BRIEFING MATERIALS
FOR
THE CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DECEMBER 11, 2007

KYNAPID™
(vernakalant hydrochloride injection)
NDA 22-034

Astellas Pharma US, Inc.

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1 EXECUTIVE SUMMARY

This briefing package has been prepared for the Cardiovascular and Renal Drugs Advisory Committee of the United States Food and Drug Administration (FDA) for the public meeting scheduled on December 11, 2007. During this meeting the committee will discuss the safety and efficacy of Astellas Pharma US, Inc.'s new drug application (NDA) 22-034, vernakalant hydrochloride injection (formerly known as RSD1235 Injection and hereafter referred to as vernakalant injection), for the rapid conversion of atrial fibrillation to sinus rhythm. The proposed dosing regimen is an initial infusion of 3 mg/kg over 10 minutes. If conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion, a second 10-minute infusion of 2 mg/kg may be administered. The NDA was submitted to the FDA on December 19, 2006.

This briefing package contains a comprehensive summary of the development of vernakalant injection and includes preclinical data and a review of clinical data from the vernakalant injection development program. These data support the following conclusions that vernakalant injection:

- provides rapid and effective conversion of atrial fibrillation to sinus rhythm,
- reduces symptoms associated with atrial fibrillation,
- has a well-characterized safety profile, with adverse events that are manageable in the clinical setting in which vernakalant injection will be administered, and
- provides an important treatment option to physicians and their patients for the rapid pharmacological conversion of atrial fibrillation to sinus rhythm.

1.1 Mechanism of Action

Vernakalant acts on the heart by blocking potassium channels, which predominantly affect atrial repolarization, combined with a concentration-, voltage- and frequency-dependent blockade of sodium channels, with no effect on calcium channels. The net result is prolonged atrial refractoriness and rate-dependent slowing of atrial conduction. Preferential effects on the atria were demonstrated in in-vitro and in-vivo pharmacology studies. During atrial fibrillation, the frequency- and voltage-dependent block of sodium channels further focuses the action of the drug toward the rapidly activating and partially depolarized atrial tissue rather than toward the normally polarized ventricle beating at lower heart rates.

1.2 Nonclinical Studies

Vernakalant preferentially increased atrial refractory periods and terminated atrial fibrillation in dog and goat models as a result of its multiple ion channel blocking properties. Vernakalant blocks potassium currents that control repolarization at all phases of the atrial action potential. Vernakalant blocks peak sodium current (I_{Na}) with enhanced potency in

fibrillating atria. In addition, vernakalant blocks the late component of I_{Na}, reducing the potential effects on ventricular repolarization.

In keeping with these relatively atrial-selective actions, vernakalant displays reduced proarrhythmic potential in nonclinical assays of ischemia-induced or delayed repolarization-related arrhythmia when compared with typical Class I or III antiarrhythmic drugs.

In safety pharmacology studies, no significant vernakalant-related effects were seen on the central nervous, cardiovascular, or respiratory systems at a clinically relevant dose. Cardiovascular depression and central nervous system (CNS) findings were seen in animals at supra-therapeutic doses or with rapid infusion rates.

Vernakalant has two active demethylated metabolites. In both nonclinical and clinical studies, these metabolites were present at very low plasma levels, and systemic exposure to these metabolites appears to be short lived due to rapid bioconjugation. The bioconjugated metabolites are relatively inactive in vitro. Vernakalant is not highly protein bound, suggesting a low potential for displacement of concomitantly administered drugs that show protein binding.

Single-dose and repeated- IV administration vernakalant toxicity studies of up to 28 days were performed with doses up to 40 mg/kg in the rat and 20 mg/kg in the dog. Toxicities appeared to be limited to neurological changes (excess salivation, tremor, impaired gait/coordination and, at high concentrations, convulsions) with no associated histopathologic findings. Vomiting and retching were also observed in dogs immediately after vernakalant (10 or 20 mg/kg/day) administration. There were no treatment-related changes in hematology, clinical chemistry, urinalysis, organ weights, nor were there macroscopic or microscopic findings beyond the mild to moderate injection site reactions. In the studies in which electrocardiograms were performed, there were no dose-related changes in hemodynamic or ECG parameters in the dog.

Vernakalant showed no discernable genotoxicity in standard assays at non-cytotoxic doses. Vernakalant did not affect fertility or reproductive performance, nor did it affect embryo-fetal development, in either the rat or rabbit.

The results from nonclinical studies indicate a low risk for toxicity (with vernakalant at clinical doses) that is manageable in the clinical setting.

1.3 Clinical Pharmacology

The pharmacokinetics of vernakalant injection have been assessed in dose ranging studies in healthy volunteers (0.1 to 5 mg/kg) as well as atrial fibrillation patients (0.5 to 2 mg/kg + 3 mg/kg). Two formal pharmacokinetic studies in healthy volunteers were conducted: safety and tolerability and a ^{14}C-labeled vernakalant (RSD1235) mass balance study. A human pharmacodynamic study was conducted in subjects undergoing electrophysiological (EP) testing. In addition, plasma and urine samples were collected in dose range-finding study CRAFT, and in efficacy studies ACT I and Scene 2; plasma samples were collected for

pharmacokinetic analyses in a pharmacodynamic study in patients undergoing electrophysiological testing, and in efficacy studies ACT II and ACT III.

Data from patients in ACT I and Scene 2 with atrial fibrillation and/or atrial flutter were pooled to evaluate the effects of CYP2D6 metabolizer genotype status, sex, renal impairment, age and co-administration of CYP2D6-inhibitor medications on the pharmacokinetics of vernakalant injection. Data from ACT III were utilized to develop a population pharmacokinetic model for vernakalant injection and determine the influence of covariates on vernakalant injection pharmacokinetics.

In healthy volunteers, following a 10-minute IV infusion, vernakalant exhibits linear pharmacokinetics for doses ranging from 0.1 mg/kg to 5 mg/kg. Vernakalant has a systemic plasma clearance of about 65 L/hr (20 L/hr in cytochrome P450 [CYP] 2D6 poor metabolizers). Vernakalant has an elimination half-life of approximately 2 hours (approximately 6 hours for poor metabolizers), and a large steady state volume of distribution (mean V_{ss}) of 86 L (112 L for poor metabolizers).

The dosing regimen utilized in all phase 3 studies was an initial infusion of 3 mg/kg over 10 minutes. If conversion to sinus rhythm did not occur during a 15-minute observation period after the end of the initial infusion, a second 10-minute infusion of 2 mg/kg was administered.

In patients with atrial fibrillation, after an intravenous infusion of vernakalant (n=35), maximum plasma concentration (C_{max}) increased in a linear fashion with increasing dose; elimination half-life was similar for each dosing group (CRAFT). Mean elimination $t_{1/2}$ values were approximately 2.7 hours (8.5 hours for poor metabolizers).

Pharmacokinetics were evaluated in two phase 3 studies (ACT I, n=216 and ACT III, n=128). Mean plasma vernakalant concentrations peaked at the end of the 10-minute infusion in patients who received a single 3 mg/kg infusion (ACT I = 4967 ng/mL; ACT III = 3730 ng/mL) and peaked at the end of the second 10-minute infusion (additional 2 mg/kg) in those who received a second infusion (ACT I = 4611 ng/mL; ACT III = 3827 ng/mL). Typical clearance of vernakalant was estimated to be 31.2 L/hr.

Plasma concentrations decreased sharply following the end of infusion with an alpha half-life of 3 to 6 minutes. CYP2D6 expression does not significantly influence the C_{max} and $AUC_{0\text{-}90min}$ after drug administration. Based on pharmacokinetic analyses of data from clinical studies in patients with atrial fibrillation or flutter, age, sex, history of congestive heart failure (CHF), renal function and concomitant CYP2D6 inhibitors or beta-blockers do not significantly influence the C_{max} and $AUC_{0\text{-}90min}$ after intravenous drug administration. Based on these results, dose adjustment is not considered necessary for these patient populations.

Vernakalant is extensively and rapidly metabolized, predominantly by CYP2D6-mediated O-demethylation and rapid glucuronidation to the relatively inactive conjugate. Direct glucuronidation of vernakalant is also relatively prominent (more important for poor metabolizers) followed by subsequent elimination by renal excretion. In healthy volunteers

given a 240 mg dose of [^{14}C] vernakalant hydrochloride, approximately 90% of total radioactivity was excreted in urine and 7% in feces.

Age, sex, race, renal function, hepatic function, and history of CHF do not appear to affect the pharmacokinetics of vernakalant. CYP2D6 expression does not appear to affect the systemic exposure of vernakalant during the first 90 minutes following intravenous administration.

1.4 Clinical Efficacy

Two pivotal studies (ACT I and ACT III) included 575 atrial fibrillation patients (n=236 placebo; n=339 vernakalant injection). Of these, 390 patients had a duration of atrial fibrillation of >3 hours to ≤7 days (n=159 placebo; n=231 vernakalant injection). The efficacy and safety of vernakalant injection with the recommended dosing were evaluated in patients with atrial fibrillation and atrial flutter ≤ 45 days of duration. The primary efficacy endpoint for the pivotal ACT I and ACT III trials was the proportion of patients with atrial fibrillation who converted to sinus rhythm within 90 minutes of first exposure to vernakalant injection for a minimum duration of 1 minute. The primary analysis was performed on patients with atrial fibrillation of >3 hours to ≤ 7 days duration. Conversion for those patients with long-duration atrial fibrillation (>7 days to ≤ 45 days) was also assessed, as well as conversion in all patients (atrial fibrillation duration >3 hours to ≤ 45 days). Conversion to sinus rhythm was determined in a blinded manner by a Clinical Events Committee (CEC) comprising four cardiologists with expertise in clinical trials and arrhythmias.

Symptomatic relief of atrial fibrillation and the maintenance of sinus rhythm were also evaluated.

Consistent with the results for the individual primary endpoints in the ACT I and ACT III studies, the pooled analysis also demonstrated the effectiveness of vernakalant injection in the conversion of atrial fibrillation to sinus rhythm. In the short-duration atrial fibrillation cohort (> 3 hours to ≤ 7 days), a statistically significant (P<0.0001) greater percentage of patients in the vernakalant injection group (51.1%) converted to sinus rhythm as compared with the placebo group (3.8%). The treatment difference (5.2%) in the long duration atrial fibrillation cohort (>7 to ≤ 45 days) was not statistically significant. However, in the overall atrial fibrillation population (>3 hours to ≤ 45 days), a statistically significant greater percentage of patients in the vernakalant injection group converted to sinus rhythm compared with the placebo group.

In patients with short-duration atrial fibrillation and in the overall population, the time to first treatment-induced conversion of atrial fibrillation to sinus rhythm was statistically and clinically significantly shorter in the vernakalant injection group compared with the placebo group. Patients in the short duration subgroup who received vernakalant injection and converted to sinus rhythm did so with a median time of 10 minutes from the start of first infusion, and in all patients who converted, the median time to conversion was 11 minutes.

The majority of patients who received vernakalant injection and converted to sinus rhythm remained in sinus rhythm. The life-table estimate for the maintenance of sinus rhythm in the short duration (>3 hours to ≤ 7 days) atrial fibrillation cohort was 97.2% at hour 24.

In the primary studies, patients were systematically queried regarding atrial fibrillation symptoms. Using a symptom questionnaire, the following symptoms were assessed at baseline and at specified time points during the study: shortness of breath, palpitations, chest tightness/pains, dizziness, edema, fatigue, rapid heart beats, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, nausea, syncope, irregular pulse, vomiting, cough, and headaches. In the pooled primary studies, presenting atrial fibrillation symptoms were generally similar in character and occurrence rates at baseline in the placebo and vernakalant injection groups. At minute 90, a statistically significant (P<0.0001) higher percentage of patients were symptom free in the vernakalant injection group compared with the placebo group in both the short-duration atrial fibrillation cohort and in the overall atrial fibrillation population (48.9% vernakalant injection vs. 26.4% placebo in short-duration, and 46.3% vernakalant injection vs. 28.0% placebo overall). At 90 minutes, the incidence of palpitations, chest tightness/pains, rapid heart beats and irregular pulse was statistically significantly higher in the placebo group as compared with the vernakalant injection group (P-values <0.05).

A comparison of the results of pooled data from the primary studies (ACT I and ACT III) for conversion to sinus rhythm revealed no apparent clinically significant differences in the efficacy of vernakalant injection in the short duration atrial fibrillation cohort based on sex, age, use of rate/rhythm control medications, history of hypertension or history of ischemic heart disease. The data suggest a trend towards a reduced benefit in patients with CHF (with history of CHF: placebo 0, vernakalant injection 26.9%; without history of CHF: placebo 4.2%, vernakalant injection 54.1%).

In the ACT II study (n=150), conducted in patients who developed sustained atrial fibrillation (3 hours to 72 hours duration) between 24 hours and 7 days following coronary artery bypass graft and/or valvular surgery, conversion to sinus rhythm was achieved in 47.0% of patients in the vernakalant injection group compared with 14.0% of patients who received placebo (p=0.0001). The time to conversion to sinus rhythm was statistically significantly shorter in the vernakalant injection group compared to the placebo group (P=0.0001). For the patients in the vernakalant injection group who converted within 90 minutes, the median time to conversion was 12.3 minutes.

In summary, vernakalant injection showed consistency in the conversion of atrial fibrillation to sinus rhythm across all studies. Conversion was rapid, with a median time of onset of 10 minutes in responders. There was no difference in efficacy based on age, sex, background use of rate or rhythm control medications, history of hypertension, or history of ischemic heart disease. Vernakalant injection also provided relief of atrial fibrillation symptoms, and sinus rhythm was maintained out to 24 hours.

1.5 Clinical Safety

Vernakalant injection was well tolerated in clinical trials. Adverse events were generally transient, rarely treatment limiting, and manageable in the clinical setting for which vernakalant injection is intended. The safety profile of vernakalant injection was similar when stratified by age, sex, race, the prior use of rate or rhythm control medications, history of hypertension or history of ischemic heart disease.

Safety analyses were conducted for the entire study period (all post-dose events), and for hours 0-2 post-dose, hours 2-24 post-dose and hours 0-24 post-dose. The 0-24 hour time period was the most informative period because it included the most intensive monitoring, and included the entire period of Holter device monitoring as well as all scheduled 12-lead ECGs except the day 7 ECG. In addition, most vernakalant is cleared from the blood by the end of 24 hours; late events unrelated to study treatments may confound interpretation of events in both the placebo group and the vernakalant injection group. Safety analyses were performed for the 0-2 hour time period because additional treatment for atrial fibrillation could be used after hour 2.

The adverse events (occurring within the first 24 hours) more frequently (>5%) experienced by patients in the vernakalant injection group in phase 2 and phase 3 efficacy and safety studies and at a higher incidence than placebo were dysgeusia (metallic taste, strange or bad taste in the mouth), sneezing, paresthesia, nausea, and hypotension. Dysgeusia, sneezing, and paresthesia generally occurred during the infusion, with a median time to onset of 7, 8, and 9 minutes, respectively, and median duration of 11, 5, and 8 minutes, respectively. The median time to onset for nausea and hypotension was 35 minutes and 34 minutes, respectively, and median duration was 16 minutes for nausea and 20 minutes for hypotension.

Based on the safety profile of other antiarrhythmic agents and in reviewing the safety data for vernakalant injection, three events of interest were identified: ventricular arrhythmia, bradycardia, and hypotension.

Incidence tables were created for these three events using multiple data sources. Holter monitoring and 12-lead ECGs were performed during the vernakalant injection studies to monitor heart rhythm. Adverse event reporting also provided information on heart rhythm. As each of these sources captured information at different time points and for different purposes, special analyses using multiple datasets from these key sources were conducted to assess the incidence of ventricular arrhythmia and bradycardia. Similarly, special analyses to assess the incidence of hypotension were generated using the adverse event and vital sign databases. These special analyses utilized conservative criteria for defining ventricular arrhythmia, bradycardia and hypotension to enable a comprehensive assessment of these events of interest.

The incidence of any ventricular arrhythmia event in the 0-2 hour time period and in the first 24 hours was greater in the placebo group than in the vernakalant injection group. Two cases of ventricular fibrillation occurred in the first 2 hours in the vernakalant injection group one

fatal (discussed below) and one following a nonsynchronized cardioversion. There were four reports of torsade de pointes. Three of the events of torsade de pointes occurred in patients receiving vernakalant injection, and one in placebo; all occurred more than 24 hours following study drug administration except for one event in the vernakalant injection group that occurred at 2 hours and 20 minutes, immediately following an infusion of ibutilide.

Unsustained monomorphic ventricular tachycardia was the most common finding from the Holter device cardiologist over-read and occurred at a similar incidence in both treatment groups in the first 2 hours post dosing.

Any bradycardia event (including adverse events) during the 0-2 hour period was more frequent in patients receiving vernakalant injection and was associated with conversion to sinus rhythm. The most common bradycardia event was sinus bradycardia (heart rate <60 bpm) seen on the 12 lead ECG. A heart rate <40 bpm occurred at a similar incidence in patients receiving placebo and vernakalant injection.

Hypotension as an adverse event was reported more frequently in patients receiving vernakalant injection (5.4%) compared with patients receiving placebo (1.0%). Hypotension was generally transient, and responded to discontinuation of vernakalant infusion, fluids administration (saline) and rarely required pharmacological intervention. The incidence was highest in patients with a history of CHF, where 12.7% of the vernakalant injection-treated patients had an adverse event of hypotension compared with none of the placebo patients. This was reflected in the vital sign database where patients with a history of CHF who received vernakalant injection had higher incidence of a decrease from baseline in systolic blood pressure ≥ 30 mmHg (20.0% vernakalant injection, 1.9% placebo) and/or a systolic blood pressure <90 mmHg (15.5% vernakalant injection, 5.6% placebo). Additional studies are required to evaluate the safety of vernakalant injection in patients with CHF.

A prolongation of the QRS complex and QT interval corrected for heart rate (using both the Bazett and Fridericia formulas) was observed after administration of vernakalant injection. The maximal placebo-subtracted changes from baseline were 8 msec for QRS, 20 msec for QTcB, and 23 msec for QTcF. The peak effect was seen at the end of the first infusion, with a second peak at the end of the second infusion. The QRS and QTcB returned to baseline within 2 hours. The placebo corrected QTcF change from baseline was < 5 msec within 4 hours. These electrocardiographic changes suggest that, at therapeutic concentrations, vernakalant injection exhibits electrophysiological effects on ventricular repolarization. However, despite the QT prolongation, the incidence of ventricular arrhythmia after vernakalant injection was similar to or less than after placebo. The incidence of QTcF outliers (>550 msec) in the 0-2 hour time period following vernakalant infusion was similar between placebo and vernakalant.

In the overall development program, there were no deaths in healthy volunteers or in patients who received placebo (0/341) and five deaths in the vernakalant injection group (0.6%, 5/823). The cause of death was unique to each patient (hypotension/ventricular fibrillation in a hemodynamically unstable patient with critical aortic stenosis; inoperable lung cancer; dissecting aortic aneurysm; heart failure/pulmonary edema; and breast cancer/GI

hemorrhage) and showed neither a temporal, nor a common pathophysiological or pharmacological cause that may have contributed to their deaths. One of the deaths occurred during the first 24 hours following vernakalant injection administration in a patient with critical aortic stenosis and acute coronary syndrome who developed hypotension following administration of metoprolol and vernakalant injection, which led to a fatal ventricular fibrillation.

In summary, vernakalant injection was well tolerated across all clinical trials. Adverse events observed were generally transient, rarely treatment limiting, and manageable in the clinical setting for which vernakalant injection is intended. Ventricular proarrhythmias are a major adverse effect of antiarrhythmic drugs. The incidence of ventricular arrhythmia in the vernakalant injection treatment group was similar to that of placebo (vernakalant injection 5.3%; placebo 6.3%) in the first 2 hours following infusion. QT prolongation was observed; however, despite the QT prolongation, the incidence of ventricular arrhythmia after vernakalant injection administration was similar to placebo. Within the first 24 hours following the administration of vernakalant injection, there was one report of torsade de pointes and two reports of ventricular fibrillation. An increase in the incidence of bradycardia was observed in the vernakalant injection group in the first 2 hours following infusion. An increased incidence of hypotension adverse events was observed in patients receiving vernakalant injection (5.4%) compared to placebo (1.0%) in the first 2 hours following infusion. These events were peri-infusional, generally mild to moderate, and responded to discontinuation of infusion and administration of fluids. Five deaths were reported in patients who received vernakalant injection, and no deaths were reported in patients who received placebo. The cause of death was unique in each patient and showed neither a temporal nor common pathophysiological or pharmacological cause that may have contributed to their deaths. One of the deaths occurred during the first 24 hours of the study and was considered related to vernakalant injection.

1.6 Benefit-Risk Assessment

Given the limitations of current pharmacological agents used to acutely convert atrial fibrillation and the necessity for conscious sedation or anesthesia for electrical cardioversion, there is a need for better agents to convert atrial fibrillation. The vernakalant injection clinical development program demonstrated that vernakalant injection was safe and effective in patients with new or recurrent atrial fibrillation, including those with post-operative atrial fibrillation. Vernakalant injection restored sinus rhythm and provided relief of symptoms in approximately 50% of patients and further demonstrated a low rate of adverse cardiac events, including arrhythmia. Bradycardia and hypotension were generally transient and responded to discontinuation of study drug and appropriate medical management. One related death was reported.

In conclusion, the data from vernakalant injection studies indicate that, in patients with recent onset atrial fibrillation for whom rapid cardioversion is indicated, the benefits of vernakalant injection outweighs its risks.

Vernakalant injection provides an important treatment option to physicians and their patients for the rapid pharmacological conversion of atrial fibrillation to sinus rhythm.

2 INTRODUCTION

2.1 Proposed Indication and Dosing

The Sponsor is seeking approval for the use of vernakalant injection for the rapid conversion of atrial fibrillation to sinus rhythm. The proposed dosing regimen is an initial infusion of 3 mg/kg over 10 minutes. If conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion, a second 10-minute infusion of 2 mg/kg may be administered.

2.2 Management of Atrial Fibrillation

2.2.1 Medical Need

Atrial fibrillation is the arrhythmia in the United States most often requiring medical therapy, and the prevalence is expected to increase to 12 million by 2050 (Miyasaka et al, 2006). It has been estimated that more than 2 million individuals in the US have paroxysmal or persistent atrial fibrillation (Go et al, 2001). The prevalence of atrial fibrillation is estimated at 0.4% to 1.0% of the general population, increasing with age. The lifetime risk to develop atrial fibrillation at 55 years of age has been estimated at 23.8% in men and 22.2% in women (Heeringa et al, 2006).

Most patients with atrial fibrillation are identified now because they have symptoms when their rhythm is abnormal; clinical guidelines and recent reviews have emphasized the importance of symptoms in the decision to initiate a rhythm control strategy in these patients. (Fuster et al, 2006; Snow, 2003; Psaty, 1997). Atrial fibrillation can cause discomfort and is associated with a number of symptoms, such as palpitations, chest pain, dyspnea, fatigue and lightheadedness. Atrial fibrillation may increase the risk of stroke five-fold (Carley et al, 2004); it can also lead to tachycardia-related cardiomyopathy, CHF, cognitive dysfunction, and a reduction in left ventricular function, exercise tolerance and quality of life (Fuster et al, 2006; NCCCC, 2006; Singh et al, 2006; Stewart et al, 2002; Kilander et al, 1998).

