that the lower than anticipated conversion rates in the placebo/amiodarone groups are unlikely to have significant confounding effects. There were a number of compensatory design features which would mitigate against any effect, not least the randomised, double blind, controlled nature of the trials. The sponsor acknowledged the limitations of the studies with regard to the detection of rare safety events, given the relatively small sizes of the trials. The Delegate noted with interest that a

post authorisation study, SPECTRUM, has been designed. The sponsor was requested to provide further details of this planned study. If vernakalant is approved, submission of this study as evaluable data in the context of a category 1 submission would be a condition of registration.

Question 17

The sponsor was asked to provide information on the proportion of adverse events of hypotension thought in any way to be causally related to vernakalant. The incidence of hypotension in the vernakalant group in the Phase II-III studies within 0-2 hours postdose was 4.7% (36/773) of which 4.0% (31/773) were assessed as drug elated by the sponsor. The corresponding rates for the placebo group were 0.9% and 0.3%. As noted previously the by the Delegate, within the period 2-24 hours post dose, the rates of hypotension in the treatment groups were relatively reversed with 1.2% (9/773, none drug related) in the vernakalant group versus 2.7% (0.3% drug related) in the placebo group. Clinically meaningful hypotension (SAE or discontinuation) was reported in 1.2% (9/773) of patients within the first 2 hours after exposure to vernakalant and in 0% of placebo patients. Of the 9 hypotension associated SAEs reported in the first 24 hours postdose in vernakalant treated patients, 4 were reported in CHF patients (2.9% or 4/139) and 5 (0.8% or 5/598) in patients without CHF. In AVRO, no vernakalant patients (0%, 0/116) and one amiodarone patient (0.9%, 1/116) had a hypotension event within 0-2 hours post dose. Within the next 2 hours (2-4 hours post dose) there was one in each treatment group and the hypotension event in the vernakalant treated patient was considered unlikely to be related to the study drug. In the AVRO protocol, it was stipulated that patients were to be adequately hydrated and haemodynamically optimized prior to receiving treatment and the minimum level of SBP was raised from 90 to 100 mmHg. It is thought that these changes may have played a role in decreasing the incidence of hypotension events in AVRO. The Delegate agreed that this is plausible. The warnings concerning adequate hydration and haemodynamic optimization are in the Precautions section of the proposed PI and the minimum level for the SBP constitutes a threshold contraindication.

Question 18

The Delegate agreed with the evaluator that the sponsor's responses are acceptable with the exception of those which address the issue of severe hepatic and renal impairment. The risk of ventricular arrhythmia, albeit mild, was shown to be increased in patients with abnormal hepatic function and in moderate/severe renal impairment. Concerning renal impairment, the sponsor was totally reliant on the small PK study, VERO-106-REN. However, this study showed that the clearance of vernakalant was lower in all renal impairment groups compared with the normal renal function group, with the lowest clearance in the moderate and severe renal impairment groups. In the hepatic impairment study, clearance was slower in patients with severe hepatic impairment and the geometric mean values of AUC and $t_{1/2}$ were also higher compared to those in the normal hepatic function group. Also as noted by the evaluator, the wide 90% confidence intervals make interpretation of the results of these studies very difficult. The Delegate agreed that mild to moderate renal or hepatic impairment do not appear to have a clinically significant impact on vernakalant pharmacokinetics. However, the situation with severe renal or hepatic impairment is entirely uncertain. The PK evidence of increased exposure to vernakalant in these conditions, coupled with the concerns with the increased rates of ventricular arrhythmia and with the fact that such people were excluded from the clinical trials necessitates the strongest and most transparent of warnings in the PI. In the view of the Delegate this implies either a contraindication or a precaution at the level of a boxed warning.

Risk management plan

The TGA's Office of Product Review undertook an evaluation of the Risk Management Plan, identified as Version No. 1.3, dated 5 October 2010 and the sponsor responded to the recommendations outlined in the evaluation. The Advisory Committee on the Safety of Medicines (ACSOM) considered this evaluation at its meeting of 5 November 2010 and a number of concerns arose out of that consideration. Prior to consideration by the ACPM, no final RMP has been recommended for acceptance, pending resolution of the relevant issues. The Delegate summarised the issues as follows:

The ACSOM advised that the risks associated with vernakalant did not appear to have been sufficiently characterised for an appropriate postmarketing pharmacovigilance and risk minimisation strategy to be developed. The committee expressed concern that there had been cases of serious hypotension and arrhythmias in clinical trials of vernakalant and a case of life threatening (fatal) cardiogenic shock in the ACT V trial. The committee considered these events to be consistent with the pharmacological effects of vernakalant. The committee advised that further information about the safety of vernakalant was needed to support its safe use in practice and that it would be difficult to identify patients at higher risk of adverse events in practice because:

- There is extensive missing information about the safety of vernakalant in patients with other conditions not well studied in the clinical trials (as noted earlier there were a number of important criteria which excluded participation by subjects in the clinical trials)
- Characteristics predisposing patients to adverse effects, such as congestive heart failure or previous myocardial infarction, may not be known or detectable at the time of treatment.

In view of the recognised limitations of spontaneous reporting, the sponsor proposes to arrange for an organised, prospective data collection and pre-specified analysis through a post authorisation registry study to further monitor all the specified ongoing concerns, except for the specific important missing information relating to "Use in pregnant or lactating women" and "Paediatric use". In fact this post authorisation registry study or PASS was an additional pharmacovigilance activity requested by the CHMP. This multicentre registry study, a prospective, observational study of IV vernakalant, will be conducted in several EU countries to collect data about normal conditions of use and dosing and to determine reporting frequencies of medically significant adverse drug reactions. 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 registry will enrol 2000 patients across the participating EU countries. In reviewing this information, the ACSOM was of the view that it would be more appropriate to further investigate the safety of vernakalant in a clinical trial rather than in a postmarketing registry or observational study. A clinical trial would allow entry criteria to be carefully controlled and protocols followed, to help ensure the safety of participants and to provide robust safety information.

An additional risk minimisation activity required in the EU was that all healthcare professionals who will be involved in the administration of Brinavess are to be provided with a Healthcare Professional Information Pack. The RMP evaluator sought a number of assurances from the sponsor with regard to the implementation of the same or similar scheme here in Australia, should the medicine be registered. These assurances were acceptable to the RMP evaluator.

The ACSOM also advised that if vernakalant was registered, then it would require a risk management plan which:

- Restricted its use to the patient population in which there is the most information about safety. (For example, the ACSOM advised that uses of vernakalant in congestive heart failure and in diseases and conditions not studied in clinical trials should be made contraindications instead of precautions. As noted earlier in this overview, the sponsor has made some amendments in this direction.)
- Ensured that health professionals administering it were appropriately qualified and aware of the potential risks of vernakalant

Without further information about the potential risks of vernakalant in patients excluded from clinical trials, the ACSOM considered that it would not be possible to have any confidence that the above measures would appropriately mitigate the risks. The ACSOM agreed that vernakalant should be considered for future risk communication scheme because it is a new chemical entity and there are significant uncertainties about its safety in practice.

The Delegate strongly endorsed the RMP evaluation and supported all of the recommendations made in that evaluation to the sponsor, including all of the recommendations for amendments to the PI. The sponsor was requested to respond to the various issues highlighted by the ACSOM.

Risk-benefit analysis

Delegate considerations

Pharmacology

Vernakalant injection has a short pharmacokinetic half-life which results in a rapid onset and offset of action. It has a low potential for proarrhythmic activity, rapid onset of action, transient adverse effects and low plasma protein binding. It is relatively selective for the atria over the ventricles.

Efficacy

Efficacy was evaluated in 4 controlled studies involving 783 patients with recent onset AF (duration > 3 hours and < 7 days). The study designs all complied with the relevant guideline for antiarrhythmic medications. However, this guideline gives very little specific advice on the construction of any endpoint, even the primary efficacy endpoint. Vernakalant was shown to be effective in converting atrial fibrillation of recent onset for at least one minute within the first 90 minutes after dose administration, thus meeting the primary efficacy endpoint of the program.

In ACT I, a statistically and clinically significantly ($p < 0.0001$) greater proportion of vernakalant recipients (75/145, 51.7%), compared with placebo recipients (3/75, 4.0%), converted to sinus rhythm within 90 minutes and met the primary efficacy endpoint (treatment difference, vernakalant – placebo = 47.7% with 95% CI [38.5%, 57%] and odds ratio = 24.0 with 95% CI [6.9, 83.6)]. There was a *post hoc* analysis which calculated what were termed "*life table estimates*" which declared 97.0% maintenance of sinus rhythm at 24 hours and 92.0% maintenance at 7 days in subjects with short duration AF treated with vernakalant. This was compared with 66.7% maintenance for the 3 subjects in the placebo group. The sponsor was asked to clarify precisely what is meant by a life table estimate and to clarify the relationship between these life table estimates and the actual percentages of subjects successfully treated with vernakalant who were still found, by clinical examination, to be in sinus rhythm at 24 hours and at 7 days. Also it appeared that, out of the three trials ACT I, II and III, ACT I was the only one in which data on AF duration was recorded. The Delegate calculated that the rate drops fairly dramatically where the AF duration has been longer than 3 days. Thus, the rate of AF conversion for

subjects with AF duration ≤ 3 days was 68/116 or 58.6% and for those whose AF duration was ≥ 4 days, the rate was 5/29, or 17.2%. There is a clear diminution in efficacy the longer the AF duration. There does not seem to have been data collected on the numbers/percentages of patients who reverted to AF after having been successfully converted to sinus rhythm. The sponsor was requested to provide information concerning the numbers/percentages of patients in ACT I who reverted to AF within the first 24 hours postdose after having been successfully converted to sinus rhythm.

In ACT III, a greater proportion of subjects treated with vernakalant converted to sinus rhythm within 90 minutes of first exposure to the study drug compared with placebo treated subjects (44/86, 51.2% versus 3/84, 3.6%, treatment difference vernakalant – placebo = 47.6% with 95% CI [36.3%, 58.9%], $p < 0.0001$ and odds ratio = 38.3 with 95% CI [9.2, 159.5]. Also, with regard to maintenance of effect, of the 44 subjects who converted to sinus rhythm after treatment with vernakalant in the short duration AF group, there were 35 (79.5%) and 33 (75.0%) who were still in sinus rhythm at 24 hours and 7 days, respectively. This result on maintenance of effect does not appear to have been based on a '*life table estimate*" but rather on actual, raw data. Would the sponsor please clarify whether this is the case? The delegate asked for clarification about whether or not data on AF duration was actually recorded in this study. As for the previous study, the sponsor was requested to give information about the numbers/percentages of patients in ACT III who reverted to AF within the first 24 hours postdose after having been successfully converted to sinus rhythm.

In ACT II, a statistically significantly greater proportion of subjects in the vernakalant group (48/107, 44.9%) converted to sinus rhythm for at least one minute within 90 minutes of first exposure to the study drug compared to subjects in the placebo group (8/54, 14.8%). The treatment difference, vernakalant minus placebo was equal to 30% (95% CI [16.7%, 43.4%], $p = 0.0002$ and odds ratio = 3.00 with 95% CI [1.53, 5.87]. With regard to the evidence for maintenance of effect, the life table estimates of the maintenance of sinus rhythm for subjects who converted to sinus rhythm within 90 minutes were 59.5% in the vernakalant treated group (n = 48) versus 50% in the placebo treated group (n = 8) at 24 hours. Although these percentage rates are comparable between vernakalant and placebo, the number of placebo treated responders was much, much smaller (8 compared with 48). The corresponding percentage rates at 7 days were 56.9% (vernakalant) and 50% for placebo. The Delegate requested the sponsor to re-do the comparative analysis of symptom rates in this study, this time stratified by responder versus nonresponder. As with the previous studies, the sponsor was asked to clarify the use of life table estimates rather than actual, raw data in determining maintenance of effect and also to provide the information about the numbers/percentages of patients in ACT II who reverted to AF within the first 24 hours postdose after having been successfully converted to sinus rhythm.