There are two general therapeutic strategies used in treating patients with atrial fibrillation. One strategy, “rate control,” is to allow the atrial fibrillation to continue and to control the ventricular response rate by slowing conduction through the AV node with digoxin, calcium channel blockers (verapamil or diltiazem) or beta-blockers. The other strategy, “rhythm control,” seeks to convert atrial fibrillation to sinus rhythm and then maintain sinus rhythm, thus avoiding the morbidity associated with chronic atrial fibrillation. Cardioversion is an important treatment option as the initial step within rhythm control for certain patients as part of the overall management strategy of their atrial fibrillation. Where cardioversion is indicated, distinct benefits are associated with rapid conversion of atrial fibrillation to sinus rhythm including reduced symptoms and improved hemodynamics (Fuster et al, 2006; Naccarelli et al, 2000; Morris et al, 1965). Conversion to sinus rhythm regularizes ventricular rate, improves cardiac function, cardiac output, blood pressure, and exercise capacity (Fuster

et al, 2006; Gosselink et al, 1994; Van Gelder et al, 1993; Alam et al, 1992). Rapid conversion of atrial fibrillation may also prevent or reverse the development of atrial electrical and structural remodeling associated with atrial fibrillation (Allessie et al, 1996; Wijffels et al, 1995). Electrophysiologic and structural remodeling (e.g., fibrosis and progressive dilatation) associated with atrial fibrillation makes it more difficult to terminate atrial fibrillation, as the duration of atrial fibrillation increases (Falk, 2001; Franz et al, 1997; Sanfilippo et al, 1990). Thus, rapid conversion of atrial fibrillation to sinus rhythm may limit atrial remodeling, prevent development of refractory atrial fibrillation, and ultimately affect disease progression (Hobbs et al, 2000). Delay of conversion may worsen atrial fibrillation symptoms in some patients (Joseph et al, 2000). The overall management of atrial fibrillation requires thoughtful consideration of the patient's need for anticoagulation, heart rate control, and rhythm control (Fuster et al, 2006).

2.2.2 Limitations of Current Therapies

Cardioversion remains an important treatment option for patients with atrial fibrillation. Pharmacological cardioversion is a simpler treatment and, unlike electrical cardioversion, does not require conscious sedation or anesthesia. Furthermore, rapid pharmacologic conversion facilitates monitoring of the patient at the time of conversion, in comparison to drugs with a delayed onset of action. In addition, electrical cardioversion is not desirable in a post-cardiac surgery population, non-fasted patients, or in patients with respiratory diseases. Pharmacological conversion might be the preferred option in these conditions. The shortcomings of pharmacological cardioversion are that existing agents are less efficacious than electrical cardioversion and there are risks associated with the toxicities of the current drugs.

Electrical cardioversion is the method of choice in hemodynamically unstable atrial fibrillation patients (Fuster et al, 2006), but has associated adverse cardiovascular effects, such as hypotension, sinus arrest, heart block, bradycardia, ventricular tachycardia or fibrillation, and pacemaker malfunction as well as skin burns, pain, aspiration risk, or pulmonary edema (Gallagher et al, 2007; Morris et al, 1965). Electrical cardioversion may prolong recovery of normal atrial contraction compared with pharmacological conversion (Mattioli et al, 1998; Harjai et al, 1997; Fatkin et al, 1994; Manning et al, 1989). Finally, although electrical cardioversion has been demonstrated to be effective at conversion of atrial fibrillation to sinus rhythm (70 to 90%) (Fuster et al, 2006; Van Gelder et al, 1999), these effects can be short-lived, with reports of immediate recurrence of atrial fibrillation (IRAF) within 1 to 10 minutes of electrical cardioversion in 9 to 12% of patients (Fuster et al, 2006; Sticherling et al, 2005; Oral et al, 2003; Daoud et al, 2000; Van Gelder et al, 1999). Maintenance of sinus rhythm over the longer time period of 24 hours and 1 week has been reported as 71 to 95% (Ozdemir, 2006; Berry et al, 2001; Tieleman et al, 1998; Bianconi et al, 1996) and 61 to 70% (Korantzopoulos et al, 2005; Ehrlich et al, 2003; Tieleman et al, 1998; Bianconi et al, 1996), respectively.

The need for light general anesthesia or conscious sedation is a significant disadvantage of electrical cardioversion, increasing the risk of the procedure and making it inappropriate for

patients in a fed state or those with impaired respiratory function. In a recent series of 388 patients admitted to emergency departments and undergoing electrical cardioversion, Burton and colleagues (2004) report that 22 (5.7%) subjects developed complications related to sedation and analgesia. Local complications (tenderness, moderate skin burns) are also common (24 to 40%) (Grönefeld, 2003).

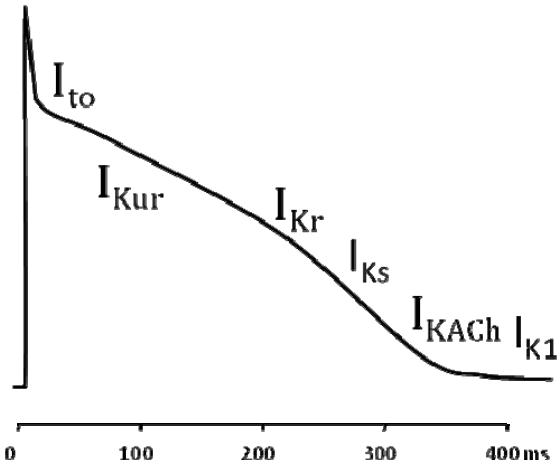
Of the antiarrhythmics that have been studied and recommended for use for pharmacological conversion of atrial fibrillation, only intravenous ibutilide and oral dofetilide are approved in the US. Both of these agents are associated with torsade de pointes (4% with ibutilide; 1 to 3.3% with dofetilide) (Fuster et al, 2006; Tikosyn [dofetilide], Pfizer, 2004) and are more effective in converting atrial flutter than atrial fibrillation; conversion rates for atrial fibrillation ranged from 6 to 30% for dofetilide and from 25 to 38% for ibutilide (Corvert [ibutilide], Pharmacia, 2002; Tikosyn [dofetilide], Pfizer, 2004). Furthermore, conversion using oral dofetilide may take days, or longer (Fuster et al, 2006).

3 MECHANISM OF ACTION

Vernakalant acts on the heart by blocking potassium channels, which predominantly affect atrial repolarization, combined with a concentration-, voltage- and frequency-dependent blockade of sodium channels, with no effect on calcium channels. The net result is prolonged atrial refractoriness and rate-dependent slowing of atrial conduction. Preferential effects on the atria were demonstrated in in-vitro and in-vivo pharmacology studies. During atrial fibrillation, the frequency- and voltage-dependent block of sodium channels further focuses the action of the drug toward rapidly activating and partially depolarized atrial tissue rather than toward the normally polarized ventricle beating at lower heart rates.

Vernakalant preferentially increased atrial refractory periods and terminated atrial fibrillation in dog and goat models. Vernakalant blocks potassium currents that control repolarization at all phases of the atrial action potential, including the transient outward (I_{to}), the ultra-rapid delayed rectifier (I_{Kur}), the acetylcholine-activated (I_{KACh}), and the rapid component of the delayed rectifier (I_{Kr}) [Figure 1]. At therapeutic concentrations, vernakalant does not block (IC_{50}>100 microM) the slow component of the delayed rectifier (I_{Ks}) or the inward rectifier (I_{K1}) (other potassium currents important in ventricular but not atrial repolarization).

Figure 1: Vernakalant-Induced Blockade of Potassium Currents Controlling Atrial Action Potential Repolarization



Potassium Currents Blocked by Vernakalant	
Current	Potency (IC_{50}) (microMolar)
I_{to}	5-30
I_{Kur}	3-13
I_{KACh}	10
I_{Kr}	7-21
I_{Ks}	>100
I_{K1}	>100

Vernakalant blocks peak sodium current (I_{Na}) with enhanced potency in depolarized and rapidly activating (fibrillating) atria and reduced potency in normal ventricle. Depolarization decreases the IC_{50} from approximately 100 microM at -120 mV to 31 microM at -60 mV. An additional factor enhancing the atrial action of vernakalant is the more depolarized resting potential in that tissue versus the ventricle. An increase in activation rate from 1 to 20 Hz further increases vernakalant's potency, as evidenced by a decrease in the IC_{50} to 9 microM [Table 1]. These rates and potentials approximate those observed in the atria during atrial fibrillation. In addition to blockade of the peak sodium current, vernakalant blocks the late component of I_{Na} (IC_{50} = 14 microM), an inward current that contributes to the plateau of the action potential.

Table 1: Voltage- and Frequency-Dependent Block of Peak I_{Na} by Vernakalant

Holding Potential (mV)	**Potency (IC_{50}) (microM)**	**Frequency (Hz)**
Voltage Dependence		
-120	107 ± 11	1
-100	60 ± 4	1
-80	43 ± 8	1
-60	31 ± 1	1
Frequency Dependence		
-80	43 ± 8	1
-80	9	20

Fedida et al, 2005

Although I_{Kr}/hERG channels are blocked by vernakalant, which may lead to QT prolongation, vernakalant is 30- to 100-fold less potent than flecainide, propafenone, quinidine, or tedisamil (Fedida et al, 2005; Jost et al, 2004) and approximately 1000-fold less potent than ibutilide or dofetilide (Yang et al, 1995). It has also been reported for vernakalant that block of late I_{Na} attenuates the prolonging effect of I_{Kr} inhibition on the cardiac action potential (Orth et al, 2006). The combination of these two mechanisms is expected to result in limited overall effects on ventricular repolarization.

4 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

4.1 Pharmacology

Preferential effects on the atria, comprising prolonged atrial refractoriness and rate-dependent slowing of atrial conduction, were demonstrated in in-vitro and in-vivo pharmacology studies. During atrial arrhythmia, the rate-dependant block of sodium channels at high activation rates further targets the action of the drug toward atrial tissue rather than toward the normally polarized ventricle beating at lower rates.

In dog, pig and goat models, vernakalant preferentially prolonged atrial effective refractory periods (ERP) compared with ventricular ERP. These actions were maintained in electrically remodeled atria, in which vernakalant doubled left atrial ERP without significantly affecting ventricular ERP at a 4 mg/kg dose. Vernakalant's frequency-dependent I_{Na} blocking actions resulted in 24-29% slowing of atrial conduction in canine atria paced at fibrillatory rates (400 beats per min [bpm]) but no significant effects at 200 bpm. Vernakalant terminated recent onset atrial fibrillation in canine models in a dose-dependent fashion, with an ED_{50} of 1-2 mg/kg. In a goat model of persistent (2-16 weeks) atrial fibrillation, vernakalant was effective at an ED_{50} of approximately 10 mg/kg.

In keeping with its relative atrial selective actions, vernakalant displayed reduced proarrhythmic potential in non-clinical assays. Vernakalant mildly prolonged action potential duration (APD) in rabbit Purkinje fibers at concentrations of 10 to 30 microM. While Purkinje fiber APD prolongation might indicate a potential for QT prolongation, vernakalant (30 microM) did not induce early after depolarizations (EADs), attenuated dofetilide-induced APD prolongation and terminated dofetilide-induced EADs in this tissue. Similarly, vernakalant suppressed torsade de pointes induced by the Class III antiarrhythmic drug, clofilium, in a rabbit proarrhythmia model. Inhibition of late I_{Na} is likely the mechanism for this protective action of vernakalant. Vernakalant also was not proarrhythmic in pig and rat ischemic arrhythmia models at therapeutically relevant concentrations.

In safety pharmacology studies, no significant vernakalant-related effects were seen on the central nervous, cardiovascular, or respiratory systems at clinically relevant doses. Cardiovascular depression and CNS adverse effects were seen in animals at supra-therapeutic doses or following rapid infusion rates. Convulsions were observed in rats during infusion of vernakalant at a rate of 64 mcmol/kg/min, which yielded plasma levels that were 10- to 30-fold higher than the clinical C_{max}. No additive cardiodepressant interactions were observed between vernakalant and verapamil or propranolol in conscious rats.

Plasma vernakalant concentrations declined rapidly following IV administration, with mean terminal half-lives of 36 minutes in the rat and 2.8 hours in the dog. Clearance and volume of distribution values were high in the dog. Vernakalant has two active demethylated metabolites, RSD1385 and RSD1390. In conscious and anesthetized rats, RSD1385 and RSD1390 displayed cardiovascular effects that were qualitatively similar to that of vernakalant. These metabolites appeared to be somewhat less potent than vernakalant with respect to effects on ECG parameters. Very low plasma levels of the metabolites have been observed in preclinical and clinical studies. The bioconjugated metabolites are inactive on ion channels in-vitro.

RSD1385 was identified as the major phase 1 metabolite of vernakalant in all non-clinical species examined, and CYP2D6 was determined to be responsible for the formation of the metabolite. CYP3A4 produced two minor metabolites. In a study in human liver microsomes, the overall extent of metabolism was moderate. Vernakalant competitively inhibits CYP2D6, with an IC_{50} of 20 mcM and K_i of 3 mcM when bufuralol was used as a substrate.

Following IV administration of [^{14}C] vernakalant in the rat, drug-derived radioactivity was widely distributed and eliminated via both bile and urine. In rats, the feces were the major route of elimination for [^{14}C] vernakalant-derived radioactivity, accounting for 60-69% of the radioactive dose in rats.

Vernakalant was not highly bound to rat plasma or human serum proteins. In vitro protein binding studies in human serum indicated that administration of vernakalant and drugs likely to be co-administered to patients would not result in significant increases in the free drug concentrations of either vernakalant or the concomitantly administered drugs.

4.2 Toxicology

Adverse signs at the maximum tolerated dose (40 mg/kg in rats; 20 mg/kg in dogs) were limited to neurological changes (excess salivation, tremor, impaired gait/coordination, and, at high concentrations, convulsions) for both rats and dogs.

In repeated dose toxicology studies, no test article-related clinical signs, or clinical chemistry, hematologic, or pathologic (gross or microscopic) findings were observed at dose levels below 20 mg/kg/day in the rat (2-minute infusion) or 5 mg/kg/day in the dog (10-minute infusion). Local injection site discoloration with mild to moderate histopathologic findings were present in dogs at all dose levels.

Table 2: Summary of Treatment Related Changes in the Rat and Dog 28-Day Repeat Dose Toxicity Studies and the Plasma Exposure Multiples Relative to that Observed in ACT I and ACT III

Study	Dose Level (mg/kg)	Cmax (ng/mL)		Observations	Plasma Multiple†
		Total	Unbound Fraction		
ACT I & ACT III	3 + 2	4631	2241	---	---
Rat 28 day study	20	13350	8611	NOAEL	3.8
	40	23100	14890	Mortality, tremors, uncoordinated gait, ↓ activity, ↓ respiration	6.6
Dog 28 day study	5	2460	1510	NOAEL	0.7
	10	5610	3445	↑Incidence (salivation, tremor, emesis)‡; injection site inflammation and hemorrhage	1.5
	20	10600	6508	↑Incidence (salivation, tremor, emesis)‡; uncoordinated gait; injection site inflammation and hemorrhage	2.9

NOAEL: No observable adverse effect level

† Plasma multiple is based on unbound fraction of vernakalant in plasma

‡ Salivation and tremor were observed in the vehicle control group; however, the incidence was increased in vernakalant treated dogs at >10 mg/kg

The effects of IV vernakalant were examined in rats with administration up to 28 days. Mortality was observed at 40 mg/kg: 4 of 10 males (main study) and 1 of 6 females (toxicokinetic cohort). One female at 20 mg/kg (toxicokinetic cohort) was sacrificed moribund (possibly due to blood collection). Clinical signs prior to death (in some animals) were tremors, uncoordinated gait, decreased respiration, and decreased activity. There were no histopathologic findings that could be interpreted as a cause of death in these animals.

There were no treatment-related effects on food consumption, body weights, ophthalmology, hematology, coagulation, urinalysis, gross or microscopic observations at any dose level. The no observable adverse event level (NOAEL) was 20 mg/kg/day.

The effects of daily 10-minute IV infusions of vernakalant were examined in dogs for up to 28 days of administration.

Neurological findings at 20 mg/kg observed over 7 days consisted of tremor, uncoordinated gait, and licking. Findings at 20 mg/kg over 14 days were similar; however, there was also one episode of clonic convulsions. In both the 7- and 14-day studies, these clinical findings were limited to the initial hour post-dose. In the 28-day repeated dose dog study, test article-related findings were reported at 10 or 20 mg/kg/day and consisted of salivation, tremors and emesis. Several animals also exhibited aggressive behavior (1 female at 10 mg/kg/day, 3 males and 1 female at 20 mg/kg/day, and one control male). A macroscopic finding of "discoloration, red" at the injection site and microscopic findings of minimal to moderate

"hemorrhage" and minimal to mild "inflammation, subacute" were noted in the various dose groups from this study.

No treatment-related changes were observed in body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, or organ weights. Gross pathology and histopathologic findings were limited to the injection site findings in the 28-day repeated dose dog study.

Vernakalant was not genotoxic in the Ames test (five tester strains of *S. typhimurium)* or in the mouse micronucleus test. In the chromosomal aberration assay with Chinese hamster ovary cells, statistically significant increases in the frequency of chromosomal aberrations (with and without S9 activation) were reported at concentrations where significant (>60%) cytotoxicity was also seen. Vernakalant was not genotoxic in a mouse lymphoma assay.

The effects of vernakalant (10, 20, 40 mg/kg/day IV; 2 minute injection) on fertility and early embryonic development were studied in male and female rats administered the drug prior to cohabitation, throughout mating, and through the implantation stage of gestation. The NOAEL for general toxicity (parent generation) was 10 mg/kg/day. The NOAEL for fertility was 40 mg/kg/day for both males and females. The NOAEL for early embryonic development was also 40 mg/kg/day.

The embryo-fetal toxicity of vernakalant was evaluated in rats and rabbits. In Sprague-Dawley rats administered vernakalant at dose levels of 10, 20, and 40 mg/kg/day IV (2-minute injection) on gestational days 6 to 17, the NOAEL for general toxicity of dams, embryo-fetal toxicity, and embryo-fetal development was determined to be 40 mg/kg/day. In New Zealand White rabbits treated with vernakalant at dose levels of 3, 10 and 30 mg/kg/day (5 minute injection) on gestational days 7 to 18, maternal mortality was reported at the highest dose level. Therefore, the NOAEL for general toxicity in the does was determined to be 10 mg/kg/day. Vernakalant administration to rabbits during organogenesis at dose levels up to 30 mg/kg/day showed no embryo-fetal toxicity and no embryo-fetal developmental findings; the NOAEL for both types of changes was determined to be 30 mg/kg/day.

The effects of vernakalant (10, 20 and 40 mg/kg/day IV; 2 minute injection) on pre- and postnatal development was determined in pregnant rats from implantation through gestation, parturition and weaning with observations continued through sexual maturity of the F_1 generation. Maternal mortality (2 of 25) of the F_0 generation was observed at the 40 mg/kg/day dose, establishing the NOAEL for general toxicity of the dams at 20 mg/kg/day. Vernakalant at dose levels up to 40 mg/kg/day had no effect on pup viability, developmental milestones, or fertility indicating that the NOAEL for these parameters was 40 mg/kg/day.

Vernakalant prepared in isotonic citrate buffer, pH 5.5 at concentrations of 0.2 mg/mL, 10 mg/mL and 20 mg/mL did not cause hemolysis of rat erythrocytes.

5 CLINICAL DEVELOPMENT PROGRAM

5.1 Clinical Studies

The clinical development program for vernakalant injection consisted of nine clinical studies conducted at investigative sites in Argentina, Canada, Chile, Denmark, India, Italy, Mexico, the Netherlands, Poland, South Africa, Sweden and United States. A total of 1164 adult subjects received study drug, of whom 823 received vernakalant injection and 341 received placebo [Table 3]. A brief summary of each study is presented below.

The clinical pharmacology of vernakalant was evaluated in three studies: a first in man safety and pharmacokinetics study (1235-1-04-12-01), a study of mass balance ^{14}C-labeled vernakalant (04-0-195) in healthy volunteers, and a study in patients undergoing electrophysiological testing (1235-SMH1). Additionally, plasma and urine samples were collected in clinical studies to define the pharmacokinetic profile of vernakalant injection in patients.

Two, phase 3, randomized, double-blind, placebo-controlled studies in patients with atrial fibrillation (ACT I, Study 1235-0703 and ACT III, Study 1235-0504/04-7-010, "primary studies") provide evidence of the efficacy of vernakalant injection for the rapid conversion of atrial fibrillation to sinus rhythm.

Study 1235-0104 (ACT II), a phase 3, randomized, double-blind, placebo-controlled study of atrial fibrillation, demonstrates the efficacy and safety of vernakalant injection in the conversion of atrial fibrillation to sinus rhythm in patients who underwent coronary artery bypass graft and/or valvular surgery.

Study 05-7-012 (ACT IV), an open-label phase 3 study, supports the safety of vernakalant injection and provides further evidence of efficacy in the conversion of atrial fibrillation to sinus rhythm.

Data from a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study in patients with atrial fibrillation (CRAFT, Study 1235-1001) provides supportive evidence of the efficacy and safety of vernakalant injection for the rapid conversion to sinus rhythm.

The development program also included a study (Scene 2, Study 1235-0703B) to evaluate vernakalant injection for the conversion of typical atrial flutter to sinus rhythm. Patients with atrial flutter were also included in ACT III. Based on the results of Scene 2, which did not demonstrate efficacy in converting typical atrial flutter to sinus rhythm, the Sponsor decided not to pursue an indication for atrial flutter.

Table 3: Enumeration of Subjects in Vernakalant Injection Clinical Development Program

	Exposure	
	Placebo	**Vernakalant Injection**
Clinical Pharmacology/Pharmacodynamic Studies		
Study 1235-1-04-12-01 (Healthy Volunteer)	6	23
Study 1235-SMH1 (EP Patients) †	0	19
Study 04-0-195	0	8
Total Clinical Pharmacology	**6**	**50**
Efficacy/Safety Studies		
ACT I (Study 1235-0703)§	115	221
ACT III (Study 1235-0504/04-7-010)§	131 (AF: N=121)	134 (AF: N=118)
CRAFT (Study 1235-1001)	20	36
Scene 2 (Study 1235-0703B)	15	39
Studies Completed After Submission of NDA‡		
ACT II (Study 1235-0104)	54	107
ACT IV (Study 05-7-012)	0	236
Total Phase 2/3 Efficacy/Safety Studies	**335**	**773**
TOTAL ALL STUDIES	**341**	**823**

AF: Patients with atrial fibrillation

† EP: Electrophysiology patients did not have atrial fibrillation but were undergoing EP testing or ablation.

‡ Preliminary safety data from these studies were included in the NDA dossier.

§ Primary studies

The intended dose for marketing is 5 mg/kg administered as an initial infusion of 3 mg/kg over 10 minutes, followed by 2 mg/kg over 10 minutes, if conversion to sinus rhythm does not occur within 15 minutes after the end of the initial infusion. A total of 719 patients received a single infusion of vernakalant injection totaling 3 mg/kg. A total of 500 patients received two doses (3 mg/kg + 2 mg/kg) of vernakalant injection for a total dose of 5 mg/kg, the maximum proposed dose.