In AVRO, the amiodarone comparator study, there was a statistically significantly ($p < 0.0001$) greater proportion of subjects converting from AF to sinus rhythm within the first 90 minutes in the vernakalant group (6/116, 51.7%) compared to amiodarone (6/116, 5.2%). Patients treated with vernakalant were 10 times more likely to convert to sinus rhythm within 90 minutes as compared to subjects treated with amiodarone (OR = 10.0, 95% CI [4.5, 22.2]. The Delegate was of the opinion that this is a deeply flawed study, with amiodarone disadvantaged from the outset. It is known that amiodarone is a slow acting drug. Yet despite this, while it was given as an infusion over 120 minutes, the primary efficacy endpoint was measured at 90 minutes. The Delegate observed that, between the time points of 90 minutes and 4 hours, there was a shift in the rate of AF conversion from 51.7% to 54.4% (almost no shift) for the vernakalant treated group compared with a shift from 5.2% to 22.6% (over a 4-fold increase) for the amiodarone treated group. Also the Delegate was unable to find any further reports of the raw conversion rates for each treatment group beyond the time point of 4 hours. The Delegate requested that the

sponsor, in its pre-ACPM response, show the numbers and rates in each treatment group who converted to sinus rhythm at any time up to 24 hours and then the corresponding numbers and rates for those who were found to be still in sinus rhythm at 7 days (out of those who had converted in the first 24 hours).

There is no doubt that vernakalant has been demonstrated to exhibit efficacy according to a narrowly focused endpoint, that is, the proportion of patients with AF duration of > 3 hours but ≤ 7 days who had treatment induced conversion to sinus rhythm for a minimum duration of 1 minute within 90 minutes of first exposure to the drug. However, the Delegate had definite concerns that the primacy of the analyses has been directed more at rapidity of effect, rather than the effect itself. To be of any demonstrable, practical, clinical value, the drug must be able to exhibit maintenance of effect, particularly to offset any ill effects of the drug. Analysis of the maintenance of effect was relegated to exploratory endpoints. The Delegate asked for clarification of the "*life table estimates*". From the AF duration data in ACT I, a striking fall was observed in the rates of AF conversion for AF duration of ≥ 4 days (actually where the AF duration has been longer than 3 days). There appears to be very little readily accessible data on rates of reversion after successful conversion. Finally, the focus on rapidity of effect has resulted in a deeply flawed AVRO study where estimation of the primary efficacy endpoint ends 30 minutes before the infusion of amiodarone has been completed. The delegate required, from the AVRO study, data on the numbers and rates in each treatment group (vernakalant versus amiodarone) who converted to sinus rhythm at any time up to 24 hours and then the corresponding numbers and rates for those who were found to be still in sinus rhythm at 7 days (out of those who had converted in the first 24 hours). There are many unanswered questions and issues which require resolution with regard to the efficacy of vernakalant.

The clinical evaluator was of the opinion that the benefit/risk profile of the second dose of vernakalant was not favourable. Compared with the first dose, the rate of conversion was roughly 4 times lower after the second and the risk of hypotension was increased at vernakalant levels associated with the maximum 5 mg/kg dose. With regard to the efficacy of the second dose, the sponsor responded that, in the first 25 minutes after initiation of therapy in the primary AF population, a single infusion was administered and a 39.8% conversion rate observed with vernakalant, compared with one of 1.2% with placebo. In patients who received either one or two infusions, the conversion rate for vernakalant rose to 51% over the 90 minute postdose period, compared to 3.8% for placebo. The corresponding vernakalant minus placebo differences are 38.6% (one infusion) and 47.2% (one or two infusions), an absolute gain of 8.6% or a relative gain of 8.6/38.6 or 22.3% in conversion with one or two infusions compared to one infusion. There is some gain but it is much diminished.

Safety and RMP

Common AEs associated with vernakalant treatment during the first 2 hr postdose were, in decreasing order of frequency in the vernakalant group: dysgeusia (vernakalant 20.3%vs placebo 2.4%), sneezing (15% versus 0%), paraesthesiae (8.2% versus 0.9%), nausea (5.2% versus 0%), hypotension (4.7% versus 0%), cough (4.3% versus 0.6%), pruritus (3.6% versus 0%),dizziness (3.5% versus 1.8%), hyperhidrosis (3.2% versus 0.3%), feeling hot (3.0% versus 0.6%), bradycardia (2.6% versus 0%), nasal discomfort (2.5% versus 0%), paraesthesiae oral (2.3% versus 0.3%), infusion site pain (2.2% versus 0%), atrial flutter (1.3% versus 0.3%), vomiting (1.3% versus 0%), dry mouth (1.2% versus 0%). Also of note were ventricular extrasystoles (vernakalant 4/773, 0.5% versus 0/335 on placebo, 0%). The incidences of these AEs during the following 22-hour period between the 2 hour and 24 hour postdose time points largely equalized with no or only minor differences between the two treatment groups.

Common AEs that occur after treatment with vernakalant injection have a reasonably predictable time of onset, occur peri-infusionally and are transient. However, it is the first 2 hours which are clearly critical in terms of the clinical safety of vernakalant.

The incidence of SAEs was higher in vernakalant treated patients compared to placebo in the first 2 hours postdose (19/773, 2.5% versus 2/335, 0.6%), including 8 SAEs of hypotension in the vernakalant group (1.0% versus 0%) and 11 SAEs of cardiac arrhythmias (supraventricular/ ventricular arrhythmia/ cardiac arrest) in the vernakalant group (1.4% versus 0%). These 11 SAEs of cardiac arrhythmia included 3 of ventricular arrhythmias and/or cardiac arrest.

The incidence of clinically relevant ventricular arrhythmia (SAE or discontinuation) was higher in the vernakalant group (0.6%, 5/773) compared to placebo (0%). The risk of ventricular arrhythmia was increased in patients with history of CHF, AMI, cardiac surgery, abnormal hepatic function and moderate/ severe renal impairment.

The majority of the bradycardia events (vernakalant 5.4% versus placebo 3.8%) occurred between 0 and 2 hours postdose, were peri-infusional and resolved spontaneously. Episodes of bradycardia were more likely to be associated with conversion to sinus rhythm. There were 2 (2/889, 0.2%) patients who experienced third degree AV block as an AE within the first 24 hours after exposure to vernakalant.