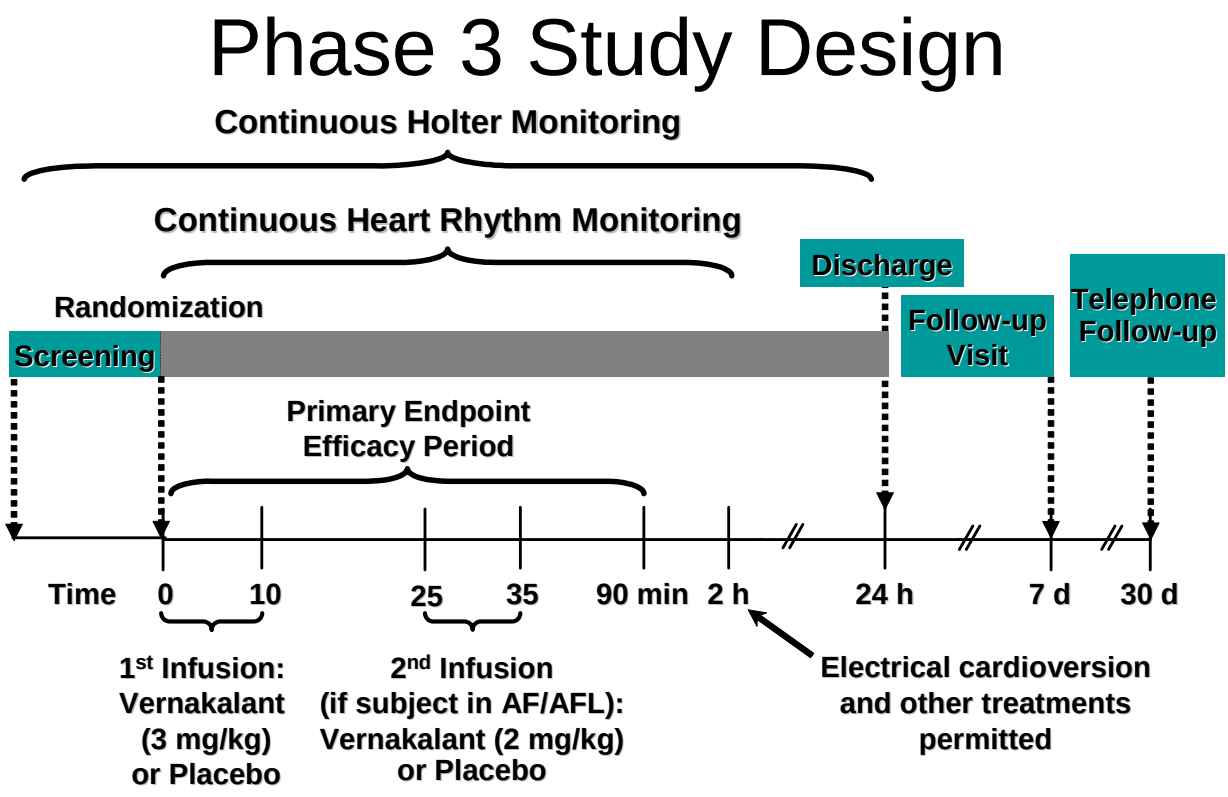
5.2 Phase 3 Study Design and Endpoints

Entry criteria used in the phase 3 studies allowed inclusion of patients representative of the population seeking treatment for symptomatic atrial fibrillation, including relevant subgroups such as patients with structural heart disease and/or history of CHF. Patients with symptomatic atrial fibrillation sustained for >3 hours and ≤ 45 days, and who were receiving adequate anticoagulant therapy in accordance with ACC/AHA/ESC practice guidelines were eligible to enroll in the studies. Patients with QT interval >440 msec (ACT II >500 msec), symptomatic bradycardia or a heart rate <50 bpm, QRS interval >140 msec, who had received intravenous class I or III antiarrhythmic drugs or intravenous amiodarone within 24 hours, class IV CHF, or who were hemodynamically unstable, or had myocardial infarction, acute coronary syndrome or cardiac surgery (except ACT II) within 30 days were not eligible for enrollment. Serum potassium was corrected if <3.5 mEq/L. Patients were

permitted to receive oral/IV background rate control and oral rhythm control medications, as well as other therapies common in this population.

Clinical and pharmacokinetic evaluations were performed at baseline and throughout the study periods. Extensive ECG and vital sign monitoring were used throughout the clinical development program. Blood pressure measurements and 12-lead ECGs were performed every 5 minutes for the first 50 minutes and at 1.5, 2, 4, 8 and 24 hours (in the primary studies) and were interpreted by the investigators for immediate clinical management. Telemetry was performed continuously from baseline until a minimum of two hours post-dose. Holter monitoring was performed from at least 30 minutes prior to randomization until 24 hours 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. With the exception of the open-label study, ACT IV, a Clinical Events Committee comprising four cardiologists blinded to treatment over-read all 12-lead ECGs for baseline rhythm interpretation and reviewed a 70-second portion of the Holter recording to confirm the conversion to sinus rhythm. The chairperson of the Data Safety Monitoring Board reviewed Holter alerts for ongoing safety monitoring.

Figure 2: Study Design of Vernakalant Injection Phase 3 Studies



AFL=atrial flutter

In ACT II, patients were discharged up to 14 days post-dose.

The dosing regimen used in all phase 3 studies consisted of an initial infusion of 3 mg/kg over 10 minutes, followed by 2 mg/kg over 10 minutes (for a total dose of 5 mg/kg) if conversion to sinus rhythm did not occur within 15 minutes after the end of the initial infusion.

The primary efficacy endpoint for the pivotal ACT I and ACT III trials was the proportion of patients with atrial fibrillation who converted to sinus rhythm within 90 minutes of first exposure to vernakalant injection for a minimum duration of 1 minute. The primary analysis was performed on patients with atrial fibrillation of >3 hours to ≤ 7 days duration. Other endpoints assessed included: conversion of atrial fibrillation to sinus rhythm in patients with atrial fibrillation duration >3 hours and ≤ 45 days, time to conversion, maintenance of sinus rhythm, and relief of atrial fibrillation symptoms.

5.3 Patient Population

Patients enrolled in the vernakalant injection phase 2 and phase 3 studies were primarily males (68%) with a mean age of 63 years (range 22-94). Approximately 50% of the patients were over the age of 65 years, and 20% were 75 years of age or older. Most of the patients were white (96%). A total of 92% of the patients had atrial fibrillation at baseline, and 8% were in atrial flutter. The patients enrolled are representative of the patients seen in clinical practice (Gentile et al, 2002; Levy et al, 1999; Benjamin et al, 1998).

Table 4: Demographics and Baseline Characteristics of All Patients in Phase 2 and Phase 3 Studies

Parameter		Placebo N=335	Vernakalant Injection N=773
Sex	Male	228 (68.1%)	526 (68.0%)
	Female	107 (31.9%)	247 (32.0%)
Age (years)	N	335	773
	Mean ± SD	62.9 ± 12.0	63.2 ± 13.2
	SD	11.99	13.16
	Median	64	65
	Min–Max	27–90	22–94
Age Group #1	< 65 years	176 (52.5%)	383 (49.5%)
	≥ 65 years	159 (47.5%)	390 (50.5%)
Age Group #2	< 75 years	279 (83.3%)	604 (78.1%)
	≥ 75 years	56 (16.7%)	169 (21.9%)
Race	White	326 (97.3%)	743 (96.1%)
	Non-white	9 (2.7%)	30 (3.9%)
Baseline Diagnosis	Atrial Fibrillation	306 (91.3%)	711 (92.0%)
	Atrial Flutter	28 (8.4%)	59 (7.6%)
	Unknown	1 (0.3%)	3 (0.4%)
AF/AFL Duration	3 Hours to 7 Days	249 (74.3%)	576 (74.5%)
	8 Days to 45 Days	86 (25.7%)	196 (25.4%)
	Unknown	0	1 (0.1%)
Number of Doses	Dose #1 only	6 (1.8%)	249 (32.2%)
	Started dose #2	329 (98.2%)	524 (67.8%)
History of CHF	Yes	60 (17.9%)	115 (14.9%)
History of IHD	Yes	95 (28.4%)	187 (24.2%)
History of Hypertension	Yes	163 (48.7%)	402 (52.0%)
Background Use† of Rate Control Medications‡	Yes	263 (78.5%)	554 (71.7%)
Background Use† of Rhythm Control Medications§	Yes	66 (19.7%)	151 (19.5%)
Any Baseline AF/AFL Symptom¶	Yes	258/315 (81.9%)	401/501 (80.0%)

All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

SD: standard deviation; AF: atrial fibrillation; AFL: atrial flutter; CHF: congestive heart failure; IHD: ischemic heart disease

† Background use is defined as medication used during the 7 day period prior to study drug administration.

‡ Rate control medications include oral/IV beta blockers, calcium channel blockers, and digoxin.

§ Rhythm control medications include class I and class III antiarrhythmics.

¶ Symptoms not collected in CRAFT or ACT IV.

5.4 Statistical Methodology

The pooled primary population presented in the clinical summary of efficacy analyses in the vernakalant injection NDA used data from all patients who received any amount of study drug in ACT I and the patients with atrial fibrillation at baseline who received any amount of study drug in ACT III ("pooled primary studies"). The primary efficacy endpoint for ACT I, ACT III and the pooled data was the proportion of patients with atrial fibrillation >3 hours to ≤ 7 days duration who converted to sinus rhythm (for a minimum duration of one minute) within 90 minutes after first exposure to vernakalant injection.

The primary analysis of efficacy was based on the full analysis set which was defined *a priori* in the individual studies as all randomized patients with atrial fibrillation who received any amount of study drug (active drug or placebo).

The primary efficacy analysis utilized the Cochran-Mantel-Haenszel test stratified by country. The frequency and percentage of successes and failures for each treatment group, the difference in the percentage of successes between treatment groups, the asymptotic 95% confidence interval (CI) of the difference in success between treatment groups, and the P-value for the difference between treatment groups were calculated. In addition, the Mantel-Haenszel Odds Ratio (OR) of the vernakalant injection group versus the placebo group along with 95% CI was also estimated.

In addition to the primary efficacy analysis, analysis of pooled ACT I and ACT III data included:

1. Analysis of the proportion of patients with atrial fibrillation of > 3 hours to ≤ 45 days duration who converted to sinus rhythm for a minimum duration of one minute within 90 minutes of first exposure to vernakalant injection or placebo utilizing identical methods as described for the primary endpoint.

2. The time from first exposure to treatment to the time of conversion to sinus rhythm for a minimum duration of one minute utilizing the Product-Limit method to obtain the estimates of the median time to conversion, the associated 95% confidence intervals and the event-free curves associated with each treatment group. The two treatment groups were compared using the Log Rank test.

   If a patient did not convert to sinus rhythm for a minimum duration of one minute within 90 minutes after first exposure to treatment, the time from first exposure to study drug until first conversion to sinus rhythm for a minimum duration of one minute was censored at 90 minutes. Additionally, patients who withdrew prior to conversion to sinus rhythm or who were electrically cardioverted before 90 minutes were to be censored at the time at which they withdrew or were electrically cardioverted.

3. The comparison of the proportion of patients with at least one symptom of atrial fibrillation and the comparison of the proportion of patients with each symptom between vernakalant injection and placebo was conducted using Fisher's exact test.

4. Conversion for those patients with long-duration atrial fibrillation (>7 days to ≤ 45 days duration) was also presented briefly in the summary of efficacy.

5. Maintenance of sinus rhythm for patients who converted from atrial fibrillation to sinus rhythm was estimated, using a life table approach, at 2 hours, 4 hours, 8 hours, 24 hours and 7 days, as requested by the FDA at the preNDA meeting on November 1, 2005.

6. The Division also requested an analysis assessing the likelihood of conversion based on the duration of atrial fibrillation. The method of data collection in the ACT I study allowed for a logistic regression analysis of treatment-induced conversion from atrial fibrillation to sinus rhythm using the duration of atrial fibrillation as covariate. This analysis was only performed for the vernakalant injection treatment group.

6 CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS

6.1 Pharmacokinetics

The pharmacokinetics of vernakalant injection have been assessed in dose ranging studies in healthy volunteers (0.1 to 5 mg/kg) as well as atrial fibrillation patients (0.5 to 2 mg/kg + 3 mg/kg). Two formal pharmacokinetic studies in healthy volunteers were conducted: safety and tolerability Study 1235-1-04-12-01 and a ^{14}C-labeled vernakalant (RSD1235) mass balance study (04-0-195). A human pharmacodynamic study was conducted in subjects undergoing electrophysiological (EP) testing (Study 1235-SMH1). In addition, plasma and urine samples were collected in dose range-finding study CRAFT and efficacy studies ACT I and Scene 2; plasma samples were collected in SMH1, ACT II and ACT III for pharmacokinetic analyses.

Data from patients in ACT I and Scene 2 with atrial fibrillation and/or atrial flutter were pooled to evaluate the effects of CYP2D6 metabolizer genotype status, sex, renal impairment, age and co-administration of CYP2D6-inhibitor medications on the pharmacokinetics of vernakalant injection. Data from ACT III were utilized to develop a population pharmacokinetic model for vernakalant injection and determine the influence of covariates on vernakalant injection pharmacokinetics.

6.1.1 Absorption

In healthy volunteers (Study 1235-1-04-12-01), vernakalant injection demonstrated linear kinetics over the dose range of 0.1 mg/kg to 5 mg/kg following a 10-minute intravenous infusion.

In patients with atrial fibrillation, after an intravenous infusion of vernakalant (n=35), maximum plasma concentration (C_{max}) increased in a linear fashion with increasing dose; elimination half-life was similar for each dosing group (CRAFT). Mean elimination $t_{1/2}$ values were approximately 2.7 hours (8.5 hours for poor metabolizers).

In patients with atrial fibrillation or atrial flutter, C_{max} was approximately 5000 ng/mL (ACT I) and occurred at the end of the first or second infusion (ACT I and Scene 2). Median C_{max} in the study with the largest atrial fibrillation population was 4245 ng/mL for a single 3 mg/kg infusion and 5200 ng/mL for two infusions (3 mg/kg over 10 minutes followed by 2 mg/kg over 10 minutes, 15 minutes after the end of the first infusion) (ACT I). Plasma concentrations declined sharply at the end of the infusion (ACT I and Scene 2), and within 24 hours post-dose were close to the lower limit of quantification (LLOQ; 5 ng/mL) (ACT I). The $AUC_{0\text{-}90min}$ was dose proportional for patients who received one versus two infusions (ACT I and Scene 2).

Mean elimination $t_{1/2}$ was 2.19 hours for extensive CYP2D6 metabolizers and 5.66 hours for poor CYP2D6 metabolizers in healthy subjects (Study 04-0-195) [see Section 6.1.3].

6.1.2 Distribution

Vernakalant is not highly bound to human serum proteins. Free fraction of vernakalant was determined to be approximately 57% in the plasma concentration range of 1.0 to 5.0 mcg/mL. Vernakalant is rapidly and extensively distributed in patients with atrial fibrillation.

Vernakalant injection is rapidly and extensively distributed into tissue, with an alpha half-life of 3 to 6 minutes, such that acute exposure ($AUC_{0\text{-}90min}$) is independent of differences in metabolism between subjects. The mean V_{ss} (85.84 L for extensive metabolizers, 112.50 L for poor metabolizers) and V_{dz} (165.70 L for extensive metabolizers, 161.82 L for poor metabolizers) were approximately 30 to 40 times the total blood volume (approximately 5.2 L for an average 70 kg human) and approximately 5 times the total body water (approximately 42 L for an average 70 kg human) (Study 04-0-195).

6.1.3 Metabolism

Vernakalant (RSD1235) is extensively and rapidly metabolized. The main metabolic route for vernakalant is 4-O-demethylation, by CYP2D6, to RSD1385, most of which is rapidly glucuronidated (Study 04-0-195). Direct glucuronidation of vernakalant is also relatively prominent, while sulphatation of the demethylated metabolite, RSD1385, and/or the other demethylated metabolite, RSD1390, are minor metabolic pathways. In poor metabolizers of CYP2D6, the metabolism of vernakalant is slower and less extensive. Following distribution in poor metabolizers, higher concentrations of 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 more important. RSD1231, a diastereomer of vernakalant, and the glucuronide of vernakalant were mostly observed at low levels in poor metabolizers. Hydroxylation of vernakalant, which is followed by excretion in the feces, was detected in poor metabolizers in Study 04-0-195.

In healthy volunteers and patients with atrial fibrillation or atrial flutter, RSD1385 is the major plasma metabolite, occurring primarily in the glucuronidated form, whereas RSD1390 is undetectable or scarcely detectable (Studies 1235-1-04-12-01, 04-0-195, ACT I, Scene 2). In subjects identified as CYP2D6 poor metabolizers, the primary plasma metabolite was the glucuronide of vernakalant (Study 04-0-195).

RSD1385 achieved peak concentrations in plasma at 35-50 minutes. $AUC_{0\text{-}90min}$ was dose proportional (Study ACT I). Plasma RSD1385 concentrations were generally below the LLOQ (5 ng/mL) at 24 hours after the first infusion (ACT I and Scene 2).

6.1.4 Excretion

In healthy volunteers and patients with atrial fibrillation or atrial flutter, mean recovery of unchanged vernakalant in urine ranged from 7.3 to 11% of the administered dose (Studies 04-0-195, 1235-1-04-12-01, ACT I, and Scene 2). In healthy subjects who were CYP2D6 poor metabolizers, urinary excretion of unchanged vernakalant was 24.4% of a dose of vernakalant injection.

In the mass balance study, mean recovery of vernakalant-derived radioactivity in urine following a dose of vernakalant injection was 92.9% in CYP2D6 extensive metabolizers and 84.3% in poor metabolizers (Study 04-0-195). Mean recovery of radioactivity in feces was 7.28% for extensive metabolizers and 5.64% for poor metabolizers.

6.2 Pharmacokinetics in Special Populations

An analysis of demographic effects on the pharmacokinetics of vernakalant injection has been performed on combined ACT I and Scene 2 data and a population pharmacokinetics analysis was performed as part of the ACT III study. Results of these analyses indicate that C_{max} and acute exposure ($AUC_{0\text{-}90min}$) is independent of age, sex, renal impairment, hepatic impairment, history of CHF, expression of CYP2D6, or background use of CYP2D6 inhibitor/substrate medications. A formal pharmacokinetic study has not been conducted in special populations.

6.2.1 Age

A comparison of the pharmacokinetic parameters was made between the geometric mean values within the age subpopulations, <65 versus ≥ 65 years (ACT I/Scene 2 Combined Analysis). Patients who received either one or two infusions had $AUC_{0\text{-}90min}$ and C_{max} values that were similar for age ≥ 65 versus <65 years, suggesting that age did not significantly influence the $AUC_{0\text{-}90min}$ and C_{max} of vernakalant injection in this patient population [Table 5].

Table 5: Plasma Vernakalant Pharmacokinetic Parameters by Age

Parameter Age Category	N	Geometric Mean†	Ratio‡	95% CI of Ratio§
Patients Who Received One Dose				
AUC_{90} (ng·h/mL)				
< 65 years	35	2346.94	111.8%	[94.16%, 132.85%]
≥ 65 years	29	2624.88		
C_{max} (ng/mL)				
< 65 years	35	4225.11	101.5%	[79.86%, 128.92%]
≥ 65 years	29	4287.24		
Patients Who Received Two Doses				
AUC_{90} (ng·h/mL)				
< 65 years	89	3835.74	107.9%	[97.41%, 119.48%]
≥ 65 years	82	4138.16		
C_{max} (ng/mL)				
< 65 years	90	4182.55	108.9%	[97.19%, 121.99%]
≥ 65 years	82	4554.16		

Pharmacokinetic set; all patients in ACT I and Scene 2 Studies.

AUC_{90}: Area under the concentration-time curve from time zero to 90 minutes post initial dose. CI: Confidence interval. C_{max}: Maximum observed concentration of study drug.

† Calculated by exponentiating the least-squares mean from a one-way ANOVA model with the subgroup as a factor and natural log of the pharmacokinetic parameter as the response variable.

‡ Calculated by exponentiating the least squares mean estimate of the differences of natural log-transformed data.

§ For ratio of parameter means (expressed as a percent) calculated by exponentiating the confidence interval for the least squares mean difference of natural log-transformed data.

Population pharmacokinetic analysis also demonstrated that age did not significantly influence the pharmacokinetics of vernakalant injection in the ACT III study population.

6.2.2 Race

Race did not appear to influence the pharmacokinetics of vernakalant injection in the ACT III study population; however, no definitive conclusions can be made because of the small number of nonwhites in the study.

6.2.3 Sex

A comparison of pharmacokinetic parameters was made between the geometric mean values within the sex subpopulation, male versus female (ACT I/Scene 2 Combined Analysis). Patients who received either one or two infusions had $AUC_{0\text{-}90min}$ and C_{max} values that were similar for female versus male, suggesting that sex did not significantly influence the $AUC_{0\text{-}90min}$ and C_{max} of vernakalant injection in this patient population [Table 6].

Table 6: Plasma Vernakalant Pharmacokinetic Parameters by Sex

Parameter Sex	N	Geometric Mean†	Ratio‡	95% CI of Ratio§
Patients Who Received One Dose				
AUC_{90} (ng·h/mL)				
Male Female	49 15	2434.39 2585.69	106.2%	[86.58%, 130.31%]
C_{max} (ng/mL)				
Male Female	49 15	4326.38 4022.46	93.0%	[70.21%, 123.12%]
Patients Who Received Two Doses				
AUC_{90} (ng·h/mL)				
Male Female	125 46	4004.64 3906.12	97.5%	[86.88%, 109.50%]
C_{max} (ng/mL)				
Male Female	126 46	4395.07 4249.91	96.7%	[85.00%, 110.01%]

Pharmacokinetic set; all patients in ACT I and Scene 2 Studies.

AUC_{90}: Area under the concentration-time curve from time zero to 90 minutes post initial dose. CI: Confidence interval. C_{max}: Maximum observed concentration of study drug.

† Calculated by exponentiating the least-squares mean from a one-way ANOVA model with the subgroup as a factor and natural log of the pharmacokinetic parameter as the response variable.

‡ Calculated by exponentiating the least squares mean estimate of the differences of natural log-transformed data.

§ For ratio of parameter means (expressed as a percent) calculated by exponentiating the confidence interval for the least squares mean difference of natural log-transformed data.

Based on the ACT III population pharmacokinetics analysis, the volume of distribution in central compartment of vernakalant appeared to be affected by sex. The typical volume of distribution in the central compartment in males was estimated to be 46.2 L. It was approximately half that value, or 23.9 L, in females. 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. Sex could be a surrogate for body mass index (BMI).

6.2.4 Renal Impairment

Renal function did not significantly influence the $AUC_{0\text{-}90min}$ and C_{max} of vernakalant injection (ACT I/Scene 2 Combined Analysis). For patients who received two infusions, the $AUC_{0\text{-}90min}$ and C_{max} values for the mild and moderate/severe renal impairment subgroups were similar to the normal renal function subgroup [Table 7]. Patients who received two infusions had a larger sample size in both the mild (n=64) and moderate/severe renal impairment (n=23) subgroups than patients who received one infusion (n=20 for mild impairment, n=7 for moderate/severe impairment); therefore, results from patients who received two infusions more closely represent the total population.

Table 7 Plasma Vernakalant Pharmacokinetic Parameters by Renal Function

Parameter Degree of Renal Impairment	N	Geometric Mean†	Ratio‡	95% CI of Ratio§
Patients Who Received One Dose				
AUC_{90} (ng·h/mL)				
Normal Function	32	2333.30		
Mild	20	2287.18	98.0%	[81.29%, 118.20%]
Moderate/Severe	7	3279.36	140.5%	[106.86%, 184.85%]
C_{max} (ng/mL)				
Normal Function	32	4237.82		
Mild	20	3609.77	85.2%	[65.76%, 110.34%]
Moderate/Severe	7	5983.21	141.2%	[96.66%, 206.21%]
Patients Who Received Two Doses				
AUC_{90} (ng·h/mL)				
Normal Function	76	4134.93		
Mild	64	3867.28	93.5%	[83.61%, 104.62%]
Moderate/Severe	23	3818.34	92.3%	[78.91%, 108.06%]
C_{max} (ng/mL)				
Normal Function	77	4539.21		
Mild	64	4180.82	92.1%	[81.42%, 104.19%]
Moderate/Severe	23	4252.50	93.7%	[78.78%, 111.41%]

Pharmacokinetic set; all patients in ACT I and Scene 2 Studies.

Creatinine clearance (CL_{CR}) was calculated using the Cockroft-Gault equation;

normal function: $CL_{CR} \geq 80$ mL/min; mild impairment: 50 mL/min $\leq CL_{CR} < 80$ mL/min;

moderate impairment: 30 mL/min $\leq CL_{CR} < 50$ mL/min; severe impairment: $CL_{CR} < 30$ mL/min;

The 'mild' and 'moderate/severe' categories were compared to the' normal' category.

AUC_{90}: Area under the concentration-time curve from time zero to 90 minutes post initial dose. CI: Confidence interval. C_{max}: Maximum observed concentration of study drug.

† Calculated by exponentiating the least-squares mean from a one-way ANOVA model with the subgroup as a factor and natural log of the pharmacokinetic parameter as the response variable.

‡ Calculated by exponentiating the least squares mean estimate of the differences of natural log-transformed data.

§ For ratio of parameter means (expressed as a percent) calculated by exponentiating the confidence interval for the least squares mean difference of natural log-transformed data.

No effect of renal function on the pharmacokinetics of vernakalant in the ACT III study was observed by population pharmacokinetic evaluation.

It is unlikely that dosing adjustments would be required in patients with compromised renal function based on clinical pharmacokinetics and population pharmacokinetic modeling.

6.2.5 Hepatic Impairment

The pharmacokinetics of vernakalant injection in patients with hepatic impairment have not been established in formal pharmacokinetic studies. In healthy volunteers (Study

1235-1-04-12-01), total body clearance of vernakalant ranged from 649 to 938 mL/min, of which 56 to 170 mL/min is contributed by renal clearance. Even though nonrenal clearance dominates total body clearance, it is unlikely that a dosing adjustment would be needed in subjects with hepatic impairment since drug distribution is rapid and extensive as evidenced by a central compartment volume of 20-40 L, 4 to 8 times blood volume. Distribution of vernakalant into this highly perfused central compartment away from blood and/or plasma appears to be the primary mechanism of drug response responsible for termination of the pharmacologic effect. As such, it is unlikely dosing adjustment would be needed in patients with hepatic impairment.

6.2.6 Expression of CYP2D6

A comparison of the pharmacokinetic parameters was made between the geometric mean values within the CYP2D6 metabolizer subpopulation: extensive versus poor metabolizers (ACT I/Scene 2 Combined Analysis). Patients who received two infusions had $AUC_{0\text{-}90min}$ and C_{max} values that were similar for poor (n=6, $AUC_{0\text{-}90min}$; n=7, C_{max}) versus extensive (n=141) metabolizers. The percent ratio for $AUC_{0\text{-}90min}$ and C_{max} of poor to extensive metabolizers was 113.3% and 102.8%, respectively, indicating that different expression of CYP2D6 did not significantly influence the C_{max} and $AUC_{0\text{-}90min}$ of vernakalant in this population. Patients who received two infusions had a larger sample size in the poor metabolizer group than patients who received one infusion (n=1); therefore, results from the subgroup that received two infusions more closely represents the total population.

6.2.7 Congestive Heart Failure

The population pharmacokinetic analysis of the ACT III study showed that a history of CHF did not significantly influence the pharmacokinetics of vernakalant injection in the ACT III study population.

6.3 Pharmacodynamics

The effects of vernakalant on atrial and ventricular electrophysiology have been explored in Study 1235-SMH1. This study evaluated the pharmacodynamic effects of two dose levels of vernakalant injection (2 mg/kg over 10 minutes followed by 0.5 mg/kg/h over 35 minutes or 4 mg/kg over 10 minutes followed by 1.0 mg/kg/h over 35 minutes) in 19 subjects without significant structural heart disease undergoing electrophysiological testing.

Vernakalant injection prolonged atrial effective refractory period (ERP) in a dose dependent manner without prolonging ventricular ERP, and exhibited a small conduction slowing effect in the atrium and AV node at the higher dose level.

Table 8: Effect of Vernakalant Injection on Atrial ERP

	Baseline		Drug Treatment		Change from Baseline		
Atrial PCL (msec)	**N**	**Mean ± SEM (msec)**	**N**	**Mean ± SEM (msec)**	**N**	**Mean ± SEM (msec)**	**P-value***
Vernakalant Injection Dose Level 1†							
600	10	206.0 ± 10.08	10	219.5 ± 10.18	10	13.5 ± 4.54	0.0078
400	9	188.3 ± 10.21	10	195.0 ± 7.53	9	5.0 ± 3.00	0.1875
300	8	180.0 ± 10.82	10	180.5 ± 4.91	8	-3.1 ± 6.68	0.5313
Vernakalant Injection Dose Level 2‡							
600	8	202.5 ± 10.86	7	227.9 ± 8.51	7	31.4 ± 5.42	0.0156
400	9	182.2 ± 10.28	9	206.7 ± 8.54	9	24.4 ± 5.92	0.0117
300	9	171.7 ± 8.29	9	192.8 ± 6.72	9	21.1 ± 5.88	0.0156

ERP: effective refractory period; PCL: Paced cycle length; SEM: Standard error of the mean.

† 2 mg/kg over 10 minutes followed by 0.5 mg/kg/h over 35 minutes

‡ 4 mg/kg over 10 minutes followed by 1.0 mg/kg/h over 35 minutes

*Wilcoxon signed-rank test

No significant effects on ventricular refractoriness or repolarization were noted during electrophysiologic study. Due to variability in QT intervals at uncontrolled heart rates and the inadequacy of standard QT correction formula, drug effects on the QT interval were assessed during pacing at constant heart rates. Vernakalant injection tended to widen QT interval during atrial pacing at 150 bpm (P=0.078), but not at 100 bpm. Vernakalant injection tended to widen QRS (P=0.0547) at the higher dose level during ventricular, but not atrial, pacing at rapid rates (150 bpm). Vernakalant injection did not slow ventricular conduction measured as HV interval. Median vernakalant plasma levels in this study population (C_{max} = 3110 ng/mL, dose level 2) approached those demonstrated to convert atrial fibrillation to sinus rhythm in patients.

In ACT III, the PK/PD analysis indicated that the relationship between plasma concentration of vernakalant and the QTcF interval was best described by a sigmoidal E_{max} model with an EC_{50} of 1730 ng/mL. Maximum change in QTcF for patients converting to sinus rhythm is expected to be 6.1 msec while maximum change in QTcF for patients who remain in atrial fibrillation is 20.3 msec. Age affected baseline QTcF value. The relationship between vernakalant concentration and systolic blood pressure can be described using a sigmoidal E_{max} model, with a typical E_{max} of 3.25 mmHg (increase) and the EC_{50} of 1140 ng/mL. Age affected baseline systolic blood pressure. The E_{max} value indicates the maximal amount of blood pressure change induced by the drug is relatively small and may reflect in part conversion to sinus rhythm.

6.4 Drug-Drug Interactions

No formal clinical drug interaction studies have been conducted with vernakalant injection; instead, population pharmacokinetic analyses were performed. Vernakalant is not highly

bound to human serum proteins. In-vitro evidence indicated that there is little risk for competition/interaction of concomitantly administered drugs such as warfarin, propranolol, acebutolol, diltiazem, verapamil, or quinidine. Vernakalant injection has been administered with concomitant medications known to inhibit CYP2D6 to several patients to date, with no safety implications related to drug-drug interactions noted. Vernakalant injection has been safely administered to subjects receiving concomitant warfarin in clinical studies.

The effect of administration of other medications inhibiting CYP2D6 on the pharmacokinetics of vernakalant injection were evaluated in the combined pharmacokinetic analysis of ACT I and Scene 2 data (ACT I/Scene 2 Combined Analysis) and the population pharmacokinetic analysis of the ACT III study population. A comparison of the pharmacokinetic parameters was made between the geometric mean values for the subpopulation of patients administered CYP2D6 inhibitor medication versus the subpopulation of patients not administered CYP2D6 inhibitor medication. Patients who received two infusions had a larger sample size in patients administered CYP2D6 inhibitors (n=24) than patients who received one infusion (n=6); therefore, results from the subgroup that received two infusions more closely represents the total population. Patients who had received CYP2D6 medications had $AUC_{0\text{-}90min}$ and C_{max} values that were similar to those who had not received CYP2D6 medications after receiving two infusions. The percent ratio for $AUC_{0\text{-}90min}$ and C_{max} for patients who had received CYP2D6 medications to patients who had not received CYP2D6 medications was 105.5% [95% CI: 91.00%, 122.23%] and 102.8% [95% CI: 87.16%, 121.20%], respectively, indicating that concomitant CYP2D6 inhibitors did not significantly influence the C_{max} and $AUC_{0\text{-}90min}$ of vernakalant in this patient population.

In summary, population pharmacokinetic analysis demonstrated that concomitant medications that are CYP2D6 inhibitors and beta-blockers did not significantly influence the acute exposure of vernakalant in the ACT III study population.

7 EFFICACY

7.1 Introduction

The rapid conversion of atrial fibrillation to sinus rhythm by vernakalant injection has been demonstrated prospectively in three controlled phase 3 clinical trials and one supportive, dose-ranging, phase 2 trial. A step-dose design (3 mg/kg + 2 mg/kg) was selected on the basis of the phase 1 dose-escalation study in healthy volunteers and a phase 2 dose-range finding study. These studies established a minimally effective dose of 2 mg/kg and a potentially maximum tolerated single dose of 5 mg/kg. Treatment success was defined as conversion from atrial fibrillation to sinus rhythm within 90 minutes of first exposure to vernakalant injection for a minimum duration of 1 minute for all phase 3 studies. The primary efficacy endpoint for both ACT I and ACT III was the proportion of patients with atrial fibrillation of >3 hours to ≤ 7 days duration who converted to sinus rhythm.

These key efficacy studies demonstrated that:

- Conversion from atrial fibrillation to sinus rhythm in patients receiving vernakalant injection was consistently demonstrated across all studies (52.9%–47.0%).

- Vernakalant injection provided symptomatic relief to patients including relief of palpitations, chest tightness/pains, rapid heart beat and irregular pulse.

- Vernakalant injection demonstrated a rapid onset of action (median time to conversion of atrial fibrillation to sinus rhythm in responders was 10 minutes from initiation of the 10-minute infusion).

- Patients who converted to sinus rhythm after receiving vernakalant injection remained in sinus rhythm (97% maintenance at 24 hours).

- Vernakalant injection has been shown to be effective in a broad group of patients with multiple associated morbidities (ischemic heart disease, CHF, hypertension, and post-cardiac surgery).

- Vernakalant injection has been shown to be effective in the presence of typical background medications for the target patient population, including rhythm and rate control medication.

- Vernakalant injection is ineffective at converting typical atrial flutter to sinus rhythm at the doses studied.

7.2 Dose Selection

Healthy Volunteers Maximum Dose 5 mg/kg:

Vernakalant injection was studied in a dose-ranging study in 28 healthy volunteers at doses of 0.10 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg and 5 mg/kg IV administered over 10 minutes. Mild adverse events were noted at the doses of 4 and 5 mg/kg and involved altered sensory sensations including drowsiness, altered taste (metallic taste), and paresthesias of the face or extremities. No significant adverse events were noted that required intervention. Side effects were intermittent and transient, occurring shortly after the start of infusion and resolving within 2 hours. No dose limiting adverse events or changes in blood pressure were noted. ECG interval changes were noted during and shortly after infusion in the 4 and 5 mg/kg dose groups. Mean PR intervals for the 4 and 5 mg/kg dose groups increased from baseline during infusion and shortly thereafter (peak increase of 23 ± 7 msec for the 4 mg/kg group at minute 9 of the infusion and 28 ± 9 msec for the 5 mg/kg group at 3 minutes following the end of the infusion). Mean QRS intervals increased from baseline for the 4 and 5 mg/kg groups near the end of infusion (peak increases of 8 ± 6 msec at minute 8 of the infusion and 11 ± 2 msec at end of infusion, respectively). At the same

time, mean QTcF intervals increased from infusion onset, with peak increases of 48 ± 6 msec at minute 7 of the infusion for the 4 mg/kg group and 63 ± 10 msec at the end of the infusion for the 5 mg/kg group. Based on the neurosensory side effects seen at doses of 4 and 5 mg/kg and the ECG changes noted at these doses, no higher doses were investigated in healthy volunteers.

Rationale for Phase 2 Dose Regimen:

The dosing for the phase 2 dose ranging study, CRAFT, was chosen on the basis of efficacy studies in the canine atrial fibrillation models in which the ED_{50} was approximately 1 mg/kg (dose given over 5 minutes), and the maximum dose studied in the phase 1 study (5 mg/kg). The CRAFT study investigated two step doses. The lower dose group received 0.5 mg/kg given IV over 10 minutes followed by a 30-minute observation period, and if no conversion to sinus rhythm or termination of atrial fibrillation was seen, a dose of 1 mg/kg was given over 10 minutes. The higher dose group received 2 mg/kg over 10 minutes and if conversion or termination of atrial fibrillation did not occur within a 30-minute observation period, a second dose of 3 mg/kg was administered. The 30-minute observation period was selected to allow a sufficient time for the drug to have an effect and to allow sufficient time to assess safety before the second dose was administered.

In the 2 mg/kg +3 mg/kg vernakalant injection group, a statistically greater percentage of patients terminated atrial fibrillation (61.1% [includes one patient who converted to atrial flutter]) during infusion or in the 30-minute follow-up periods as compared with the placebo (5.3%, P= 0.0003) or the 0.5+1.0 mg/kg groups (11.1%, P= 0.0018). Administration of vernakalant injection (2 mg/kg+3 mg/kg) also resulted in a significantly greater proportion of patients in sinus rhythm at 60 minutes post administration compared to placebo (52.9% versus 5.3%, P= 0.0015). Finally, vernakalant injection at a dose of 2 mg/kg+ 3 mg/kg, resulted in a faster median time to sinus rhythm conversion than did placebo (14 versus 162 minutes from time of first infusion, P= 0.0161). The results of this study showed that the two dose regimen of 2 mg/kg + 3 mg/kg was more effective and was well tolerated, and the minimally effective dose was determined to be 2 mg/kg IV given over 10 minutes.

Figure 3: Patients in Sinus Rhythm at 60 Minutes Post dosing—CRAFT

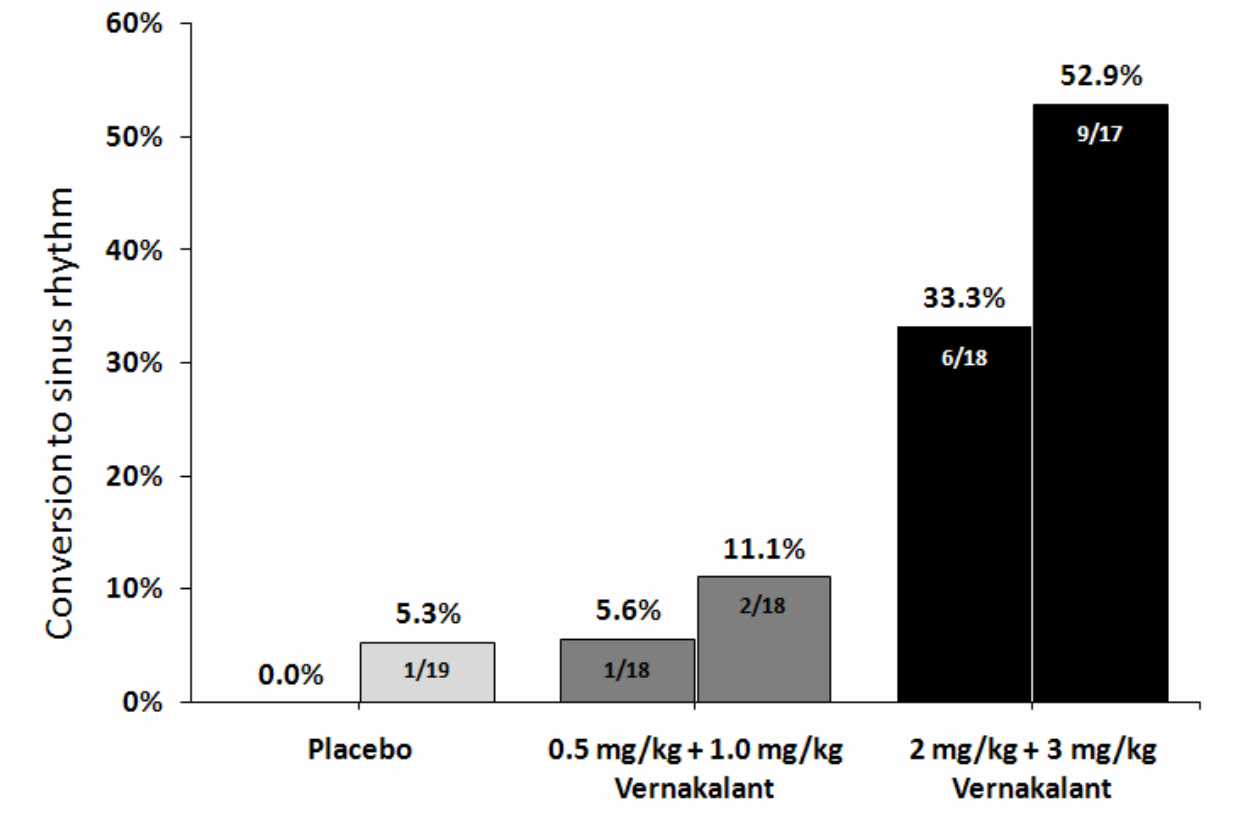


Chart bars show cumulative efficacy; in each treatment group, first bar = dose 1, second bar = dose 1 + dose 2
P= 0.0015 placebo vs vernakalant injection 2 mg/kg + 3 mg/kg (Cochran-Armitage trend test)
P= 0.5148 placebo vs vernakalant injection 0.5 mg/kg + 1 mg/kg (Cochran-Armitage trend test)
One patient in the higher dose group was electrically cardioverted prior to the 60 minute time point.

Phase 3 Dose Regimen:

In the phase 3 studies, the sequence of 2 mg/kg and 3 mg/kg doses was reversed based on the assumption that more patients would convert if the higher dose was given first and was supported by the safety and efficacy data from CRAFT. Therefore the dose selected for the phase 3 studies was 3 mg/kg infused over 10 minutes followed by a 15-minute observation period and, if no conversion to sinus rhythm was seen, a second dose of 2 mg/kg infused over 10 minutes was administered. A 15-minute observation period was selected to ensure completion of the alpha distribution phase prior to adding the second dose. Based on pharmacokinetic modeling, the initial dose of 3 mg/kg was expected achieve an average C_{max} of 4100 ng/mL. If conversion to sinus rhythm did not occur at this plasma concentration, the addition of the 2 mg/kg dose after the 3 mg/kg initial dose would serve not only to maintain, but also raise the plasma concentration (expected C_{max} = 5200 ng/mL). This increased time at therapeutic plasma concentrations was postulated to increase the probability for conversion without adding risk of potential adverse events.

7.3 Efficacy Across Studies

7.3.1 Efficacy in Pooled Primary Studies (ACT I and ACT III AF Patients)

7.3.1.1 Conversion to Sinus Rhythm

Conversion success was defined as conversion from atrial fibrillation to sinus rhythm within 90 minutes of first exposure to vernakalant injection for a minimum duration of 1 minute for all phase 3 studies.

The primary efficacy endpoint for both ACT I and ACT III was the proportion of patients with atrial fibrillation of >3 hours to ≤ 7 days duration who converted to sinus rhythm.

Consistent with results for the primary endpoints from the individual studies reported in Table 9, the pooled analysis also demonstrated the effectiveness of vernakalant injection in the conversion to sinus rhythm. In the short-duration atrial fibrillation cohort (> 3 hours to ≤ 7 days), a statistically significant (P<0.0001) greater percentage of patients in the vernakalant injection group (51.1%) converted to sinus rhythm as compared with the placebo group (3.8%). Similarly, in the overall atrial fibrillation population (> 3 hours to ≤ 45 days), a statistically significant greater percentage of patients in the vernakalant injection group converted to sinus rhythm (36.9%) compared with the placebo group (3.0%). The treatment difference (5.2%) in the long duration atrial fibrillation cohort (>7 days to ≤ 45 days) was not statistically significant.

Table 9: Comparison of Conversion to Sinus Rhythm—Primary Studies

	ACT I	ACT III	TOTAL
CONVERSION: Short–duration Atrial Fibrillation Cohort (>3 hours to ≤ 7 days)			
Short duration (>3 hrs to ≤ 7 days)	N=220	N=170	N=390
Vernakalant Injection	74/145 (51.0%)	44/86 (51.2%)	118/231 (51.1%)
Placebo	3/75 (4.0%)	3/84 (3.6%)	6/159 (3.8%)
Treatment Difference (vernakalant injection minus placebo)	47.0%	47.6%	47.3%
95% Confidence Interval	(37.8%, 56.3%)	(36.3%, 58.9%)	(40.2%, 54.4%)
P-value†	<0.0001	<0.0001	<0.0001
Odds Ratio 95% Confidence Interval			26.7 (11.2, 63.7)
CONVERSION: Overall Population (>3 hours to ≤ 45 days)			
All (>3 hours to ≤ 45 days)	N=336	N=239	N=575
Vernakalant Injection	78/221 (35.3%)	47/118 (39.8%)	125/339 (36.9%)
Placebo	3/115 (2.6%)	4/121 (3.3%)	7/236 (3.0%)
Treatment Difference (vernakalant injection minus placebo)	32.7%	36.5%	33.9%
95% Confidence Interval	(25.7%, 39.6%)	(27.1%, 45.9%)	(28.3%, 39.5%)
P-value†	<0.0001	<0.0001	<0.0001
Odds Ratio 95% Confidence Interval			18.0 (8.2, 39.6)
CONVERSION: Long-duration Atrial Fibrillation Cohort (>7 days to ≤ 45 days)			
Long duration (> 7 days to ≤ 45 days)	N=116	N=69	N=185
Vernakalant Injection	4/76 (5.3%)	3/32 (9.4%)	7/108 (6.5%)
Placebo	0/40	1/37 (2.7%)	1/77 (1.3%)
Treatment Difference (vernakalant injection minus placebo)	5.3%	6.7%	5.2%
95% Confidence Interval	(0.2%, 10.3%)	(-4.7%, 18.0%)	(-0.1%, 10.5%)
P-value§	0.30	0.33	0.142

Conversion defined as conversion to sinus rhythm for a minimum duration of 1 minute within 90 minutes after first exposure to study drug.

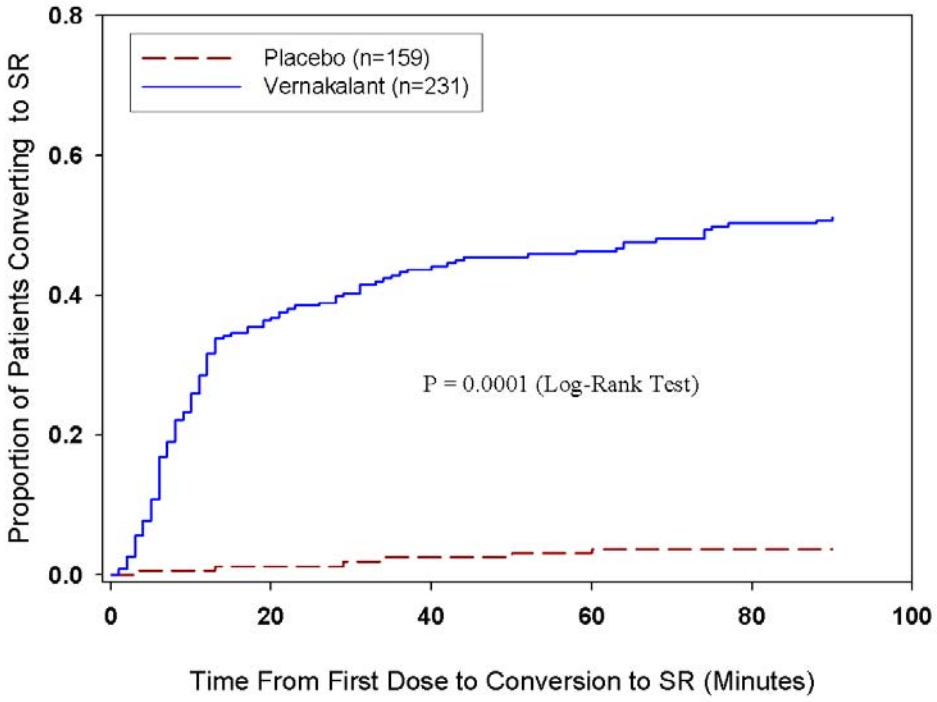
Analysis based on treatment induced conversion as determined by the Clinical Events Committee from Holter monitor or 12-lead ECG data if Holter results were missing or not interpretable.