Hypotension occurred either during the infusion or early after the end of the infusion and was usually corrected by standard supportive measures. SAEs of hypotension (including SAEs leading to discontinuation), although uncommon, were reported more frequently among vernakalant treated patients than among placebo treated patients (9 vernakalant, 1.2% versus 1 placebo, 0.3%). However, the risk of hypotension was increased in patients with history of CHF, low baseline SBP and vernakalant plasma levels of 4000 ng/mL (associated with the maximum 5 mg/kg dose). In congestive heart failure patients, 22 of 137 treated with vernakalant (16.1%) experienced a hypotensive episode in the first 2 hours postdose compared to 3 of 64 placebo treated patients (4.7%). Hypotension was much less common in non-CHF patients.

With regard to the assertion that the risk of hypotension was increased in patients with vernakalant plasma levels of 4000 ng/mL and therefore associated with the maximum 5 mg/kg dose, the sponsor responded. The sponsor contended that the median onset of most AEs occurred prior to the initiation of the second infusion, indicating that the majority of AEs occurred during and immediately following the first, rather than the second, infusion. Hypotension had a median time to onset of 17.0 minutes after initiation of the first infusion in Phase II and III patients (prior to the start of the second infusion which was at 25 minutes after the start of the first infusion). However, the Delegate was of the opinion that this is a flawed analysis, particularly with regard to safety events. All that a median of 17.0 minutes indicates is that 50% of the AEs occurred before 17 minutes and 50% of the AEs occurred after 17 minutes. While a majority of AEs may have occurred during and immediately following the first infusion, it is clear that a substantial minority of AEs occurred during and following the second infusion. These cannot be discounted.

In the AVRO study, no vernakalant patients (0%, 0/116) and one amiodarone patient (0.9%, 1/116) had a hypotension event within 0-2 hours postdose. Within the next 2 hours (2-4 hours post dose) there was one in each treatment group and the hypotension event in the vernakalant treated patient was considered unlikely to be related to the study drug. In the AVRO protocol, it was stipulated that patients were to be adequately hydrated and haemodynamically optimized prior to receiving treatment and the minimum level of SBP was raised from 90 to 100 mmHg. It is thought that these changes may have played a role in decreasing the incidence of hypotension events in AVRO. The Delegate agreed that this is plausible.

The ACSOM advised that the risks associated with vernakalant did not appear to have been sufficiently characterised for an appropriate postmarketing pharmacovigilance and risk minimisation strategy to be developed. The committee expressed concern that there had been cases of serious hypotension and arrhythmias in clinical trials of vernakalant and a case of life-threatening (fatal) cardiogenic shock in the ACT V trial.

It is the unpredictability and rapidity of the hypotensive response which was of most concern to the Delegate. In the case of the 64 year old man with critical aortic stenosis and AF complicating acute coronary syndrome, hypotensive episodes occurred with each infusion of vernakalant, the second more profound than the first and therefore indicative of a dose response. The man went into VF and could not be resuscitated. As already noted, he should not have been enrolled in the trial and certainly should not have been given the second dose of vernakalant. Once the drug is registered, its use becomes much less controlled than in the context of a clinical trial. There have been two cases of cardiogenic shock, one non-fatal and one fatal. Both subjects developed severe hypotension with the first dose and neither was given a second dose. In the non-fatal case, the cardiogenic shock did not develop until a day later and may not have been directly related to the vernakalant. This subject was later found to be suffering from idiopathic cardiomyopathy. In the fatal case, the subject, a 77 year old man with hypertension and chronic alcohol abuse, developed profound hypotension from which he never recovered. Echocardiography had shown global hypokinesia. The Delegate considered whether this could have been due to an alcoholic cardiomyopathy. All these cases highlight the concerns of the ACSOM that characteristics predisposing patients to AEs like severe hypotension may not be known or detectable at the time of treatment.

It is somewhat reassuring that in the AVRO trial the incidence of severe hypotensive AEs was considerably reduced. In this study, patients were to be adequately hydrated and haemodynamically optimized prior to receiving treatment and that the minimum level of SBP was raised from 90 to 100 mmHg. Whether or not this is the full explanation for the reduction in rates of hypotension is not entirely certain. It should really be tested (or have been tested) in pivotal studies such as ACT I, II and III.

Whether the risk of profound hypotension can be mitigated by warnings in the PI is the issue of most concern to the Delegate. If the drug were to be registered, then the Delegate was of the view that, as a minimum, there would have to be a boxed warning outlining the risk and the management of such hypotension as well as a summary in the Adverse Effects section of the fatal case of VF and the two cases of cardiogenic shock. The boxed warning must indicate that the hypotension can be profound.

Little appears to have been written concerning the precise mechanism of action of the hypotensive response and the sponsor is requested to comment on this.

Data deficiencies

Data deficiencies include the following:

- Shortcomings in the ways in which data on maintenance of effect has been measured and presented (exploratory endpoints, life table estimates, lack of raw data which the delegate could identify concerning the actual maintenance of effect rates at 24 hours and 7 days, only limited data on maintenance of effect in the AVRO study)
- No or limited data on the rates of reversion to AF following successful conversion to sinus rhythm
- The concern over the internal validity of the AVRO clinical trial
- No clinical outcome, that is, morbidity/mortality data, as endpoints

Summary

Vernakalant has been demonstrated to exhibit efficacy according to a narrowly focused endpoint, that is, the proportion of patients with AF duration of > 3 hours but ≤ 7 days who had treatment induced conversion to sinus rhythm for a minimum duration of 1 minute within 90 minutes of first exposure to the drug. The Delegate expressed a number of concerns and requested clarification of these issues.

However, what concerned the Delegate most is the safety profile of the medicine. There are increased rates of hypotension, ventricular arrhythmia, bradycardia and atrial flutter. It is the hypotension in particular which is of great concern. It is rapid in onset, unpredictable in terms of patients at risk and can be profound. Its unpredictability is only highlighted by the fatal case of cardiogenic shock in the ACT V trial which is presently on hold. While the hypotension does occur more commonly in those with a prior history of congestive cardiac failure, this is by no means always the case and was not the case for the subject in the ACT V trial. At this stage, the Delegate agreed with the ACSOM that the risks associated with vernakalant do not appear to have been sufficiently characterised for an appropriate postmarketing pharmacovigilance and risk minimisation strategy to be developed. The Delegate was not confident that the risks can be satisfactorily ameliorated with appropriate warnings in the PI, even to the extent of boxed warning at the head of the PI.