† P-value from Cochran-Mantel-Haenszel test.

§ P-value from Fisher exact test.

In patients with short-duration atrial fibrillation and in the overall population, the distribution of time to first treatment-induced conversion was statistically and clinically significantly shorter in the vernakalant injection group compared with the placebo group [Figure 4].

Figure 4: **Kaplan-Meier Curve of Time to First Treatment Induced Conversion to Sinus Rhythm within 90 Minutes of First Exposure to Study Drug in the Short-Duration Population - Pooled Primary Studies**



Conversion to sinus rhythm occurred rapidly. Patients in the short duration subgroup (n=118) who received vernakalant injection and converted to sinus rhythm did so with a median time of 10 minutes, and in all patients who converted (n=125), the median time to conversion was 11 minutes.

The pooled primary studies were not designed to compare a one dose regimen of 3 mg/kg to a two dose regimen of 3 mg/kg + 2 mg/kg; however, analyses showed that, for patients with short duration (≥ 3 hours to ≤ 7 days) atrial fibrillation, 92 of 231 (39.8%) treated with vernakalant injection converted to sinus rhythm with the first infusion and did not require the second dose, compared to 2 of 159 (1.3%) placebo patients. Among the patients who further received the second infusion, 26 of 132 (19.7%) patients treated with vernakalant injection converted to sinus rhythm, compared to 4 of 155 (2.6%) placebo patients.

7.3.1.2 Maintenance of Sinus Rhythm

The majority (97.2%) of the 118 patients who received vernakalant injection and converted to sinus rhythm remained in sinus rhythm at hour 24. Maintenance of sinus rhythm was assessed using the 12-lead ECGs collected at hours 2, 4, 8 and 24 after initiation of dosing and at the day 7 follow-up visit. The ECGs were interpreted by the Clinical Events Committee. The primary analysis presented in the NDA follows these patients at each of the above scheduled time points and, using the life-table methodology, estimates the probability of remaining in sinus rhythm at these time points. Patient with missing data were censored at the time of the first missing ECG.

Patients receiving concomitant antiarrhythmic medications were allowed in the study. Analysis was performed excluding these patients, and the results were no different from those obtained when these patient were included. Sinus rhythm was maintained in most patients irrespective of the background use of antiarrhythmics.

Table 10: Life Table Estimate of the Maintenance of Sinus Rhythm for Patients Who Converted to Sinus Rhythm within 90 Minutes—Pooled Primary Studies

AF Duration >3 hrs to ≤ 7 days			
	All Responders		Excluding Patients Who Received Antiarrhythmics
Timepoint	Placebo (n=6)	Vernakalant Injection (n=118)	Vernakalant Injection (n=72)
2 hours	83.3%	98.2%	100%
4 hours	83.3%	98.2%	100%
8 hours	83.3%	98.2%	100%
24 hours	83.3%	97.2%	100%

Pooled Primary Studies: pooled data from patients with atrial fibrillation in ACT I and ACT III.

At each time point, only patients who remained in sinus rhythm at the previous time points were included in the calculation.

Method of M. Stokes, C. Davis and G. Koch, Section 17.2 of Categorical Data Analysis (2nd edition). SAS Institute.

An alternative analysis is to assess the number of patients who had documented evidence of atrial fibrillation on any ECG within the first 24 hours. Three patients receiving background antiarrhythmic medications reverted to atrial fibrillation within 24 hours [Table 11].

Table 11: Patients Who Reverted to Atrial Fibrillation Following Conversion to Sinus Rhythm within 90 Minutes—Pooled Primary Studies

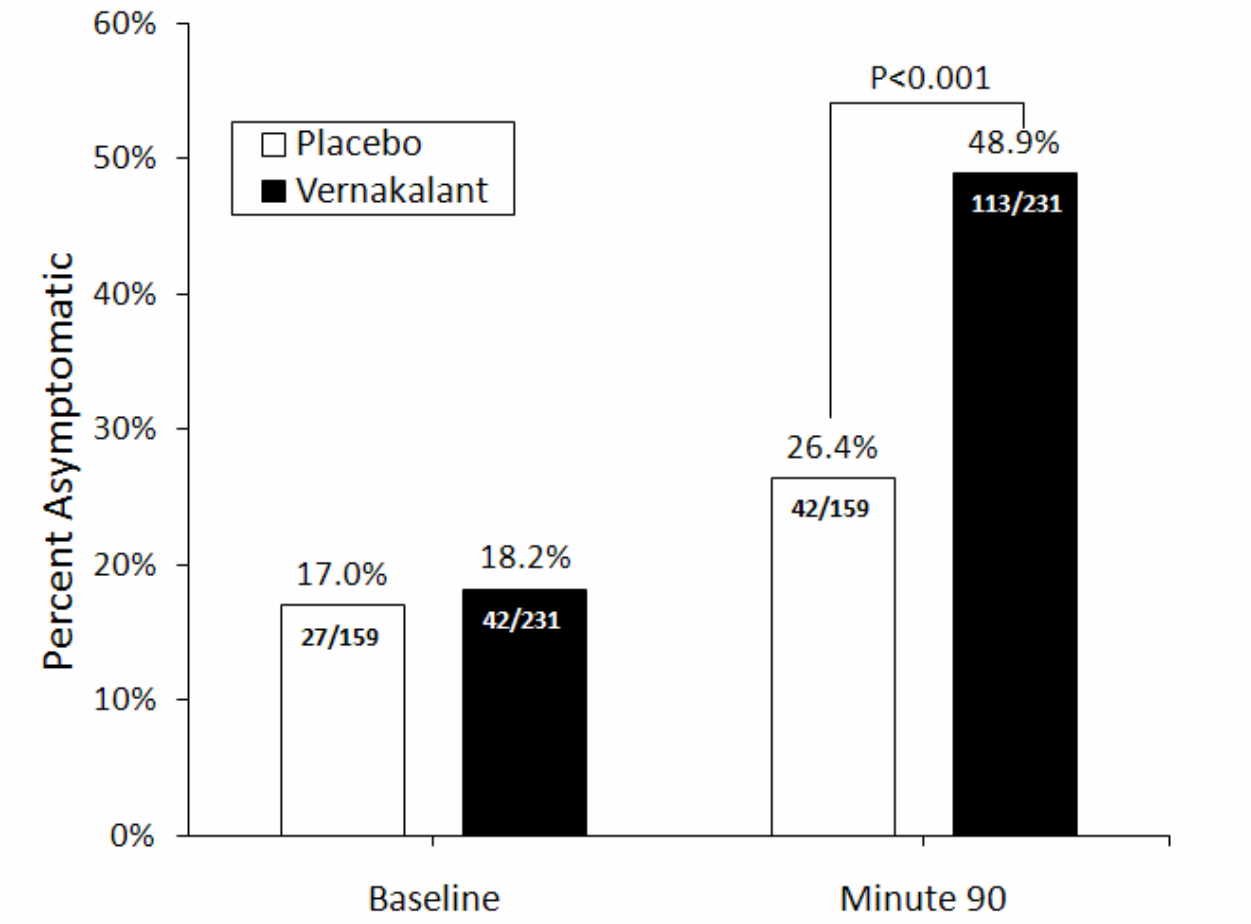
		AF Duration >3 hrs to ≤ 7 days	
			Excluding Patients Who Received Antiarrhythmics
Timepoint	Status	Vernakalant Injection (n=118)	Vernakalant Injection (n=72)
Within 24 hours	Atrial fibrillation	3 (2.5%)	0 (0%)

Pooled Primary Studies: pooled data from patients with atrial fibrillation in ACT I and ACT III.

7.3.1.3 Symptom Relief

Vernakalant injection was also shown to provide rapid relief of atrial fibrillation symptoms. In the primary studies, symptoms were assessed at baseline, minute 90, hour 24/discharge, at the one-week follow-up visit, and during the 30-day telephone contact. Using a symptom questionnaire, patients were systematically queried for the presence of the following symptoms: shortness of breath, palpitations, chest tightness/pains, dizziness, edema, fatigue, rapid heart beats, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, nausea, syncope, irregular pulse, vomiting, cough, and headaches. In the overall atrial fibrillation population in the pooled primary studies, presenting atrial fibrillation symptoms were generally similar in character and occurrence rates at baseline in the placebo and vernakalant injection groups. At minute 90, a statistically significant higher percentage of patients were symptom free in the vernakalant injection group compared with the placebo group in both the short-duration atrial fibrillation cohort and in the overall atrial fibrillation population (48.9% vernakalant injection vs. 26.4% placebo in short-duration, and 46.3% vernakalant injection vs. 28.0% placebo overall;[Figure 5]).

Figure 5: Patients Free of Atrial Fibrillation Symptoms—Pooled Primary Studies



Pooled Primary Studies: pooled data from patients with atrial fibrillation in ACT I and ACT III.

Symptoms included: shortness of breath, palpitations, chest tightness/pains, dizziness, edema, fatigue, rapid heart beats, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, nausea, syncope, irregular pulse, vomiting, cough, headaches.

***Fisher's exact test, P<0.001

Vernakalant injection provided statistically significant relief of palpitations, chest tightness/pains, rapid heart beats, and irregular pulse compared with the placebo group (P-values <0.05) [Table 12].

Table 12: Atrial Fibrillation Symptoms at Minute 90—Pooled Primary Studies

	Treatment Group	
	Placebo	**Vernakalant Injection**
Short duration (3 hours to ≤ 7 days)	**N = 159**	**N = 231**
Any AF symptom	116 (73.0%)	116 (50.2%)***
Palpitations	63 (39.6%)	43 (18.6%)***
Chest tightness/pains	15 (9.4%)	7 (3.0%)*
Rapid heart beats	46 (28.9%)	27 (11.7%)***
Shortness of breath	22 (13.8%)	18 (7.8%)
Irregular pulse	70 (44.0%)	46 (19.9%)***
Overall (3 hours to ≤ 45 days)	**N = 236**	**N = 339**
Any AF symptom	169 (71.6%)	180 (53.1%)***
Palpitations	75 (31.8%)	60 (17.7%)***
Chest tightness/pains	19 (8.1%)	15 (4.4%)
Rapid heart beats	57 (24.2%)	38 (11.2%)***
Shortness of breath	39 (16.5%)	31 (9.1%)**
Irregular pulse	104 (44.1%)	76 (22.4%)***

AF: atrial fibrillation

Pooled Primary Studies: pooled data from patients with atrial fibrillation in ACT I and ACT III.

*P<0.05, **P<0.01, ***P<0.001, Fisher's exact test

Other symptoms included dizziness, edema, fatigue, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, nausea, syncope, vomiting, cough and headaches.

7.3.2 Study 1235-0104/ACT II (Atrial Fibrillation Post Cardiac Surgery)

7.3.2.1 Study Population

Patients with sustained atrial fibrillation or atrial flutter (3 hours to 72 hours duration) occurring between 24 hours and 7 days following coronary artery bypass graft (CABG) and/or valvular surgery and who were hemodynamically stable were eligible to enroll in this study. Patients with QTcB >0.46 seconds pre-surgery were excluded. Patients with QRS duration >0.14 seconds or uncorrected QT interval >0.50 seconds post-surgery were also excluded. The use of antiarrhythmic medications was not allowed.

The majority of patients in both treatment groups were white males with a mean age of 68 years. The majority of patients (93%) in both treatment groups were in atrial fibrillation at baseline. Most patients in both treatment groups underwent CABG surgery. Approximately 22% of patients in the placebo group and 30% of patients in the vernakalant injection group had an abnormal ejection fraction. There were no statistically significant differences between

treatment groups in left atrial diastolic dimension, left ventricular end diastolic dimension, left ventricular function, or left ventricular hypertrophy.

There were no statistically significant differences in the baseline use of any rate control medications, including beta-blockers, calcium channel blockers, and digitalis glycosides. Approximately 46% of patients in the placebo group and 38% of patients in the vernakalant injection group had baseline use of any rate control medication.

Table 13: Demographics and Baseline Characteristics—ACT II

		Treatment Group	
Parameter		**Placebo N = 54**	**Vernakalant Injection N = 107**
Sex	Male	40 (74.1%)	81 (75.7%)
	Female	14 (25.9%)	26 (24.3%)
Race	White	50 (92.6%)	101 (94.4%)
	Asian	4 (7.4%)	5 (4.7%)
	Other	0 (0.0%)	1 (0.9%)
Age (years)	Mean ± SD	67.8 ± 6.4	68.3 ± 7.7
	Median	68.0	69.0
	Min – Max	54.0 – 80.0	45.0 – 82.0
Surgery type	CABG	37 (68.5%)	71 (66.4%)
	Valvular	10 (18.5%)	28 (26.2%)
	Both	7 (13.0%)	8 (7.5%)
Medical History	CHF	5 (9.3%)	9 (8.4%)
	Ischemic Heart Disease	42 (77.8%)	80 (74.8%)
	Hypertension	40 (74.1%)	72 (67.3%)
Ejection Fraction	Normal (≥ 50%)	27 (50.0%)	55 (51.4%)
	Mild dysfunction (36-49%)	12 (22.2%)	25 (23.4%)
	Moderate dysfunction (26-35%)	0	3 (2.8%)
	Severe dysfunction (≤ 25%)	0	3 (2.8%)
	Unknown	15 (27.8%)	21 (19.6%)

SD: standard deviation; CABG: coronary artery bypass graft; CHF: congestive heart failure

7.3.2.2 Efficacy in ACT II (Atrial Fibrillation Post Cardiac Surgery)

A greater proportion of patients in the vernakalant injection group who were in atrial fibrillation at baseline converted to sinus rhythm (47.0%, 47/100) compared to patients in the placebo group (14.0%, 7/50). The 33% treatment difference was clinically and statistically significant (P=0.0001).

Table 14: Treatment-Induced Conversion of AF to Sinus Rhythm Within 90 Minutes—ACT II

	Number (%) of Patients with Conversion		Treatment Difference (95% CI)†	P value‡	Relative Risk (95% CI)§
	Placebo N = 50	Vernakalant Injection N = 100			
All Sites	7 (14.0%)	47 (47.0%)	33.0 (19.3, 46.7)	0.0001	3.25 (1.61, 6.57)

Conversion was determined by the Clinical Events Committee.

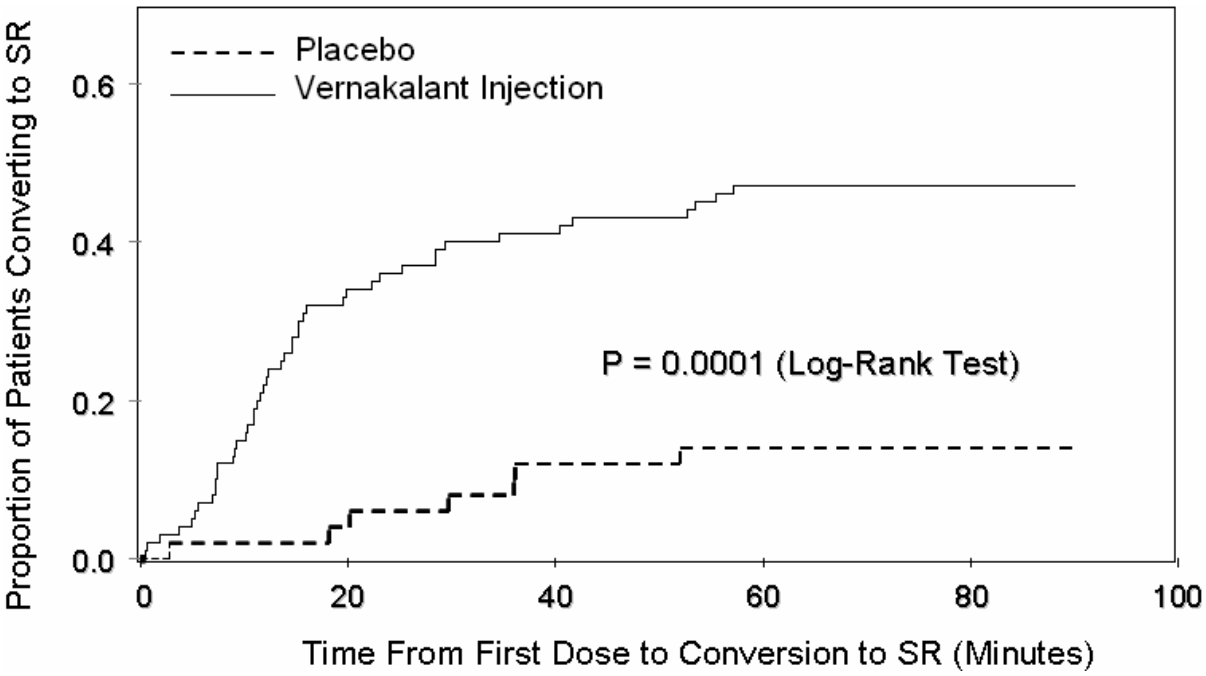
† (% Success in vernakalant injection group) – (% success in placebo); missing values were considered not converted

‡ P value from Cochran-Mantel-Haenszel test

§ Relative risk in favor of conversion for vernakalant injection versus placebo

The time to conversion to sinus rhythm was statistically significantly shorter in the vernakalant injection group compared to the placebo group [Figure 6].

Figure 6: Time to Conversion to Sinus Rhythm—ACT II



For the patients in the vernakalant injection group who converted to sinus rhythm within 90 minutes, the median time to conversion was 12.3 minutes.

7.3.3 Study 05-7-012/ACT IV

ACT IV was an open-label study designed to provide additional safety information of a 3 mg/kg + 2 mg/kg dose of vernakalant injection in patients with atrial fibrillation. Patients enrolled in the study had atrial fibrillation of >3 hours to ≤ 45 days duration. Efficacy was also assessed in this safety study; consistent with the primary studies, the main efficacy endpoint was the proportion of patients with short duration atrial fibrillation (>3 hours to ≤ 7 days) who had treatment-induced conversion to sinus rhythm within 90 minutes of first exposure to study drug.

The majority of patients were white males with a mean age of 63 years. A total of 167 of 236 enrolled patients had short duration atrial fibrillation (>3 hours to ≤ 7 days), and 85 of 167 (50.9%) had treatment-induced conversion to sinus rhythm. The median time to conversion was 14 minutes in patients who converted within 90 minutes.

7.3.4 Efficacy Across All Phase 2 and Phase 3 Studies

Efficacy in all the phase 2 and 3 studies is shown in Table 15 and Figure 7. Efficacy was consistent across all studies. The CRAFT and ACT II studies enrolled patients with a duration of atrial fibrillation of 3–72 hours. The data shown for ACT I and ACT III are for patients with a duration of atrial fibrillation of 3 hours to ≤ 7 days. The ACT IV study was an open-label study, but efficacy was assessed and was found to be similar to that observed in ACT I and ACT III.

Table 15: Comparison of Conversion of Short Duration Atrial Fibrillation to Sinus Rhythm—All Phase 2 and Phase 3 Studies

	CRAFT†	ACT I	ACT III (AF only)	ACT IV	ACT II (AF only)
Short duration (>3 hrs to ≤ 7 days)	N=36 (AF duration 3-72 hrs)	N=220	N=170	N=167	N=150 (AF duration 3-72 hrs)
Vernakalant Injection	9/17 (52.9%)	74/145 (51.0%)	44/86 (51.2%)	85/167 (50.9%)	47/100 (47.0%)
Placebo	1/19 (5.3%)	3/75 (4.0%)	3/84 (3.6%)	NA	7/50 (14.0%)
Treatment Difference 95% CI	NA	47.0% (37.8%, 56.3%)	47.6% (36.3%, 58.9%)	NA (43.3%, 58.5%)	33.0% (19.3%, 46.7%)
P-value	0.00147‡	<0.0001§	<0.0001§	NA	0.0001§

Vernakalant injection minus placebo

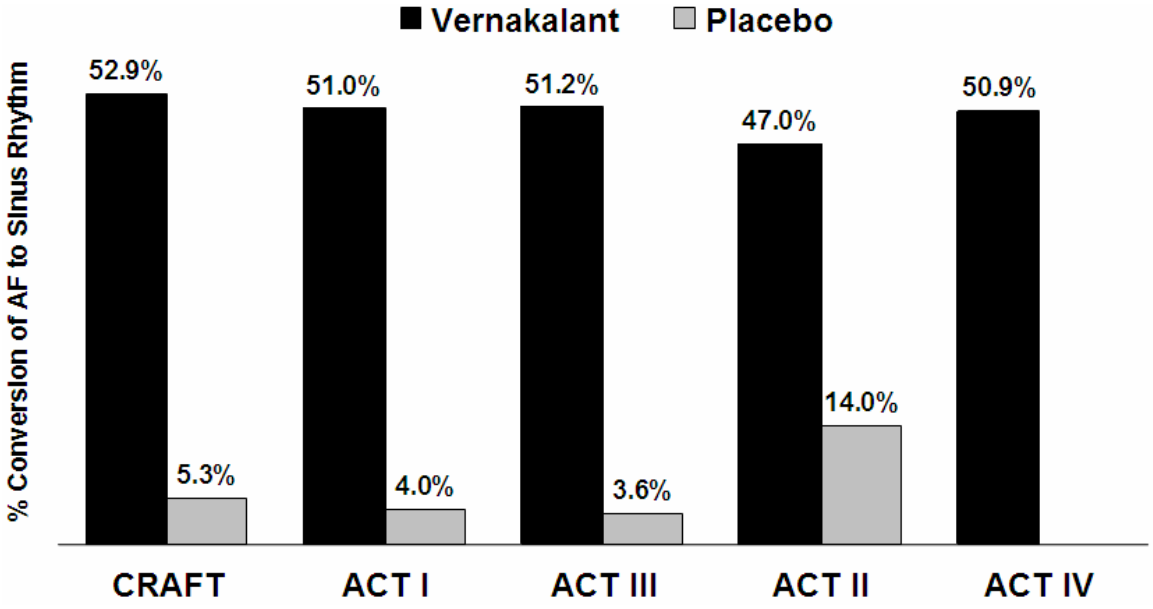
CI: confidence interval

† Only efficacy evaluable in the 2 mg/kg +3 mg/kg group and placebo; number of patients in sinus rhythm 1 hour post dosing

‡ Cochran-Armitage trend test

§ Cochran-Mantel-Haenszel test, stratified by site (ACT I, ACT III) or country (ACT II).

Figure 7: Conversion Rates of Short Duration Atrial Fibrillation Across Studies—All Phase 2 and Phase 3 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.

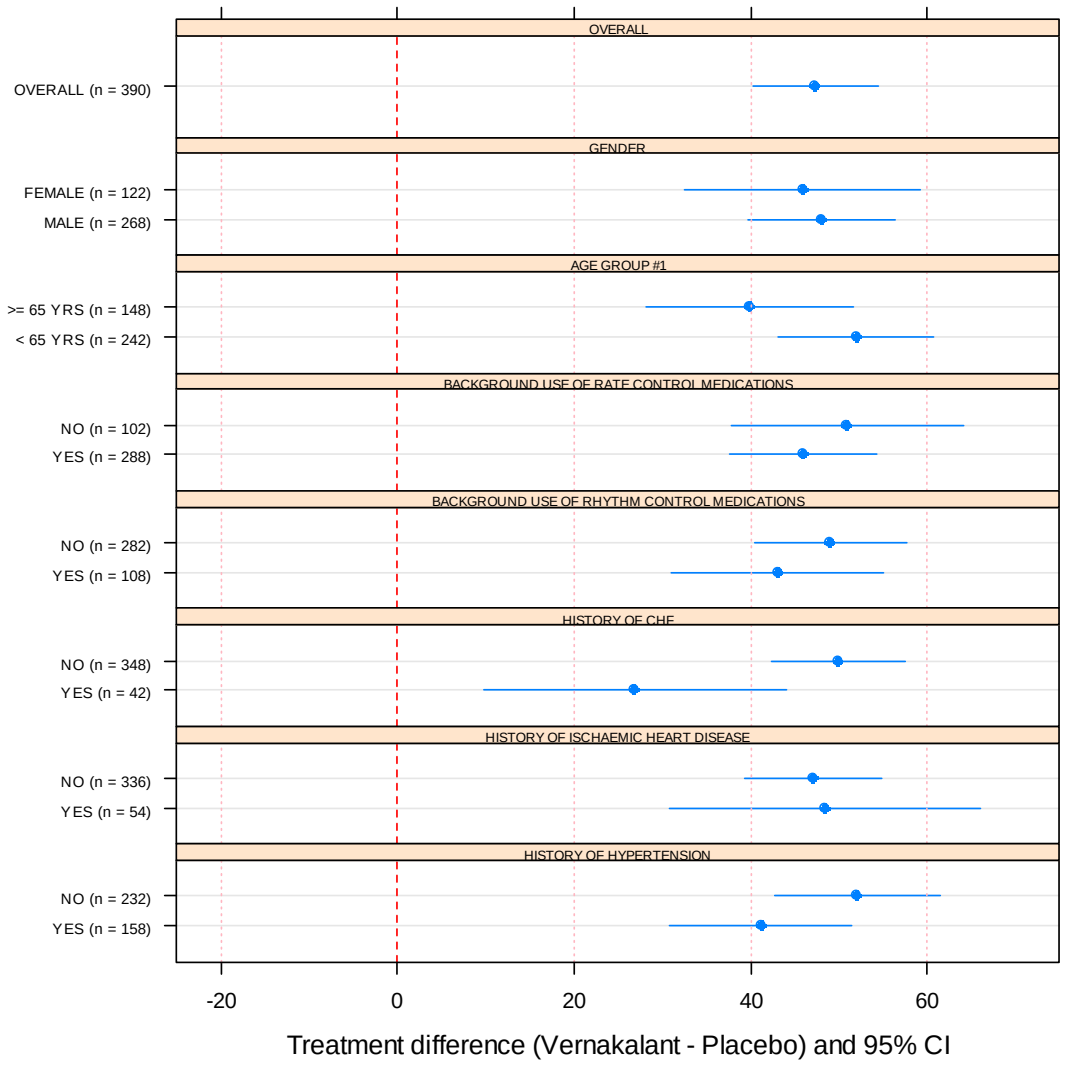
ACT I, III and IV: atrial fibrillation >3 hours to ≤ 7 days; ACT IV: a placebo group was not included in this open-label study; ACT II: atrial fibrillation post coronary artery bypass graft and/or valvular surgery; atrial fibrillation duration >3 to <72 hours.

7.3.5 Efficacy in Special Populations and Groups

In the pooled primary studies, conversion to sinus rhythm was assessed in a number of subgroups to evaluate the consistency of the treatment effect within each subgroup. The following subgroups were evaluated; age, sex, rate and rhythm control medications, history of CHF, history of hypertension and history of ischemic heart disease. In these exploratory analyses, the number of patients in some subgroups is small and the results should be interpreted with this in mind.

As shown in Figure 8, the treatment effect (vernakalant injection minus placebo) was significant within all subgroups, demonstrating that vernakalant injection is effective in converting atrial fibrillation to sinus rhythm within each of the subgroups. Additionally, the treatment effect (vernakalant injection minus placebo) was similar in the following subgroups: by sex, age, use of rate or rhythm control medications, history of hypertension or history of ischemic heart disease. The data suggest a trend towards a reduced benefit in patients with CHF (with history of CHF: placebo 0, vernakalant injection 26.9%; without history of CHF: placebo 4.2%, vernakalant injection 54.1%).

Figure 8: **Treatment Effect of Vernakalant Injection (and 95% CI) by Subgroup in the Short Duration Atrial Fibrillation Population – Pooled Primary Studies**



Patient base: Full Analysis Set (short-duration atrial fibrillation cohort), all randomized patients who received any amount of study drug

Pooled Primary Studies: pooled data from patients with atrial fibrillation in ACT I and ACT III.

Bars around the percent differences represent the 95% confidence intervals.

The results suggest that vernakalant injection is effective in the conversion of atrial fibrillation to sinus rhythm in a broad population.

7.3.5.1 Efficacy in Patients with Atrial Flutter

Study 1235-0703B (Scene 2) evaluated the efficacy of vernakalant injection in converting atrial flutter to sinus rhythm. In this study, 1 of 39 (2.6%) patients in the vernakalant injection group converted to sinus rhythm within 90 minutes of treatment; no placebo patients converted. Subsequently it was determined that this patient was not in atrial flutter at baseline but was in atrial fibrillation. ACT III included 23 patients with atrial flutter; 14 patients received vernakalant injection and nine patients received placebo. One of the 14 patients in the vernakalant injection group converted from atrial flutter to sinus rhythm after receiving study drug; no placebo patients converted from atrial flutter. In ACT II, 10 patients were in atrial flutter at baseline. None of the six patients in the vernakalant injection group converted to sinus rhythm, and one of four patients in the placebo group converted to sinus rhythm.

In summary, vernakalant injection was not effective in the conversion of atrial flutter to sinus rhythm.

Outcomes in Patients Developing Atrial Flutter following Administration of Vernakalant Injection

Following initiation of study drug, 10.6% (36/339) of patients with baseline atrial fibrillation in the pooled primary studies who received vernakalant injection had at least one ECG showing atrial flutter within the first 90 minutes compared with 0.4% (1/236) of placebo-treated patients. Of the patients receiving vernakalant injection, 27.8% (10/36) converted to sinus rhythm within 90 minutes, 47.2% (17/36) were electrically cardioverted to sinus rhythm within 24 hours, and 2.8% (1/36) were electrically cardioverted to sinus rhythm approximately 27 hours after initiation of study drug. Of the remaining eight patients:

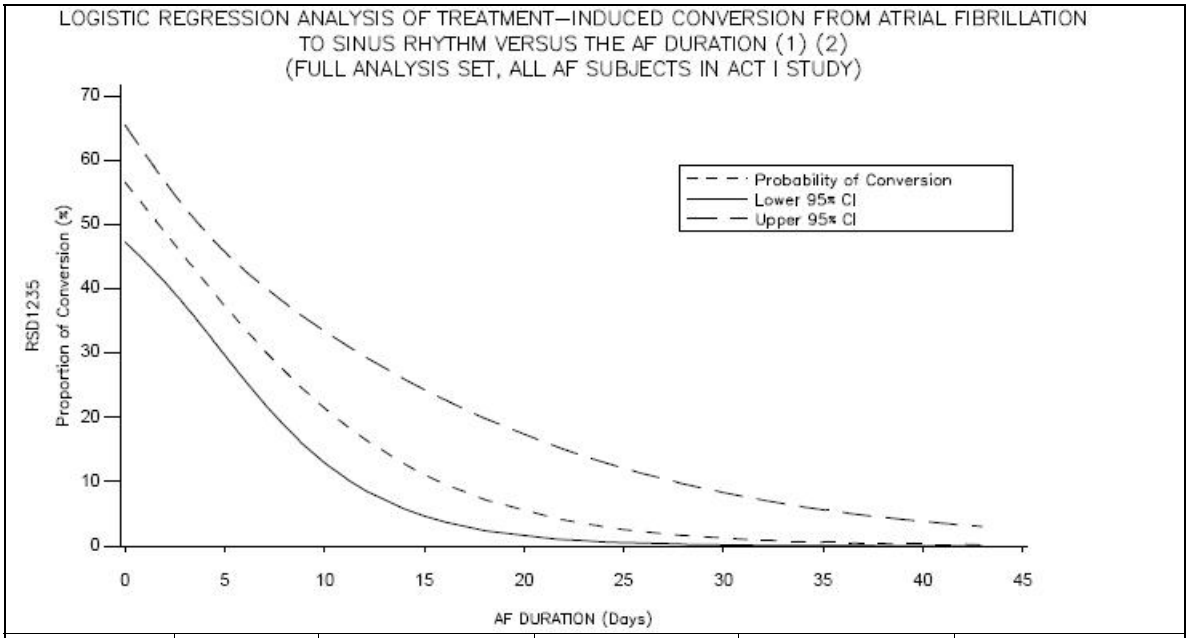
- six reverted to atrial fibrillation (3 converted to sinus rhythm by hour 8; 1 converted to sinus rhythm by day 7; 2 remained in atrial fibrillation and received rate control medications), and
- two remained in atrial flutter and converted to sinus rhythm by hour 4.

No patient with atrial flutter following administration of vernakalant injection developed 1:1 AV conduction.

7.3.5.2 Efficacy by Duration of Atrial Fibrillation

In ACT I, the method of data collection allowed for a detailed stratification of atrial fibrillation duration and analysis of conversion rates versus atrial fibrillation duration. Based on logistic regression analysis, increased likelihood of conversion was significantly associated with briefer duration of atrial fibrillation [Figure 9].

Figure 9: Logistic Regression Analysis of Treatment-Induced Conversion from Atrial Fibrillation to Sinus Rhythm versus the Duration of Atrial Fibrillation



Parameter	Estimate	Standard Error	P-value (3)	Odds Ratio (4)	95% Wald CI (4)
AF duration	-0.15635	0.03758	<0.0001***	0.855	(0.795, 0.921)

Full Analysis Set: all randomized patients who received any amount of study drug (ACT I)
Analysis based on treatment induced conversion as determined by the CEC from Holter monitor or 12-lead ECG data if Holter results were missing or not interpretable.
(1) A logistic regression model with AF duration (hours) as explanatory variable.
(2) Treatment-induced conversion from AF to sinus rhythm as determined by the CEC from results of the Holter monitor or 12-lead ECG data if Holter results were missing or not interpretable.
(3) P-value from Wald chi-square test
(4) The extent to which the odds of conversion decrease per day.

8 SAFETY

Vernakalant injection was well tolerated in clinical trials. Adverse events were generally transient, rarely treatment limiting, and manageable in the clinical setting for which vernakalant injection is intended. The development program for vernakalant injection included a total of 1134 subjects, of whom 823 received vernakalant injection and 341 received placebo. The patients in the development program were generally reflective of the population who present for the acute treatment of atrial fibrillation, including those with pacemakers and a variety of cardiac conditions (ischemic heart disease, CHF, history of myocardial infarction and hypertension) (O'Hara et al, 2005; Nieuwlaat et al, 2005; Levy et al, 1999).

Extensive ECG and vital sign monitoring were used throughout the development program. Blood pressure recordings and 12-lead ECGs were performed at screening, baseline, and at every 5 minutes for the first 50 minutes, and at 1.5, 2, 4, 8 and 24 hours (in the primary studies) and interpreted by the investigators for immediate clinical management. Holter

monitoring was performed from at least 30 minutes prior to randomization until 24 hours post-dose in all phase 3 trials. All ECG recordings were over-read by independent cardiologists blinded to treatment assignment. All key data sources were used to present the most comprehensive safety profile: adverse event reporting, ECG (Holter and 12-lead ECG) and vital sign data).

Three specific safety analyses were conducted based on the patient population, known side effects of other antiarrhythmic drugs and the pharmacological profile of vernakalant injection. Events of interest were ventricular arrhythmia, bradycardia and hypotension. Conservative definitions were employed for these events of interest to capture all relevant events and ensure that a comprehensive assessment of proarrhythmic risk, hypotension and bradycardia was conducted.

The safety findings were:

- Adverse events more frequently experienced, and at a higher incidence than placebo, were sneezing, nausea, dysgeusia, paresthesia and hypotension. These events were generally transient, rarely treatment limiting, and manageable in the setting for which vernakalant injection is intended.

- Serious adverse events that were experienced by more than one patient and at a higher incidence than placebo included: hypotension (vernakalant injection 1.2%, 9/773; placebo 0.3%, 1/335); sinus arrest (vernakalant injection 0.3%, 2/773; placebo 0); sinus bradycardia (vernakalant injection 0.3%, 2/773; placebo 0); complete AV block (vernakalant injection 0.3%, 2/773; placebo 0); and ventricular fibrillation (vernakalant injection 0.3%, 2/773; placebo 0).

- Of the 29 (3.8%, 29/773) patients who discontinued vernakalant injection due to an adverse event or serious adverse event, 7 of these patients experienced hypotension (0.9%, 7/773), and 4 patients experienced bradycardia (0.5%, 4/773).

- The incidence of any ventricular arrhythmia event in the 0–2 hour time period (vernakalant injection 5.3%, 39/737; placebo 6.3%, 20/315) and in the first 24 hours (vernakalant injection 12.5%, 92/737; placebo 16.5%, 52/315) was greater in the placebo group than in the vernakalant injection group. Of those events, unsustained monomorphic ventricular tachycardia (≥ 3 wide complex beats with heart rate ≥ 100 bpm) was the most common finding from the Holter and occurred at a similar incidence in both treatment groups in the first 2 hours post dosing (vernakalant injection 2.3%, 17/737, placebo 1.6%, 5/315).

- There were two events of ventricular fibrillation within the first 2 hours. One occurred following a non-synchronized electrical shock delivered during electrical cardioversion; the patient was successfully defibrillated. The second occurred in patient with critical aortic stenosis and acute coronary syndrome who developed hypotension following

administration of metoprolol and vernakalant injection, which led to fatal ventricular fibrillation.

- There was one event of an asymptomatic 9-beat run of torsade de pointes in the 0-24 hour time period in the vernakalant injection group (0.1%, 1/823). This event immediately followed infusion of ibutilide; however, the administration of vernakalant injection could not be excluded as a contributing factor due to the timing of the event (2 hours and 20 minutes after initiation of vernakalant injection dosing).

- An increased incidence of bradycardia adverse events was seen in the vernakalant injection group compared with placebo in the 2 hours following infusion, which was associated with the conversion to sinus rhythm.

- An increased incidence of hypotension adverse events in the first 24 hours was observed in patients receiving vernakalant injection (6.6%, 49/737) compared with placebo (3.5%, 11/315). The majority of these events occurred within the first 2 hours following infusion (vernakalant injection 5.4%, 40/737; placebo 1.0%, 3/315). These events were peri-infusional, generally mild or moderate, and responded to cessation of dosing and administration of fluids. Hypotension was considered a serious adverse event or led to discontinuation of study drug in 10 patients receiving vernakalant injection. These events of hypotension were generally transient and manageable in the setting for which the drug is intended.

- Prolongation of the QRS complex and QT interval corrected for heart rate (using both the Bazett and Fridericia formulas) was observed after vernakalant injection administration. The maximal placebo-subtracted changes from baseline were 8 msec for QRS, 10 msec for QTcB, and 23 msec for QTcF. The peak effect was seen at the end of the first infusion, with a second peak at the end the second infusion. Despite the observed QT prolongation, the incidence of ventricular arrhythmia after administration of vernakalant injection was no different than placebo. The incidence of QTcF outliers (>550 msec) in the 0-2 hour time period following vernakalant infusion was similar between placebo and vernakalant.

8.1 Adverse Events in All Patients in Phase 2 and Phase 3 Studies

Adverse events occurring within the first 24 hours of study drug administration were considered to be of clinical importance due to the short half-life of vernakalant injection. The adverse events more frequently (>5%) experienced by patients in the vernakalant injection group in phase 2 and phase 3 efficacy and safety studies and at a higher incidence than placebo were dysgeusia (metallic taste, strange or bad taste in the mouth), sneezing, paresthesia, nausea, and hypotension. Dysgeusia, sneezing, and paresthesia generally occurred during the infusion, with a median time to onset of 7, 8, and 9 minutes, respectively, and median duration of 11, 5, and 8 minutes, respectively. The median time to onset for

nausea and hypotension was 35 minutes and 34 minutes, respectively, and median duration was 16 minutes for nausea and 20 minutes for hypotension.

Treatment-emergent adverse events occurring in ≥ 1% of patients in the vernakalant injection group and at a higher incidence than in the placebo group in the first 24 hours of the study are presented in Table 16.

Table 16: Common Treatment Emergent Adverse Events in the First 24 Hours—All Patients in Phase 2 and Phase 3 Studies

System Organ Class Preferred Term	Placebo N=335 n (%)	Vernakalant Injection N=773 n (%)
CARDIAC DISORDERS		
Atrial Flutter	2 (0.6%)	15 (1.9%)
Atrioventricular block first degree	1 (0.3%)	8 (1.0%)
Bradycardia	7 (2.1%)	26 (3.4%)
Sinus bradycardia	5 (1.5%)	13 (1.7%)
GASTROINTESTINAL DISORDERS		
Diarrhoea	3 (0.9%)	10 (1.3%)
Dry mouth	0	8 (1.0%)
Nausea	4 (1.2%)	50 (6.5%)
Vomiting	1 (0.3%)	12 (1.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	6 (1.8%)	26 (3.4%)
Feeling hot	2 (0.6%)	22 (2.8%)
Infusion site pain	0	12 (1.6%)
Injection site paraesthesia	2 (0.6%)	9 (1.2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1 (0.3%)	8 (1.0%)
NERVOUS SYSTEM DISORDERS		
Dizziness	9 (2.7%)	34 (4.4%)
Dysgeusia	8 (2.4%)	158 (20.4%)
Headache	11 (3.3%)	29 (3.8%)
Hypoaesthesia	0	9 (1.2%)
Paraesthesia	5 (1.5%)	68 (8.8%)
Paraesthesia oral	1 (0.3%)	15 (1.9%)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS		
Cough	4 (1.2%)	34 (4.4%)
Dyspnoea	2 (0.6%)	12 (1.6%)
Nasal passage irritation	0	16 (2.1%)
Sneezing	0	116 (15.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Hyperhidrosis	2 (0.6%)	28 (3.6%)
Pruritus	0	29 (3.8%)
VASCULAR DISORDERS		
Hypotension	12 (3.6%)	45 (5.8%)

All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

Common treatment-emergent adverse events are defined as occurring in ≥ 1% vernakalant injection group and at a higher incidence than in the placebo group.

Within a system organ class, patients may have experienced more than one adverse event.

8.2 Serious Adverse Events

Common treatment-emergent serious adverse events are presented in Table 17, and are discussed under events of interest, Section 8.3.

The incidence of serious adverse events within the first 24 hours following study drug administration was similar in patients receiving vernakalant injection or placebo. Serious adverse events that occurred at a greater incidence in vernakalant-treated patients than in placebo-treated patients were hypotension, complete AV block, sinus arrest, sinus bradycardia and ventricular fibrillation.

Table 17: Common Treatment Emergent Serious Adverse Events in the First 24 Hours—All Patients in Phase 2 and Phase 3 Studies

System Organ Class Preferred Term	**Placebo** **N=335** **n (%)**	**Vernakalant Injection** **N=773** **n (%)**
Any Serious Adverse Event	**13 (3.9%)**	**32 (4.1%)**
CARDIAC DISORDERS		
AV block complete	0	2 (0.3%)
Sinus arrest	0	2 (0.3%)
Sinus bradycardia	0	2 (0.3%)
Ventricular fibrillation	0	2 (0.3%)
VASCULAR DISORDERS		
Hypotension	1 (0.3%)	9 (1.2%)

All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV. Common treatment-emergent serious adverse events are defined as occurring in more than one patient and at a higher incidence with vernakalant injection than in the placebo group. Within a system organ class, patients may have experienced more than one adverse event.

8.3 Events of Interest

Based on the safety profile of other antiarrhythmic agents and in reviewing the safety data for vernakalant injection, three events of interest were identified: ventricular arrhythmia, bradycardia, and hypotension.

Incidence tables were created for these three events using multiple data sources. Holter monitoring was performed from at least 30 minutes prior to randomization until 24 hours post-dose, and 12-lead ECGs (up to 15 ECGs per patient within the first 24 hours) were performed to monitor heart rhythm. Adverse event reporting also provided information on heart rhythm. As each of these sources captured information at different time points and for different purposes, special analyses using multiple datasets from these key sources were conducted to assess the incidence of ventricular arrhythmia and bradycardia. Similarly, special analyses to assess the incidence of hypotension were generated using the adverse event and vital sign databases. These special analyses consistently utilized conservative criteria for defining ventricular arrhythmia, bradycardia and hypotension to enable a comprehensive assessment of these events of interest. There were no formal definitions for

adverse events (e.g., bradycardia and hypotension); thus, these events were not adjudicated. Investigator judgment was used to assess these adverse events.

The methods used to generate these data and the results of the analyses are discussed below. The analyses were conducted for the entire study period (all post-dose events) and for hours 0-2 post-dose (the time period during which other new or additional rhythm medications were not to be administered), hours 2-24 post-dose, and hours 0-24 post-dose.

The events of interest were summarized for ACT I, ACT II, ACT III, ACT IV and Scene 2. The CRAFT study was not included in this analysis.

8.3.1 Ventricular Arrhythmia

8.3.1.1 Methods Used to Assess the Incidence of Ventricular Arrhythmia

Analyses to assess the incidence of ventricular arrhythmia in the vernakalant injection studies are summarized below.

Ventricular arrhythmia events from adverse event data, 12-lead ECG cardiologist over-read data and Holter device cardiologist over-read data summarize the risk of ventricular arrhythmia for vernakalant injection using three mechanisms (adverse events, 12-lead ECG and 3-lead Holter monitoring) for capturing data.

- The following MedDRA preferred terms were selected to define ventricular events:
    - cardiac arrest
    - syncope
    - tachycardia
    - torsade de pointes
    - ventricular arrhythmia
    - ventricular bigeminy
    - ventricular extrasystoles
    - ventricular fibrillation
    - ventricular tachycardia

- The 12-lead ECG cardiologist over-read represents the most comprehensive and consistent safety review of the 12-lead ECG data. Findings of accelerated idioventricular rhythm, idioventricular rhythm, torsade de pointes, ventricular fibrillation, ventricular flutter and ventricular tachycardia as well as other ventricular events were selected to define ventricular events.

- The Holter device cardiologist over-read, a post-hoc, blinded interpretation of wide complex events ≥ 3 consecutive beats with a heart rate ≥ 100 bpm, provides the most comprehensive ECG monitoring with a conservative definition of ventricular tachycardia (≥ 3 consecutive beats and a heart rate ≥ 100 bpm).

Events of polymorphic and monomorphic ventricular tachycardia are classified as "ventricular tachycardia" in the various analyses, with the exception of the Holter device cardiologist over-read data, which allowed for classification of ventricular tachycardia events as monomorphic or polymorphic and sustained or unsustained. Sustained ventricular tachycardia was defined as ventricular tachycardia with a duration of >30 seconds.

8.3.1.2 Incidence of Ventricular Arrhythmia

Using all three data sources, 19.1% (60/315) of patients in the placebo group and 12.9% (95/737) of patients in the vernakalant injection group were reported to have a ventricular arrhythmia event. The 0-24 hour time period, however, is the most informative period because it includes the entire period of Holter device monitoring and all scheduled 12-lead ECGs except the day 7 ECG. In addition, most vernakalant is cleared from the blood by the end of 24 hours; late events unrelated to study treatments may confound interpretation of events in both the placebo group and the vernakalant injection group.

In the 0-24 hour time period, the incidence of any ventricular arrhythmia event was 16.5% (52/315) in the placebo group and 12.5% (92/737) in the vernakalant injection group [Table 18]. The incidence of any ventricular arrhythmia event in the 0-2 hour time period was similar in the placebo group (6.3%, 20/315) and the vernakalant injection group (5.3%, 39/737). One event of torsade de pointes and two events of ventricular fibrillation occurred during the 0-24 hour time period in patients in the vernakalant injection group and are discussed in Section 8.3.1.3 below.