The Delegate agreed with the clinical evaluator that the benefit/risk balance of the product for the indication is not favourable while there are so many unresolved issues, with respect to both efficacy and safety. The Delegate proposed to reject the submission.

As well as the answers to questions posed by the Delegate to the sponsor. The Delegate directed the following questions to the ACPM:

Is the ACPM of the opinion that Brinavess is approvable perhaps with appropriate strengthening of precautions and contraindications, including the provision of a boxed warning at the head of the PI concerning the risk and management of hypotension as an adverse event?

Does the ACPM agree with the Delegate that Brinavess should be contraindicated in all heart failure NYHA III and not just unstable NYHA III?

Response from sponsor

The sponsor disagreed with the Delegate's proposed action to reject the application based on the safety and efficacy of the product not having been satisfactorily established for the proposed indication. The sponsor maintained that the benefit/risk assessment for Brinavess remains favourable to support the registration for the indication:

Brinavess is indicated for 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

Brinavess was approved in Europe on 1 September 2010. Since the approval in the EU, the sponsor initiated revisions in the EU prescribing information subsequent of the serious adverse event (hypotension, cardiogenic shock) in a clinical study to strengthen the importance of proper patient selection and monitoring before, during and after administration of vernakalant.

A 6 month Periodic Safety Update Report (PSUR), during the period of 1 September 2010 to 28 February 2011 was provided. During the PSUR data period, 10 spontaneous individual case safety reports (ICSRs) (2 serious) and 2 serious, related study ICSRs were received. The data contained within the PSUR support the adequacy of the current Company Core Data Sheet (CCDS) for vernakalant in terms of product safety. During the reporting period of this PSUR, there were safety related updates to the CCDS for vernakalant that are also reflected in the proposed for PI in Australia.[48]

In the USA, the FDA Cardiovascular and Renal Advisory Committee recommended approval for vernakalant at their meeting in December 2007. In August 2008, the FDA issued an approvable letter but requested an additional study to be conducted (ACT V).

Efficacy

Duration of Effect (maintenance of SR)

Life table estimates refers to the statistical procedure used to calculate the estimated proportions of patients who maintained SR. This is analogous to the Kaplan-Meier (KM) procedure in that both take a 'time-to-event' approach to estimate the proportion, and censor subjects in which the event is not observed (for example, when you have missing data). The life table method is used when there are fixed follow up times (as was the case in these studies, since follow up was at scheduled time points) and the KM procedure is used when patients are followed continuously.

As requested by the Delegate, the actual numbers and percentages of patients with AF (> 3 hours to ≤7 days duration), who converted to SR within 90 minutes and were found, by clinical (that is, absence of an adverse event of AF or AFL) and/or ECG examination, to be in SR at 24 hours and 7 days were presented. In the ACT I and III pivotal studies, more than 96% of patients who converted to SR within 90 minutes on vernakalant remained in SR out to 24 hours, demonstrating conversion, as defined by the primary efficacy end point, with vernakalant was lasting and hence clinically meaningful. In postcardiac surgery patients (ACT II study), 56% of patients maintained SR out to Hour 24 which is consistent with other antiarrhythmic drugs. A reason for the difference in ACT II is the cause of AF in the ACT II population is different from that studied in ACT I and III, with postcardiac surgery patients tending to be more susceptible to recurrent AF.

All patients in AVRO study were followed, and data collected at scheduled time points up to Hour 4, at discharge (which could occur as early as Hour 6) and at Day 7. Per protocol, the infusion period for vernakalant was over the first 35 minutes and for amiodarone over the first 2 hours. After 2 hours, if a patient was not in SR, the investigator could use electrical cardioversion to restore SR.

The sponsor presented the number/percentage of patients who converted to sinus rhythm pharmacologically or spontaneously (successful electrical cardioversions after 2 hours are not included) at anytime up to discharge, where discharge occurred within 24 hours, and the number/percentage of these patients found to be in SR at Day 7 (based on ECG or clinical assessment) (Table 28).

[48] A Company Core Data Sheet (CCDS) is a company-internal global reference labelling document used to direct the content of local (affiliate) labelling.

Table 28: The number (percentage) of patients who converted to sinus rhythm pharmacologically or spontaneously at anytime up to discharge (within 24 hours) and maintained SR to Day 7.

Time Point and Rhythm Status (SR)	Vernakalant (N=116)	Amiodarone (N=116)
SR at Discharge within 24 hours	66 (56.4%)	33 (28.4%)
Maintained SR to Day 7	61 (52.5%)	31 (26.7%)

Conversion to SR based on duration of AF prior to treatment

The duration of AF prior to treatment was collected in ACT I and ACT IV studies. In ACT III study, based on the investigator's assessment, subjects were randomized into those with AF or AFL of between 8 days and 45 days duration and those with less than or equal to 7 days. The date and time of the onset of AF or AFL was not collected in ACT III.

The sponsor concurred with the Delegate's calculation that the conversion rate in patients with AF duration ≤ 3 days in ACT I is 68/116 (58.6%) as compared to 5/29 (17.2%) in patients with AF duration >3 days.

The ACT I study was powered to examine the efficacy of vernakalant in AF patients with a duration of 3 hours to 7 days. Within this group, there were a smaller number of patients enrolled with AF duration > 3 days compared to those with AF duration ≤ 3 days, resulting in greater uncertainty in the point estimate for conversion in the group of patients with AF duration > 3 days. In comparison, ACT IV data showed a conversion rate of 75/140 (53.6%) in patients with AF duration ≤ 3 days and 10/27 (37.0%) for patients with AF duration > 3 days. Combined results from ACT I and ACT IV comparing the conversion to SR to the duration of AF were presented. The results demonstrated that vernakalant is effective at converting patients from AF to SR whose AF duration is between 3 hours and 7 days, and superior to placebo.