Table 18: Incidence of Ventricular Arrhythmia Events Occurring in the First 24 Hours—All Phase 3 Studies

Data Source/ Ventricular Arrhythmia Event†	0-2 Hrs Post Dosing		2-24 Hrs Post Dosing		0-24 Hrs Post Dosing	
	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)
All Sources						
Any ventricular arrhythmia event	**20 (6.3%)**	**39 (5.3%)**	**41 (13.0%)**	**69 (9.4%)**	**52 (16.5%)**	**92 (12.5%)**
Any torsade de pointes	0	0	0	1 (0.1%)‡	0	1 (0.1%)‡
Any ventricular fibrillation	0	1 (0.1%)	0	0	0	1 (0.1%)
Any ventricular tachycardia	9 (2.9%)	23 (3.1%)	38 (12.1%)	63 (8.5%)	41 (13.0%)	73 (9.9%)

Table continued on next page

Data Source/ Ventricular Arrhythmia Event†	0-2 Hrs Post Dosing		2-24 Hrs Post Dosing		0-24 Hrs Post Dosing	
	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)
Adverse Event Database						
Any ventricular arrhythmia event	1 (0.3%)	6 (0.8%)	4 (1.3%)	8 (1.1%)	5 (1.6%)	14 (1.9%)
Syncope	0	1 (0.1%)	0	1 (0.1%)	0	2 (0.3%)
Tachycardia	0	1 (0.1%)	0	0	0	1 (0.1%)
Ventricular bigeminy	0	1 (0.1%)	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Ventricular extrasystoles	0	1 (0.1%)	1 (0.3%)	3 (0.4%)	1 (0.3%)	4 (0.5%)
Ventricular fibrillation	0	1 (0.1%)	0	0	0	1 (0.1%)
Ventricular tachycardia	1 (0.3%)	1 (0.1%)	2 (0.6%)	4 (0.5%)	3 (1.0%)	5 (0.7%)
12-lead ECG Cardiologist Over-read						
Any ventricular arrhythmia event	13 (4.1%)	19 (2.6%)	2 (0.6%)	3 (0.4%)	14 (4.4%)	21 (2.8%)
Idioventricular rhythm	0	0	1 (0.3%)	0	1 (0.3%)	0
Other rhythm§	13 (4.1%)	17 (2.3%)	1 (0.3%)	3 (0.4%)	13 (4.1%)	19 (2.6%)
Ventricular flutter	0	1 (0.1%)	0	0	0	1 (0.1%)
Ventricular tachycardia	0	2 (0.3%)	0	0	0	2 (0.3%)
Holter Device Cardiologist Over-read						
Any ventricular arrhythmia event	8 (2.5%)	20 (2.7%)	38 (12.1%)	61 (8.3%)	40 (12.7%)	69 (9.4%)
Sustained¶ monomorphic VT	0	1 (0.1%)	0	0	0	1 (0.1%)
Unsustained monomorphic VT	5 (1.6%)	17 (2.3%)	29 (9.2%)	51 (6.9%)	30 (9.5%)	58 (7.9%)
Unsustained polymorphic VT	4 (1.3%)	5 (0.7%)	13 (4.1%)	23 (3.1%)	14 (4.4%)	24 (3.3%)

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

VT: ventricular tachycardia

† Within a data source, patients may have experienced more than one ventricular arrhythmia event.

‡ A nine beat run of a ventricular arrhythmia was captured by Holter monitoring.

§ Other rhythm includes aberrant beats, ventricular pairs, ventricular bigeminy, and ventricular runs of 5-7 beats

¶ Sustained: >30 seconds

8.3.1.3 Ventricular Fibrillation and Torsade de Pointes Events

Ventricular fibrillation and torsade de pointes were the most important ventricular arrhythmia events reported in the entire vernakalant injection program. These infrequent but important events are discussed below.

8.3.1.3.1 Ventricular Fibrillation

One patient in ACT III developed ventricular fibrillation resulting in death within the first 2 hours after receiving vernakalant injection [refer to Section 8.4 for further details]. The rhythm is shown in Table 18 as a serious adverse event of ventricular fibrillation, an occurrence of ventricular flutter on the 12-lead ECG cardiologist over-read and as sustained monomorphic ventricular tachycardia on the Holter device cardiologist over-read.

An adverse event of ventricular fibrillation also occurred in the phase 2 CRAFT study and is not included in Table 18 as CRAFT was not included in this analysis. This patient developed ventricular fibrillation following a nonsynchronized electrical shock delivered during electrical cardioversion. The patient, a 24-year-old female, presented to the emergency room in atrial fibrillation with a rapid ventricular response (150 -185 bpm). The patient received vernakalant injection 0.5 mg/kg followed by 1 mg/kg without conversion. 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 nonsynchronized cardioversion shock was delivered with ensuing ventricular fibrillation noted on the cardiac monitor. Immediate defibrillation attempt was successful with 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 defibrillator was tested and found to be functional. The investigator determined the event was unlikely to be related to study drug and resulted primarily due to the delivery of a nonsynchronized electrical shock during attempted cardioversion as the result of a loose cardiac monitor lead. This is a case of nonsynchronized cardioversion due to a technical malfunction which is known to happen rarely.

8.3.1.3.2 Torsade de Pointes

Using all three data sources and in all subjects exposed, a total of four events of torsade de pointes occurred. Three of the events (2 in vernakalant injection, 1 in placebo) occurred more than 24 hours following study drug administration and were not captured on Holter tracings and are not represented on Table 18.

- One patient randomized to vernakalant injection experienced torsade de pointes on days 17 and 18 of the study (post valvuloplasty) and recovered from the event.
- One patient developed torsade de pointes 32 hours post dosing of vernakalant injection and recovered from the event.
- One patient in the placebo group developed torsade de pointes on day 2, 1 hour after electrical cardioversion while receiving increasing doses of sotalol. The patient recovered from the event.

One event of torsade de pointes occurred within the first 24 hours after vernakalant injection administration and was captured on Holter (0.12%, 1/823):

- A nine beat run of a ventricular arrhythmia was captured by Holter monitoring 2 hours 20 minutes after initiation of the infusion of vernakalant injection and

immediately following an infusion of ibutilide. The event was not observed by the investigator and was not recorded by the investigator as an adverse event. The patient was asymptomatic. The rhythm was interpreted as torsade de pointes by the Chair of the DSMB.

In summary, the incidence of any ventricular arrhythmia event in the 0-24 hour time period was 16.5% in the placebo group and 12.5% in the vernakalant injection group. One event of torsade de pointes occurred in the 0-24 hour time period in a patient receiving vernakalant injection. An association with vernakalant injection cannot be ruled out in this case since it occurred 2 hours and 20 minutes after initiation of the infusion of vernakalant injection and immediately following an infusion of ibutilide. Two other reports of torsade de pointes occurred more than 24 hours after vernakalant injection administration and were not considered to be related to vernakalant infusion.

In the 0-2 hour time period, the incidence of ventricular arrhythmia events was similar in the placebo and vernakalant injection groups. Of the ventricular arrhythmia events, unsustained monomorphic ventricular tachycardia was the most common finding from the Holter reading and occurred at a similar incidence in both treatment groups in the first 2 hours post dosing. Two events of ventricular fibrillation occurred in the first 2 hours; one patient was successfully resuscitated and the second patient, who was hemodynamically unstable, died [see Section 8.4].

8.3.2 Bradycardia

8.3.2.1 Methods Used to Assess the Incidence of Bradycardia

The incidence of bradycardia was assessed using data from three sources with five analyses:

- adverse event data: the following MedDRA preferred terms were summarized:
    - atrioventricular block complete
    - bradycardia
    - bundle branch block
    - bundle branch block left
    - bundle branch block right
    - nodal rhythm
    - heart rate decreased
    - sick sinus syndrome
    - sinus arrest
    - sinus bradycardia

- 12-lead cardiologist over-read: the following findings were summarized:
    - second degree atrioventricular block (Mobitz type I)
    - second degree atrioventricular block (Mobitz type II)
    - third degree atrioventricular block
    - junctional rhythm

  - other rhythms (sinus pause, marked sinus bradycardia, ventricular rate <40 bpm during atrial fibrillation, bradyarrhythmia with heart rate <40 bpm, marked bradyarrhythmia with pause)
  - sinus atrial block
  - sinus bradycardia (heart rate <60 bpm)

- 12-lead ECG alerts:
  - heart rate <40 bpm
  - second degree atrioventricular block (Mobitz type I)
  - second degree atrioventricular block (Mobitz type II)
  - third degree atrioventricular block
  - idioventricular rhythm

- Holter alerts:
  - complete heart block
  - heart rate <40 bpm

- 12-lead ECG interval
  - heart rate <40 bpm

8.3.2.2 Incidence of Bradycardia

It is widely recognized that bradycardia occurs with conversion of atrial fibrillation to sinus rhythm. In all phase 3 studies, the incidence of any bradycardia event occurring in the 0-24 hour time period post dosing was 39.4% (124/315) in the placebo group and 36.9% (272/737) in the vernakalant injection group [Table 19]. The most frequent bradycardia event was sinus bradycardia (defined as heart rate <60 bpm) read on the 12-lead ECG by the central cardiologist occurring in 30.2% (95/315) of the patients receiving placebo and 31.1% (229/737) of patients receiving vernakalant injection. Heart rate <40 bpm occurred more frequently in the patients receiving placebo than patients receiving vernakalant injection during the 2-24 hour period.

Table 19: Incidence of Bradycardia Events Occurring in the First 24 Hours—All Phase 3 Studies

Data Source/ Bradycardia Event†	0-2 Hours Post Dosing		2-24 Hours Post Dosing		0-24 Hours Post Dosing	
	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)
All Sources						
Any bradycardia event	**15 (4.8%)**	**123 (16.7%)**	**117 (37.1%)**	**227 (30.8%)**	**124 (39.4%)**	**272 (36.9%)**
Adverse Event Database						
Any bradycardia event	3 (1.0%)	33 (4.5%)	9 (2.9%)	18 (2.4%)	12 (3.8%)	51 (6.9%)
AV Block complete	0	1 (0.1%)	0	1 (0.1%)	0	2 (0.3%)
Bradycardia	1 (0.3%)	20 (2.7%)	5 (1.6%)	6 (0.8%)	6 (1.9%)	26 (3.5%)
BBB	0	0	0	1 (0.1%)	0	1 (0.1%)
BBB left	0	4 (0.5%)	0	0	0	4 (0.5%)
BBB right	0	1 (0.1%)	0	0	0	1 (0.1%)
Heart rate decreased	1 (0.3%)	0	0	0	1 (0.3%)	0
Nodal rhythm	0	0	0	2 (0.3%)	0	2 (0.3%)
Sinus arrest	1 (0.3%)	4 (0.5%)	0	1 (0.1%)	1 (0.3%)	5 (0.7%)
Sinus bradycardia	0	5 (0.7%)	4 (1.3%)	8 (1.1%)	4 (1.3%)	13 (1.8%)
12-Lead ECG Cardiologist Over-read						
Any bradycardia event	4 (1.3%)	105 (14.2%)	96 (30.5%)	202 (27.4%)	96 (30.5%)	236 (32.0%)
2° AV block	0	1 (0.1%)	0	0	0	1 (0.1%)
3° AV block	0	1 (0.1%)	0	0	0	1 (0.1%)
Junctional rhythm	0	3 (0.4%)	0	3 (0.4%)	0	5 (0.7%)
Other rhythm §	1 (0.3%)	6 (0.8%)	3 (1.0%)	4 (0.5%)	3 (1.0%)	10 (1.4%)
Sinus atrial block	0	0	0	1 (0.1%)	0	1 (0.1%)
Sinus bradycardia	3 (1.0%)	100 (13.6%)	95 (30.2%)	196 (26.6%)	95 (30.2%)	229 (31.1%)
12-Lead ECG Alerts						
Any bradycardia event	3 (1.0%)	9 (1.2%)	13 (4.1%)	7 (1.0%)	13 (4.1%)	15 (2.0%)
2° AV block	0	1 (0.1%)	0	0	0	1 (0.1%)
3° AV block	0	1 (0.1%)	0	0	0	1 (0.1%)
Heart rate < 40 bpm	3 (1.0%)	8 (1.1%)	12 (3.8%)	7 (1.0%)	12 (3.8%)	14 (1.9%)
Idioventricular rhythm	0	0	1 (0.3%)	0	1 (0.3%)	0
Holter Alerts¶						
Any bradycardia event	6 (1.9%)	16 (2.2%)	30 (9.5%)	25 (3.4%)	36 (11.4%)	39 (5.3%)
Complete heart block	0	2 (0.3%)	5 (1.6%)	6 (0.8%)	5 (1.6%)	8 (1.1%)
Heart rate < 40 bpm	6 (1.9%)	14 (1.9%)	28 (8.9%)	20 (2.7%)	34 (10.8%)	33 (4.5%)
12-Lead ECG Interval Data – Calc						
Any bradycardia event	1 (0.3%)	9 (1.2%)	3 (1.0%)	3 (0.4%)	4 (1.3%)	12 (1.6%)
Heart rate < 40 bpm	1 (0.3%)	9 (1.2%)	3 (1.0%)	3 (0.4%)	4 (1.3%)	12 (1.6%)

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

AV: atrioventricular, BBB: bundle branch block, bpm: beats per minute; CEC: Clinical Events Committee

† Within a data source, patients may have experienced more than 1 bradycardia event.

§ Other rhythm includes sinus pause, marked sinus bradycardia, ventricular rate < 40 bpm during atrial fibrillation, bradyarrhythmia with heart rate < 40 bpm, and marked bradyarrhythmia with pause.

¶ ACT IV not reflected in this group as no CEC was utilized and Holter alerts were not part of the study.

The incidence of any bradycardia event during the 0-2 hour period was 4.8% (15/315) for patients receiving placebo and 16.7% (123/737) for patients receiving vernakalant injection.

This difference is largely due to the reporting of sinus bradycardia on the 12-lead ECG by the central cardiologist (placebo 1.0%, vernakalant injection 13.6%).

If bradycardia is analyzed for the 0-2 hour period (excluding the 12-lead ECG cardiologist over-read since most of these events were sinus bradycardia), combining the adverse event database with the Holter and ECG database, the incidence of bradycardia is 3.8% (12/315) for patients receiving placebo and 5.6% (41/737) for patients receiving vernakalant injection [Table 20]. Of the patients who remained in atrial fibrillation the incidence of bradycardia was similar in placebo and vernakalant injection groups (4.0% [12/300] of the patients receiving placebo and 4.3% [20/469] of the patients receiving vernakalant injection). Of the patients who converted to sinus rhythm, none (0/15) of the patients receiving placebo and 7.8% (21/268) of the patients receiving vernakalant injection had a bradycardia event. Bradycardia occurred in 15 of the 21 patients within 5 minutes of conversion. Therefore, the increased incidence of bradycardia seen in patients receiving vernakalant injection was associated with conversion to sinus rhythm.

Table 20: Bradycardia and Conversion to Sinus Rhythm 0-2 Hours Post dosing—All Phase 3 Studies

Data Source	Placebo (N = 315)		Vernakalant Injection (N = 737)	
Any Bradycardia AE ECG Holter	3.8% (12/315)		5.6% (41/737)	
	Converted to SR	**Remained in AF**	**Converted to SR**	**Remained in AF**
	0 (0/15)	4.0% (12/300)	7.8% (21/268)	4.3% (20/469)

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.
AE: adverse event; ECG: electrocardiogram; AF: atrial fibrillation; SR: sinus rhythm

Of particular interest are the patients who had a serious adverse event of bradycardia or had study drug discontinued due to bradycardia within the first 24 hours of study medication. Fifteen patients met these criteria, 13 received vernakalant injection and 2 received placebo [Table 21]. Bradycardia in the 0-2 hour time period was associated with conversion to sinus rhythm in four of the patients who received vernakalant injection (B1, B3, B4 and B5).

Table 21: Bradycardia Reported as a Serious Adverse Event and/or Leading to Discontinuation of Study Drug Within 24 Hours

ID	Demographics & Baseline Characteristics	Time from start of first infusion to bradycardia	Duration of bradycardia event	Treatment	Minimum Heart Rate (bpm) Symptoms
Vernakalant Injection					
B1	63 yo male Hypertension Mitral insufficiency	SAE of sinus bradycardia at 12 min (2 min after the end of the first infusion and 1 min after conversion to sinus rhythm)	3 days	None	44 bpm Asymptomatic
B2	54 yo male AF/AFL Ablation x2	SAE of bradycardia at 5 hr, 43 min (5 hr, 16 min after conversion to sinus rhythm)	About 4 days	Flecanide and bisoprolol discontinued, amiodarone started	30-50s bpm Asymptomatic
B3	58 yo male MI CABG	SAE of sinus bradycardia at 13 min (3 min after end of first infusion and at the time of conversion to sinus rhythm; sinus arrest also reported at the time of conversion)	9 min	Atropine x3 Trendelenburg	30 bpm BP 79/44 mmHg
B4	61 yo male Hypertension	SAE of bradycardia at 15 min (5 min after end of first infusion and at the time of conversion to sinus rhythm)	11 min	Atropine x1	36 bpm BP 65/35 mmHg
B5	60 yo male AF Stroke	SAE of bradycardia at 19 min (9 min after end of infusion and 12 min after conversion to sinus rhythm)	13 min	Atropine x2	19 bpm BP 53/34 mmHg
B6	45 yo male AF	SAE of bradycardia and hypotension at 5 min (Dose #1 DC after 5 min due to decrease in blood pressure)	2 min	None	54 bpm BP 70/30 mmHg Diaphoretic
B7	76 yo male Diabetes AF EF≥ 50%	SAE of bradycardia and hypotension at 33 min at 8 min into the second infusion	20 min	Neosynephrine, atropine, saline	44 bpm 70/NA mmHg Diaphoretic
B8	84 yo male MI Angina	DC of vernakalant due to bradycardia at 18 min (8 min after the end of the infusion) Did not convert	7 min	Atropine x1	42 bpm BP 85/50mmHg

Table continued on next page

ID	Demographics & Baseline Characteristics	Time from start of first infusion to bradycardia	Duration of bradycardia event	Treatment	Minimum Heart Rate (bpm) Symptoms
B9	41 yo male NYHA Class I CHF Hypertension Sleep apnea EF 36-49%	SAE of bradycardia at 2 min into the first infusion	13 min	None	30 bpm
B10	67 yo male Ischemic heart disease CHF	DC of vernakalant due to bradycardia at 6 min into the first infusion	1 min	None	41 bpm
B11	67 yo female Hypertension Aortic stenosis	SAE of complete heart block 8 min into first infusion	12 min	External pacing by epicardial wire	35 bpm SBP 70 mmHg
B12	90 yo female Angina Pulmonary edema EF 45%	SAE of complete heart block 3 hr 4 min after study drug and following attempted electrical cardioversion	<1 min	Atropine x2 Isoprenalin	40 bpm BP 47/23 mmHg
B13	58 yo male Hypertension	SAE of sinus arrest 4 hr 13 min after study drug (4 hr 9 min after conversion to sinus rhythm)	1 min	None	Asymptomatic
Placebo					
B14	64 yo female Septal hypertrophy Hypertension Cardiomegaly	SAEs of asystole, bradycardia and hypotension 4 hr and 13 min after study drug and immediately following electrical cardioversion	Unknown	Trendelenburg Atropine x4 Saline	38 bpm BP 69/54 mmHg
B15	56 yo male CHF NYHA Class III EF 26-35% Diabetes CAD Bradycardia	SAE of bradycardia at 20 hr after study drug	6 days	Pacemaker insertion	32 bpm

BP: blood pressure; HR: heart rate; EF: ejection fraction; CABG: coronary artery bypass graft; AF: atrial fibrillation; AFL: atrial flutter; MI: myocardial infarction; CHF: congestive heart failure; CAD: coronary artery disease; SAE: serious adverse event; DC: discontinuation; yo: year-old; SBP: systolic blood pressure; NYHA: New York Heart Association; bpm: beats per minute; AV: atrioventricular; NA: not available

In summary, the incidence of any bradycardia event during the 0-24 hour period was similar in the placebo and vernakalant injection groups (placebo 39.4%; vernakalant injection 36.9%). During the 0-2 hour period, the incidence was higher in patients receiving

vernakalant injection and was associated with conversion to sinus rhythm. The most common bradycardia event was sinus bradycardia (heart rate <60 bpm) seen on the 12-lead ECG. The event of heart rate <40 bpm occurred at a similar incidence in patients receiving placebo and vernakalant injection.

Fifteen patients (2 receiving placebo and 13 receiving vernakalant injection) had a serious adverse event or had study drug discontinued due to a bradycardia event. Bradycardia, in general, was of short duration and responded to discontinuation of study drug and atropine (if required).

8.3.3 Hypotension

In most of the efficacy and safety studies, blood pressure was recorded every 5 minutes during vernakalant injection administration and every few hours post dosing.

8.3.3.1 Methods Used to Assess the Incidence of Hypotension

The incidence of hypotension was assessed through the adverse event database and blood pressure data:

- adverse event database: the following MedDRA preferred terms were summarized:
    - dizziness postural
    - blood pressure decreased
    - blood pressure systolic decreased
    - hypotension
    - hypovolemia
    - orthostatic hypotension
    - syncope
    - syncope vasovagal
- vital signs: the incidence of the following events were summarized:
    - decrease of ≥15 mmHg from baseline in diastolic blood pressure
    - decrease of ≥30 mmHg from baseline in systolic blood pressure
    - systolic blood pressure <90 mmHg

8.3.3.2 Incidence of Hypotension

In the 0-24 hour time period, the incidence of any hypotension event was 45.7% (144/315) for patients receiving placebo and 36.8% (271/737) for patients receiving vernakalant injection [Table 22]. There were more hypotension events in the adverse event database for the vernakalant injection group (6.6%, 49/737) compared with placebo (3.5%, 11/315). In the vital sign database, a decrease in diastolic blood pressure of ≥ 15 mmHg was the most common event and was more frequent in placebo-treated patients.

Table 22: Incidence of Hypotension Events Occurring in the First 24 Hours— All Phase 3 Studies

Data Source/ Hypotension Event†	0-2 Hours Post Dosing		2-24 Hours Post Dosing		0-24 Hours Post Dosing	
	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)	Placebo (N=315)	Vernakalant Injection (N=737)
All Sources						
Any hypotension event	**95 (30.2%)**	**152 (20.6%)**	**99 (31.4%)**	**181 (24.6%)**	**144 (45.7%)**	**271 (36.8%)**
Adverse Event Database						
Any hypotension event	3 (1.0%)	40 (5.4%)	8 (2.5%)	10 (1.4%)	11 (3.5%)	49 (6.6%)
BP decreased	0	1 (0.1%)	0	0	0	1 (0.1%)
SBP decreased	0	1 (0.1%)	0	0	0	1 (0.1%)
Hypotension	3 (1.0%)	35 (4.7%)	8 (2.5%)	9 (1.2%)	11 (3.5%)	44 (6.0%)
Syncope vasovagal	0	2 (0.3%)	0	0	0	2 (0.3%)
Syncope	0	1 (0.1%)	0	1 (0.1%)	0	2 (0.3%)
Vital Signs						
Any hypotension event	95 (30.2%)	148 (20.1%)	97 (30.8%)	177 (24.0%)	142 (45.1%)	264 (35.8%)
Decrease from baseline DBP ≥15 mmHg	82 (26.0%)	125 (17.0%)	87 (27.6%)	159 (21.6%)	126 (40.0%)	232 (31.5%)
Decrease from baseline SBP ≥30 mmHg	15 (4.8%)	63 (8.5%)	26 (8.3%)	42 (5.7%)	35 (11.1%)	96 (13.0%)
SBP <90 mmHg	16 (5.1%)	45 (6.1%)	13 (4.1%)	18 (2.4%)	26 (8.3%)	55 (7.5%)

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

† Within a data source, patients may have experienced more than one hypotension event.