Analysis of symptoms in ACT II (responder versus non responder)

The sponsor summarised the percent of subjects in ACT II with at least one symptom at the pre-specified assessment time points, by treatment group and responder status. Symptoms generally declined with time in all groups, with the greatest reduction in symptoms occurring in responders between baseline and 90 minutes (conversion to sinus rhythm in the 90 minute period, defining a responder). Since other treatments which could influence symptoms were permitted after 2 hours in both treatment groups for responders and non responders, comparison of symptoms after 2 hours (that is, at 24 hours, follow up and 30 days) between treatment groups or between responders and non responders could not be attributed to the study drug (vernakalant or placebo). This explains the lack of difference in symptoms at 24 hours and after, as noted by the Delegate.

Safety

Mechanism for the hypotensive response

Vernakalant injection was associated with rare clinically meaningful events (defined as those involving serious adverse events or requiring study drug discontinuation) of hypotension, although a significantly increased incidence of hypotension was observed in patients with congestive heart failure (CHF).

In experiments in anesthetized rats, vernakalant did not have negative hemodynamic effects at therapeutically relevant plasma concentrations. However, at elevated doses, data suggested that vernakalant had negative inotropic and possibly negative chronotropic

actions. Notably, vernakalant had no vasomotor effects on hind limb vasculature, even at more than threefold greater than the highest therapeutic plasma levels. In contrast, flecainide, a Class IC antiarrhythmic agent, decreased hind limb vascular resistance 18% even at therapeutically relevant plasma concentrations (0.8 μg/mL).

In a hemodynamic study in anesthetized dogs, a dose dependent left ventricular negative inotropic effect was seen with intravenous vernakalant at high plasma concentrations (there is a ≥3-fold margin above the C_{max} observed at therapeutic doses in clinical trials to the negative inotropic effect seen in dog studies). Little or no vasodilatory effects were observed at these high concentrations. While in animal models only observed at supratherapeutic doses, these data support the suggestion that a potential underlying mechanism for the hypotension events seen in the vernakalant clinical trials may have been due to a negative inotropic effect.

The preclinical negative inotropic responses seen at supratherapeutic concentrations suggest that vernakalant may exacerbate the increased risk of hypotension already present in patients with compromised cardiac function. Subjects with CHF 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. Since hemodynamic compromise was not observed in experiments in conscious dog studies, it is reasonable to assume that sympathetic reflexes may compensate for the direct negative inotropic effects of vernakalant in patients. Patients with compromised cardiac function may show greater sensitivity to, or a reduced ability to compensate for potential negative inotropic effects.

Patients with compromised cardiac function, presenting with low systolic BP and CHF, may be readily identified in the monitored clinical setting where vernakalant is to be administered. The use of vernakalant in haemodynamically unstable patients, who may be at heightened risk for potential negative inotropic effects, is contraindicated in the proposed PI. Furthermore, hypotension is an identified risk and clear instructions regarding dosing and monitoring are provided in the proposed PI. Therefore, a black box warning on the risk and management of hypotension is not warranted in the opinion of the sponsor.

Risk management plan for Brinavess

The sponsor disagreed with the advice provided by ACSOM that the risk associated with vernakalant appears to have not been sufficiently characterized for an appropriate postmarketing pharmacovigilance and risk minimisation strategy to be developed. The issues raised were addressed:

Arrhythmias, hypotension

The sponsor agreed that the use of vernakalant in patients with advanced heart failure (class III and IV) be contraindicated in the PI and will emphasized this to prescribers via the Healthcare Professional (HCP) Education Card as part of its postmarketing risk minimisation strategy as outlined in its RMP. The proposed PI and HCP Education Card are to contain explicit requirements that vernakalant should be administered by specialists, in a well monitored, controlled, hospital environment. In addition, the proposed PI and the HCP Education Card will provide descriptions of the identified and potential risks of vernakalant injection, with appropriate advice to the prescriber to minimise these risks. The HCP education package would be distributed to prescribers prior to or at the time of launch and will reinforce important information from the PI, specifically with respect to patient selection, adverse reactions, and correct preparation and dosing of vernakalant injection.

Other conditions not studied in the clinical trials

The sponsor agreed the use of vernakalant should not be recommended in patients with other diseases and conditions which had not been studied in clinical trials (that is, with

clinically meaningful valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis, and severe hepatic impairment). Therefore, while the benefit risk of vernakalant has not been specifically evaluated in these populations, the risks to these patient groups are adequately minimised by the proposed PI. The HCP Card will be harmonized with the approved PI when this is available.

With respect to patients with renal impairment, these patients were included in the clinical program. Evidence from a Phase I study (VERO-106-REN) and an analysis of safety data from the pivotal studies by degree of renal impairment supports a similar safety profile in these patients, compared to patients with normal renal function. Therefore, a contraindication in patients with severe renal impairment is not warranted.

Characteristics predisposing patients to adverse effects that may not be known or detectable at the time of treatment

Evaluations for congestive heart failure or previous myocardial infarction should be performed for all patients being considered for treatment with vernakalant injection, because the proposed PI contains important Contraindications and Precautions for patients with these pre-existing conditions. The proposed PI and HCP Education Card will include a specific instruction that "patients should be studied for signs and symptoms of cardiac failure before administration of vernakalant" to provide appropriate guidance to prescribers.

ACSOM was of the view that it would be more appropriate to further investigate the safety of vernakalant in a clinical trial rather than in a postmarketing observational study

The sponsor disagreed with the advice from ACSOM and believes the non-interventional, observational study design of the PASS (SPECTRUM Registry) has a number of scientific advantages that enable the sponsor to evaluate physician behaviour in the postmarketing context and compliance with several aspects of the proposed PI that cannot be assessed in the setting of an interventional clinical trial, including:

- Appropriate patient selection and compliance with contraindications for use
- Physician compliance per the PI with the weight based dosing scheme and patient monitoring of blood pressure and cardiac rhythm during and after each infusion
- Quantification of the pre-specified health outcomes of interest (HOIs) and other serious adverse events in a broader population of patients administered vernakalant in the post-marketing (real world) environment as opposed to the more narrow selected patients in a clinical trial design

Further, in terms of safeguarding patient safety, the PASS study will employ strict adherence to the study protocol in terms of collection and reporting of both the pre-specified health outcome of interest as well as any serious adverse events not otherwise meeting the clinical definition of the HOIs and will ensure timely reporting of any serious suspected adverse drug reactions to the appropriate regulatory authorities. Compliance of prescribers with the important safety information in the PI and HCP Card will be evaluated in the PASS study. If evidence emerges suggesting inadequate adherence to the recommended safety measures, the sponsor would propose appropriate counter measures. The sponsor understood that the RMP will be a condition of the registration.

Monitoring safety aspect according to EU guidelines

All of the trials in the vernakalant IV program were intensively monitored to identify any potential arrhythmogenic, conduction, vascular or other significant effects. In the postmarketing setting for this product, as has been done with the PI for other antiarrhythmic medications, the sponsor takes the following measures to ensure proper

patient selection (Contraindications, Precautions/Warnings), appraisal by the physician of potential adverse events and their management.

1. To closely monitor the activity of vernakalant, the proposed PI has been revised to ensure appropriate monitoring during and shortly after vernakalant infusion. It is specified that Brinavess "should be administered only by qualified medical personnel in a monitored clinical setting appropriate for cardioversion." In addition, the intensity of monitoring has been enhance by mandating that "patients should be observed with assessment of vital signs and continuous cardiac rhythm monitoring during administration of Brinavess for 2 hours after the start of infusion, and until clinical and ECG parameters have stabilised. Continuous monitoring of blood pressure is also required during and at least 15 minutes after the completion of the infusion."
2. To evaluate adherence to the recommended monitoring in the proposed PI in real world settings, the PASS protocol has also been revised to collect information on patient monitoring performed by healthcare providers, including: a) duration and frequency of blood pressure measurements during each vernakalant infusion and the following 15 minute post infusion and two hour post infusion periods and type of healthcare provider performing such monitoring and b) type and duration of cardiac rhythm monitoring during and up to two hours post infusion, and type of healthcare provider performing such monitoring. Furthermore, one of the primary objectives of the PASS is to quantify the incidence of any pre-specified medically significant health outcomes of interest (HOIs) and any other serious adverse events occurring within patients administered vernakalant as part of standard care.

Choice of only patients without CHF in ACT V study

The ACT V study design was reviewed, under the terms of the FDA's Special Protocol Assessment (SPA) process, as part of an ongoing discussion between the US sponsor and the FDA to prospectively assess the risk/benefit profile in patients with atrial fibrillation duration <7 days and without CHF. Due to the increased risk of hypotension and ventricular arrhythmia in patients with CHF, it was appropriate to exclude patients with severe heart failure (corresponding to NYHA IV and NYHA III) and vernakalant should be used cautiously in patients with haemodynamically stable CHF.

In conclusion, the sponsor maintained that the clinical program has consistently demonstrated that vernakalant injection provides rapid conversion (within 10 min) of recent onset AF (≤7 days duration) to SR in approximately 50% of patients and reduces the clinical symptoms associated with AF. SR was maintained for >90% patients at 7 days post treatment, irrespective of whether patients received additional antiarrhythmics or not. Vernakalant injection was well tolerated and effective in patients with multiple associated morbidities (ischaemic heart disease, CHF, hypertension, mild LVEF dysfunction, and a history of MI) and in the presence of typical background medications used by the target patient population. Important adverse events that were observed following study drug administration included ventricular arrhythmia, bradycardia, hypotension and AFL, which are not unexpected in this patient population, were predictable in time of onset, generally transient and typically responded to discontinuation of study drug and routine medical management in the clinical setting appropriate for cardioversion. The product information, HCP education, pharmacovigilance and a registry study are therefore the cornerstone of risk minimisation/management. Given the limitations of current pharmacological agents used to acutely convert AF and the necessity for an alternative to electrical cardioversion, the benefits of vernakalant infusion outweigh its risks in patients with recent onset AF for whom rapid cardioversion is indicated. Vernakalant injection provides a new important treatment option to physicians and their patients for the rapid pharmacological conversion of AF to sinus rhythm.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission on the grounds that safety and efficacy of the product have not been satisfactorily established.

In making the recommendation that the overall risk benefit profile for this product was negative, the ACPM considered the following matters:

Efficacy

In the opinion of the ACPM the data submitted demonstrated moderate efficacy for vernakalant compared to placebo according to a narrowly focused endpoint. The exclusions from the trials population were extensive and included advanced CCF. The sponsor acknowledged that the study findings cannot be extrapolated to all patients with short term AF. The numbers and extent of the exclusions would make it difficult to generalise the results to any primary AF population. A resolution to the issue of how to handle the large number of exclusion criteria might be to propose these as Contraindications.

Although in the AVRO trial an active comparator (amiodarone) was included it was considered that the time over which data was submitted provided an unfair comparison as amiodarone is known to be slower acting. The inadequacy of the design of the AVRO trial which compared the two drugs only for a relatively short time and also the lack of comparisons with other products which may be used for this treatment make efficacy assessment problematic. Published data suggests that although amiodarone has been shown to provide a more rapid response than comparators, by 24 - 48 hours efficacy appears similar. The evidence in the AVRO trial suggests similar efficacy by 24-48 hours.

The ACPM noted the Delegate's concern over maintenance of effect, however, the committee was of the opinion that, by 24 hours post administration, most patients would have reverted spontaneously and as the half-life of the drug is around 8 hours, even for CYP2D6 poor metabolisers, maintenance was not a significant concern for the population with recent onset AF.

Safety

The safety data suggest that there is a small but significant rate of serious and apparently unpredictable adverse events. There are increased rates of hypotension, ventricular arrhythmia, bradycardia and atrial flutter. The hypotension is rapid in onset, unpredictable in terms of patients at risk and can be profound. There is evidence of significant QT interval prolongation which is proportional to dose. The increased incidence of any ventricular event occurring by itself is a concern, however, the major concern is the increased numbers of outliers or potential outliers with regard to QT prolongation in the vernakalant population compared to placebo. This was compounded by the fact that there were only relatively small numbers of patients exposed to vernakalant in the clinical trials. So the chances of picking up rare events such as torsades de pointes are very small.

There is no mention in the proposed PI of caution in patients with severe hepatic or renal impairment although these patients were excluded from the Phase III studies. Furthermore, the studies evaluating effect of renal and hepatic impairment on vernakalant PKs only used 2 mg/kg while the proposed dose is 3+2 mg/kg.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Brinavess containing vernakalant 500 mg/25 mL and 20 mg/mL for the amended indication:

Brinavess is indicated for 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.*

The reasons for the Delegate's decision not to register Brinavess, vernakalant (as hydrochloride) for the indication sought are outlined below.

The Delegate has, in his opinion, allowed both fair and ample opportunity for the sponsor to present and explain the case for acceptance of the submission. The sponsor has had the opportunity to provide responses to questions asked by the clinical, RMP and other evaluators under s31 of *The Therapeutic Goods Act* as well as to provide a response to the clinical evaluation report, a pre-ACPM response and finally a response to the Resolution No. 9541 of the ACPM. All of these, together with all of the documents listed earlier in this letter (full letter and list not included in the AusPAR), have been considered by the Delegate.

The particular reasons for the Delegate's decision are outlined below:

1. **Increased rates of serious cardiac disorders:** The combined rates of serious cardiac disorders (composed of AV block complete, sinus arrest, sinus bradycardia/bradycardia and ventricular fibrillation) were 13/889 or 1.5% in the vernakalant-treated group versus 2/335 or 0.6% in the placebo-treated group. For each of the single events of AV block complete, sinus arrest and ventricular fibrillation, the comparative rates were 2/889 or 0.2% versus 0/335 or 0.0%, respectively. In other words, these 3 events did not occur at all in the placebo-treated group. Although these results were not statistically significant, the studies from which these results are derived were not powered for such safety endpoints. Trends they may only be but such trends with regard to safety results cannot be ignored. It is also of concern that the incidence of clinically relevant ventricular arrhythmias (SAE or discontinuation) was higher in the vernakalant group (5/773, 0.6%) than in the placebo group (0%). The Delegate therefore considered that the safety of vernakalant has not been satisfactorily established for the proposed indication.
2. **The QT interval prolongation caused by vernakalant:** It is known that vernakalant does prolong the QT interval and that the degree of QT prolongation is proportional to dose. The Delegate was concerned by the observation that the frequencies of change in both QTcB and QTcF from baseline of at least 60 msec and that the percentages of patients whose QTcB interval shifted from ≤ 550 msec at baseline to > 550 msec were substantially higher in the vernakalant-treated group than in the placebo-treated group. Such effects persisted for at least 50 minutes and generally, did not equalise until sometime between 50 and 90 minutes after the commencement of the infusion. Thus, there is a clear excess of outliers with respect to QT prolongation in the vernakalant-treated group compared with the placebo-treated group and this excess lasted well beyond the termination of the infusion. It is not surprising that there were no instances of patients experiencing torsades de pointes in the clinical trial population because the latter was both small and highly selected. In an effort to counter the effect of the small population studied, the sponsor has examined the rates of torsades de pointes and other potentially fatal arrhythmias in the larger postmarketing population, thus far estimated to consist of 1,925 persons. The Delegate did not agree that the estimate of a true risk of such events of less than 0.5%, that is, 1 in 200 is acceptable. An acceptable risk is at least of an order of magnitude lower, for example, in the range of 0.05%-0.1%. However, whether one should even consider relying upon spontaneous adverse event reporting from post-marketing experience in order to register a new chemical entity for the management of an emergency condition, when there is no prior experience with closely related

entities, is highly debatable. As is well known, spontaneous adverse event reporting is subject to a multitude of biases and confounders and to allow such data to stand on an equal footing with randomised, double-blind, placebo-controlled data would be, in the opinion of the delegate, potentially dangerous. The Delegate therefore considered that the safety of vernakalant has not been satisfactorily established for the proposed indication.

3. **The unsatisfactory hypotensive effects of vernakalant:** The Delegate rejected the contention of the sponsor that hypotension has been well characterised in the clinical trial program. Clinically meaningful hypotension (reported as a serious adverse experience or leading to medicine discontinuation) occurred within the first 2 hours after exposure to Brinavess in 0.8% of patients compared to 0% in placebo. Hypotension had a median time of onset of 17.0 minutes after initiation of the first infusion in patients in the Phase II & III trials. Thus, despite vernakalant's apparent rapid onset and offset of action, 50% of hypotensive events occurred after 17.0 minutes had elapsed from the commencement of the first infusion. While it is true that there have been a small number of episodes of profound hypotension in the clinical development program and while this may have led to a greater knowledge of the patients at risk of such hypotension, it is also true that there have been two deaths in the setting of profound hypotension. The first was a fatal case of ventricular fibrillation in the context of more and more profound hypotension, firstly with oral and IV metoprolol, then following the first injection of vernakalant and then following the second injection of vernakalant. The first case highlights the frequency and nature of hypotensive events which may occur postmarketing in a much less constrained clinical environment than obtained in the clinical trials and where patients with a much broader range of cardiovascular co-morbidities than allowed in the clinical trials are exposed to the drug. The second was the more recent and fatal case of cardiogenic shock in the ACT V trial. Five minutes after the start of the vernakalant infusion, the patient developed severe hypotension refractory to treatment and never recovered. Both of these deaths are directly attributable to the effect of vernakalant. The hypotensive response can be alarmingly profound. It is precisely because of the death from cardiogenic shock that the ACT V is still on hold. Clearly there are unresolved issues surrounding the latter for there has been no decision about whether the trial may proceed or should be terminated. In such a context of uncertainty, it would be negligent of the Delegate to entertain any notion of approving the submission. The Delegate therefore considered that the safety of vernakalant has not been satisfactorily established for the proposed indication.

The sponsor applied for a review of this decision under section 60 of the *Therapeutic Goods Act 1989*(the Act). As the review of the initial decision was not completed within 60 days, the initial decision was taken to be confirmed in accordance with subsection 60(4) of the Act on 3 January 2012. The sponsor withdrew their application to the Administrative Appeals Tribunal for a review of the TGA's decision not to register Brinavess.

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Reference/Publication #