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure

In the first 2 hours post dosing, the incidence of any hypotension event was 30.2% (95/315) for patients receiving placebo and 20.6% (152/737) in patients receiving vernakalant injection. During this period, hypotension as any adverse event was 1.0% (3/315) of patients receiving placebo and 5.4% (40/737) in the patients receiving vernakalant injection. Evaluation of hypotension using the vital sign database showed that any hypotension event occurred more frequently in patients in the placebo group due to a decrease in diastolic blood pressure of ≥ 15 mmHg. More patients in the vernakalant injection group had a decrease from baseline ≥ 30 mmHg in systolic blood pressure or a systolic blood pressure of < 90 mmHg compared with placebo patients.

Of particular interest are the patients who had a serious adverse event of hypotension or had study drug discontinued due to hypotension [Table 23]. During the first two hours after the infusion, there were nine serious adverse events or discontinuation of vernakalant injection due to hypotension and none for placebo. Four of these patients had a history of CHF or had

an ejection fraction <50%. The ages ranged from 29 to 79 years; there were one female and eight male patients. The onset of hypotension in these nine patients occurred either during the first or second infusion or within 15 minutes after the infusion was stopped. The duration of the hypotension ranged from 2 minutes to 2 hours 16 minutes. Not all patients required treatment. In general, patients were placed in Trendelenburg position and the hypotension responded to saline. Some required pharmacological support for the blood pressure (norepinephrine or neosynephrine). All cases responded to treatment.

Table 23: Hypotension Reported as a Serious Adverse Event and/or Leading to Discontinuation of Study Drug Within 24 Hours

ID	Demographics & Baseline Characteristics	Time from start of first infusion to hypotension	Duration of hypotension event	Treatment	Minimum blood pressure/ Symptoms
Vernakalant Injection					
H1	48 yo male EF < 25% CHF NYHA class II	SAE of hypotension and DC of vernakalant at 10 min (end of first infusion)	2 hr 16 min	Saline, Trendelenburg	70/55 mmHg Sweating, pallor, nausea LOC and seizure
H2	49 yo male EF 25% Cardiomyopathy	SAE of hypotension and DC of vernakalant at 10 min (end of first infusion)	15 min	Saline, Trendelenburg	82/68 mmHg Sweating, pallor, diarrhea, feeling hot and cold.
H3	41 yo male	SAE of hypotension at 45 min (14 min after the end of second infusion)	46 min	Saline, Trendelenburg	88/53 mmHg Nausea, dizziness
H4	79 yo female CHF at admission NYHA class III Hypertension Sick sinus syndrome with pacemaker Aortic and tricuspid regurgitation	SAE of hypotension and DC of vernakalant at 25 min (at the start of the second infusion)	61 min	Saline, Trendelenburg	70/50 mmHg Dizziness, nausea

Table continued on next page

ID	Demographics & Baseline Characteristics	Time from start of first infusion to hypotension	Duration of hypotension	Treatment	Minimum blood pressure/ Symptoms
H5	72 yo male EF 45% CAD CABG	SAE of hypotension and DC of vernakalant at 10 min (3 min after stopping first infusion; DC due to wide complex arrhythmia)	3 min	NE, Ringer's lactate Trendelenburg	49/39 mmHg Asymptomatic
H6	45 yo male AF	SAE of hypotension and bradycardia at 5 min (Dose #1 DC after 5 min due to decrease in blood pressure)	2 min	None	70/30 mmHg Nausea
H7	76 yo male Diabetes AF EF ≥ 50%	SAE of hypotension and bradycardia and DC of vernakalant at 33 min (8 min into second infusion)	38 min	Neosynephrine, atropine, saline	70/NA mmHg Diaphoretic HR 44 bpm
H8	56 yo male Hypertension EF≥ 50%	SAE of hypotension and DC of vernakalant at 15 min (5 min after first infusion)	20 min	Saline and pentastarch	70/48 mmHg Asymptomatic
H9	29 yo male	SAE of hypotension and DC of vernakalant at 15 min (5 min after end of first infusion)	10 min	Unknown	75/47 mmHg Clammy skin, dizziness, nausea
H10	69 yo male CHF NYHA Class II AF Hypertension	SAE of hypotension at 6 hr, 45 min (6 hr, 20 min after end of second infusion)	Unknown	Unknown	68/40 mmHg Associated with diagnosis of cholecystitis

Table continued on next page

ID	Demographics & Baseline Characteristics	Time from start of first infusion to hypotension	Duration of hypotension	Treatment	Minimum blood pressure/ Symptoms
Placebo					
H11	64 yo female Septal hypertrophy Hypertension Cardiomegaly	SAEs of asystole, bradycardia and hypotension 4 hr and 13 min after study drug and immediately following electrical cardioversion	Unknown	Trendelenburg Atropine x4 Saline	69/54 mmHg HR 38 bpm
H12	83 yo female CHF NYHA Class I Hypertension	SAE of hypotension at 5 hr, 6 min (4 hr, 31 min after end of second infusion)	32 min	Saline Trendelenburg	81/32 mmHg Dizziness

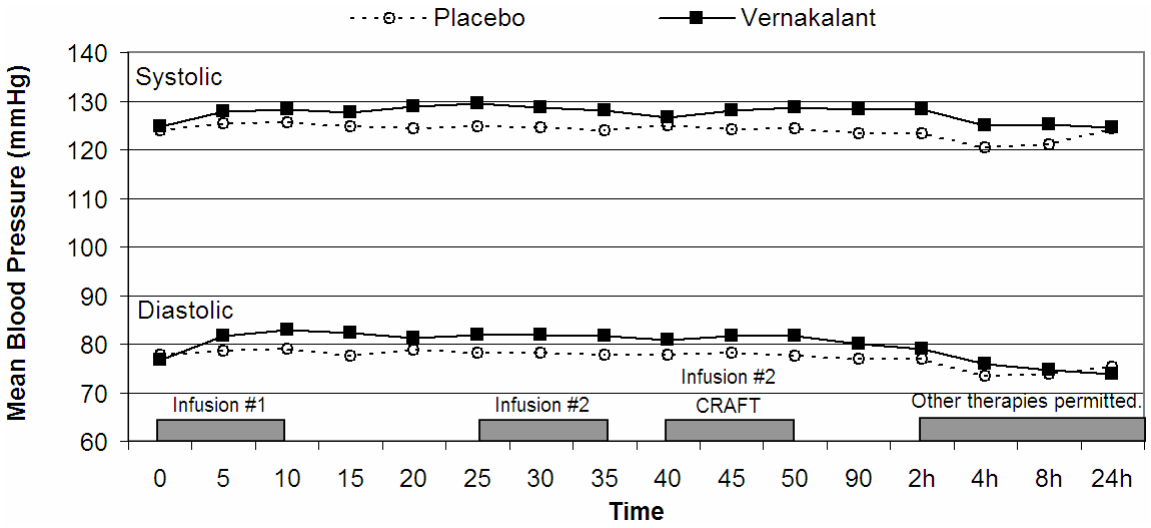
CHF: Congestive heart failure; EF: Ejection fraction; AE: Adverse event; DC: Discontinued; NYHA: New York Heart Association; yo: Years old; BP: Blood pressure; LOC: Loss of consciousness; NE: Norepinephrine; CAD: coronary artery disease; DC: discontinuation; yo: year-old; HR: heart rate; NA: not available

In summary, the incidence of hypotensive events within the first 24 hours was not different in patients receiving vernakalant injection or placebo; however, within the first 2 hours, there was an increased incidence of hypotension in the vernakalant injection group. Hypotension tended to be transient and responded to discontinuation of the infusion and administration of fluids (i.e., saline). More severe hypotension, which was considered a serious adverse event or resulted in discontinuation of study medication, has been observed (1.4%, 10/773) in patients receiving vernakalant injection and may be associated with bradycardia. These events can usually be managed by Trendelenburg positioning, discontinuing vernakalant infusion and administering saline infusion, and in the case of bradycardia, with atropine.

8.3.3.3 Blood Pressure Changes

In the pooled population of phase 2 and phase 3 studies, baseline systolic blood pressure was similar in the placebo group (123.8 mmHg) and the vernakalant injection group (124.7 mmHg). When looking at vital signs, systolic blood pressure in the placebo group was essentially unchanged through hour 2, while small mean increases in the vernakalant injection group ranging from 2.6 to 4.3 mmHg were recorded. Similar findings were observed in diastolic blood pressure, with mean increases in the vernakalant injection group ranging from 2.0 to 5.1 mmHg. Mean increases in systolic and diastolic blood pressure in the vernakalant injection group were statistically significant compared to placebo at all time points through hour 8.

Figure 10: Mean Blood Pressure Over Time—All Phase 2 and Phase 3 Studies



All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.
Note: The observation period in CRAFT was 30 minutes, not 15 as in other studies.

8.4 Deaths

In the overall development program, there were no deaths in healthy volunteers or in patients who received placebo. Five deaths occurred in the vernakalant injection group in the overall development program (0.6%, 5/823). One of the five deaths occurred during the first 24 hours of the study. A summary of the deaths is provided below.

- A 64-year-old male with critical aortic stenosis (120 mmHg), dilated left ventricle, ejection fraction of 40%, CHF NYHA Class II, hypertension, and hyperlipidemia. He was admitted with chest pain, atrial fibrillation with a ventricular rate of 150 bpm and blood pressure of 130/90 mmHg. Troponin levels were 6 times the upper limit of normal. He was treated with intravenous metoprolol and the blood pressure fell to 90/70 mmHg. The blood pressure increased after saline infusion. Vernakalant injection was administered. At the end of the first infusion the blood pressure was 75/42 mmHg. He was nauseated and diaphoretic. Blood pressure fell further to a minimum of 62/42 mmHg. ECG tracings suggested acute coronary syndrome. He was placed in Trendelenburg position and hydroxyethyl starch was given. Blood pressure recovered and at the time of the second infusion it was 104/74 mmHg. The second infusion of vernakalant injection resulted in a decrease in blood pressure to 65/41 mmHg. He vomited and became unresponsive and developed ventricular fibrillation. Defibrillation resulted in pulseless bradycardia. Resuscitation attempts were not successful. Autopsy showed critical aortic stenosis and myocardial hypertrophy. Concomitant medications included metoprolol, aspirin, lisinopril, metoclopramide, simvastatin, bumetanide. Genotyping was not done. The investigator assessed the events as possibly related to study drug.

  Per Section 8.3.1.3.1, the event of ventricular flutter was noted on the 12-lead cardiologist over-read and an event of sustained monomorphic ventricular tachycardia was noted on the Holter device cardiologist over-read.

- A 68-year-old white female received two doses of vernakalant injection. She did not convert to sinus rhythm. She was subsequently electrically cardioverted to sinus rhythm. A serious adverse event of hemopericardium due to rupture of dissecting aortic aneurysm during a gastroscopy procedure (scheduled for assessment of daily vomiting) began one day after receiving study drug, and resulted in death on day 2. The investigator assessed the event to be not related to study drug.

- A 90-year-old female with a history of angina pectoris and pulmonary edema, died on day 26 from respiratory and heart failure. The investigator assessed the event to be not related to study drug.

- A 67-year-old male with a history of non-small cell lung cancer with bone metastases developed pneumonia on day 4, and on day 6 he became unresponsive with no pulse. He was resuscitated and placed on a ventilator. The patient's family decided to withdraw respiratory support and the patient died on day 8. The investigator assessed the severity of the respiratory arrest serious adverse event to be life threatening and the relationship to study drug unlikely.

- A 70-year-old female with breast cancer was hospitalized with leukopenia which responded to treatment. While hospitalized she developed atrial fibrillation and received

two doses of vernakalant injection. She died 24 days later of an upper gastrointestinal hemorrhage. The investigator assessed the event to be not related to study drug.

In summary, five deaths (0.6%, 5/823) occurred in subjects who received vernakalant injection and none occurred in patients receiving placebo. The cause of death was unique in each patient with no common pathophysiological or pharmacological cause that may have contributed to their deaths. Further, four of these deaths were not temporally related to administration of vernakalant injection (2, 8, 24 and 26 days after administration). The fifth death was in a hemodynamically unstable patient with acute coronary syndrome and was related to vernakalant injection. The patient's blood pressure decreased following administration of metoprolol and vernakalant injection, which lead to ischemia in a already compromised heart and resulted in a fatal ventricular arrhythmia.

8.5 Safety in Special Populations in Phase 2 and Phase 3 Studies

Adverse event data and events of interest data were evaluated for the effect of age, sex, race, background use of rate or rhythm control medications, history of ischemic heart disease, and history of hypertension. No clinically important differences in the safety profile of vernakalant injection were noted in these subgroups.

Details regarding the bradycardia events for the special populations will not be discussed since these analyses were not informative. There was no increased incidence of bradycardia events in these subgroups, particularly in patients receiving rate or rhythm control medications.

8.5.1 Dose Exposure: One and Two Doses of Vernakalant Injection

In the 0-24 hour time period, the incidence of any ventricular arrhythmia event for patients receiving placebo was 16.5% (52/315) [Table 24]. A similar incidence of any ventricular event was seen in patients receiving one or two doses of vernakalant injection (12.9%, 31/241 single-dose; 12.3%, 61/496 two doses). One patient who received two doses of vernakalant injection had an event of torsade de pointes; and two patients who received two doses of vernakalant injection had an event of ventricular fibrillation within the first 24 hours.

In the 0-2 hour time period, the incidence of any ventricular arrhythmia event for patients receiving placebo was 6.3% (20/315), 5.8% (14/241) for patients receiving a single dose of vernakalant injection and 5.0% (25/496) for patients receiving two doses of vernakalant injection. Two patients who received two doses of vernakalant injection had an event of ventricular fibrillation [see Section 8.3.1.3]. There was no clinically important difference in the incidence of ventricular tachycardia in patients who received placebo (2.9%, 9/315) or one or two doses of vernakalant injection (3.7%, 9/241 and 2.8%, 14/496, respectively).

Table 24: Incidence of Ventricular Arrhythmia Events in the First 24 Hours by Dose Exposure—All Phase 3 Studies

	0-2 Hours Post Dosing			0-24 Hours Post Dosing		
		1 Dose	2 Doses		1 Dose	2 Doses
	Placebo n=315	**Ver Inj n=241**	**Ver Inj n=496**	**Placebo n=315**	**Ver Inj n=241**	**Ver Inj n=496**
Any Ventricular Arrhythmia Event†	**20 (6.3%)**	**14 (5.8%)**	**25 (5.0%)**	**52 (16.5%)**	**31 (12.9%)**	**61 (12.3%)**
Any torsade de pointes	0	0	0	0	0	1 (0.2%)‡
Any ventricular fibrillation	0	0	1 (0.2%)	0	0	1 (0.2%)
Any ventricular tachycardia	9 (2.9%)	9 (3.7%)	14 (2.8%)	41 (13.0%)	25 (10.4%)	48 (9.7%)

Ver Inj: vernakalant injection

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

†Within a data source, patients may have experienced more than one ventricular arrhythmia event. "Any ventricular arrhythmia event" summarizes all data sources; however, only the first three categories are shown for simplicity and ease of review.

‡ A nine beat run of a ventricular arrhythmia was captured by Holter monitoring.

In the 0-24 hour time period, the incidence of any hypotension event in the placebo group was 45.7% (144/315) [Table 25]. The incidence in patients receiving one and two doses of vernakalant injection was similar (36.5% single-dose; 36.9% two doses).

In the 0-2 hour time period, the incidence of any hypotension event in the placebo group was 30.2% (95/315). The incidence of any hypotension event in patients receiving only one dose of vernakalant injection was 25.3% (61/241) and in patients who received two doses of vernakalant injection was 18.3% (91/496). The incidence of hypotension as an adverse event or from the vital sign database was less in patients who received two doses of vernakalant injection when compared with those who received one dose.

Table 25: Incidence of Hypotension Events in the First 24 Hours by Dose Exposure—All Phase 3 Studies

	0-2 Hours Post Dosing			0-24 Hours Post Dosing		
		1 Dose	2 Doses		1 Dose	2 Doses
	Placebo n=315	**Ver Inj n=241**	**Ver Inj n=496**	**Placebo n=315**	**Ver Inj n=241**	**Ver Inj n=496**
Any Hypotension Event†	**95 (30.2%)**	**61 (25.3%)**	**91 (18.3%)**	**144 (45.7%)**	**88 (36.5%)**	**183 (36.9%)**
Adverse Events Database	3 (1.0%)	16 (6.6%)	24 (4.8%)	11 (3.5%)	17 (7.1%)	32 (6.5%)
SBP decrease ≥ 30 mmHg	15 (4.8%)	22 (9.1%)	41 (8.3%)	35 (11.1)	30 (12.4%)	66 (13.3%)
SBP < 90 mmHg	16 (5.1%)	23 (9.5%)	22 (4.4%)	26 (8.3%)	23 (9.5%)	32 (6.5%)
DBP ≥ 15 decrease mmHg	82 (26.0%)	53 (22.0%)	72 (14.5%)	126 (40.0%)	78 (32.4%)	154 (31.0%)

Ver Inj: vernakalant injection; DBP: diastolic blood pressure; SBP: systolic blood pressure

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

† Within a data source, patients may have experienced more than one hypotension event.

In summary, the incidence of ventricular arrhythmia or hypotensive events was no different in patients receiving one or two doses of vernakalant injection.

8.5.2 Patients with Background Use of Antiarrhythmic Medications

Background use of rhythm control medications was defined as any administration of a Class I or Class III rhythm control medication within the 7 days prior to study drug administration.

During the 0-24 hour period there was no difference in the incidence of ventricular events in patients receiving background rhythm control medications. During the 0-2 hour period there was no difference in the incidence of ventricular events in patients receiving background rhythm control medications [Table 26].

Table 26: Incidence of Ventricular Arrhythmia Events in the First 24 Hours by Background Use of Rhythm Control Medications—All Phase 3 Studies

	0-2 Hours Post Dosing				0-24 Hours Post Dosing			
	Rhythm Control Medications		No Rhythm Control Medications		Rhythm Control Medications		No Rhythm Control Medications	
	Placebo n=66	Ver Inj n=149	Placebo n=249	Ver Inj n=588	Placebo n=66	Ver Inj n=149	Placebo n=249	Ver Inj n=588
Any Ventricular Arrhythmia Event†	**5 (7.6%)**	**11 (7.4%)**	**15 (6.0%)**	**28 (4.8%)**	**10 (15.2%)**	**17 (11.4%)**	**42 (16.9%)**	**75 (12.8%)**
Any torsade de pointes	0	0	0	0	0	0	0	1 (0.7%)‡
Any ventricular fibrillation	0	0	0	1 (0.2%)	0	0	0	1 (0.2%)
Any ventricular tachycardia	3 (4.5%)	6 (4.0%)	6 (2.4%)	17 (2.9%)	8 (12.1%)	11 (7.4%)	33 (13.3%)	62 (10.5%)

Ver Inj: vernakalant injection

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

† Within a data source, patients may have experienced more than one ventricular arrhythmia event.

‡ A nine beat run of a ventricular arrhythmia was captured by Holter monitoring.

There was no clinically important difference in hypotension events during the 0-24 hour period in patient receiving background rhythm control medications compared with those who did not [Table 27]. The incidence of any hypotension event during the 0-2 hour period was less in patients who received vernakalant injection compared with patients who received placebo.

Table 27: Incidence of Hypotension Events in the First 24 Hours by Background Use of Rhythm Control Medications—All Phase 3 Studies

	0-2 Hours Post Dosing				0-24 Hours Post Dosing			
	Rhythm Control Medications		No Rhythm Control Medications		Rhythm Control Medications		No Rhythm Control Medications	
	Placebo n=66	Ver Inj n=149	Placebo n=249	Ver Inj n=588	Placebo n=66	Ver Inj n=149	Placebo n=249	Ver Inj n=588
Any Hypotension Event†	**23 (34.8%)**	**28 (18.8%)**	**72 (28.9%)**	**124 (21.1%)**	**34 (51.5%)**	**54 (36.2%)**	**110 (44.2%)**	**217 (36.9%)**
Adverse events database‡	1 (1.5%)	6 (4.0%)	2 (0.8%)	34 (5.8%)	3 (4.5%)	8 (5.4%)	8 (3.2%)	41 (7.0%)
SBP decrease ≥ 30 mmHg	4 (6.1%)	10 (6.7%)	11 (4.4%)	53 (9.0%)	8 (12.1%)	17 (11.4%)	27 (10.8%)	79 (13.4%)
SBP < 90 mmHg	6 (9.1%)	7 (4.7%)	10 (4.0%)	38 (6.5%)	7 (10.6%)	8 (5.4%)	19 (7.6%)	47 (8.0%)
DBP decrease ≥ 15mmHg	17 (25.8%)	24 (16.1%)	65 (26.1%)	101 (17.2%)	27 (40.9%)	47 (31.5%)	99 (39.8%)	185 (31.5%)

Ver Inj: vernakalant injection; DBP: diastolic blood pressure; SBP: systolic blood pressure

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

† Within a data source, patients may have experienced more than one hypotension event.

There was no difference in ventricular or hypotensive events in patients receiving vernakalant injection and background rhythm control medications compared with those who did not. Vernakalant injection does not appear to increase the risk of ventricular arrhythmia events compared to placebo in patients with background use of rhythm control medications.

8.5.3 Patients with Background Use of Rate Control Medications

Background use of rate control medications (beta blockers, calcium channel blockers, and digoxin) was defined as any administration of a rate control medication within the 7 days prior to study drug administration.

In all phase 3 studies, the incidence of any ventricular arrhythmia event occurring in the 0-24 hour time period post dosing in patients receiving background rate control medications was 18.3% (46/252) in the placebo group and 13.4% (72/537) in the vernakalant injection group [Table 28]. In the phase 3 studies within the first 24 hours, there was one report of torsade de pointes and one adverse event report of ventricular fibrillation (an additional adverse event of ventricular fibrillation was reported in CRAFT) in patients with background

use of rate control medications. Ventricular tachycardia in patients receiving rate control medication was similar in both the placebo and vernakalant injection groups.

The incidence of ventricular arrhythmia events during the 0-2 hour period was not different between patients who received or did not receive background rate control medication.

Table 28: Incidence of Ventricular Arrhythmia Events in the First 24 Hours by Background Use of Rate Control Medications—All Phase 3 Studies

	0-2 Hours Post Dosing				0-24 Hours Post Dosing			
	Rate Control Medications		No Rate Control Medications		Rate Control Medications		No Rate Control Medications	
	Placebo n=252	Ver Inj n=537	Placebo n=63	Ver Inj n=200	Placebo n=252	Ver Inj n=537	Placebo n=63	Ver Inj n=200
Any Ventricular Arrhythmia Event†	**18 (7.1%)**	**28 (5.2%)**	**2 (3.2%)**	**11 (5.5%)**	**46 (18.3%)**	**72 (13.4%)**	**6 (9.5%)**	**20 (10.0%)**
Any torsade de pointes	0	0	0	0	0	1 (0.2%)‡	0	0
Any ventricular fibrillation	0	1 (0.2%)	0	0	0	1 (0.2%)	0	0
Any ventricular tachycardia	7 (2.8%)	18 (3.4%)	2 (3.2%)	5 (2.5%)	36 (14.3%)	59 (11.0%)	5 (7.9%)	14 (7.0%)

Ver Inj: vernakalant injection

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

† Within a data source, patients may have experienced more than one ventricular arrhythmia event.

‡ A nine beat run of a ventricular arrhythmia was captured by Holter monitoring.

The incidence of any hypotension event during the 0-24 hour period was higher in the placebo group (with or without background rate control medication) when compared to the vernakalant injection groups [Table 29]. In the adverse event database, there were more reports of hypotension in patients receiving vernakalant injection irrespective of the use of background rate control medication.

In the 0-2 hour period, there was a higher incidence of hypotension adverse events, systolic blood pressure <90mmHg and systolic blood pressure decrease ≥ 30 mmHg in patients receiving vernakalant injection and background rate control medication compared to placebo patients receiving background rate control medication.

Table 29: Incidence of Hypotension Events in the First 24 Hours by Background Use of Rate Control Medications—All Phase 3 Studies

	0-2 Hours Post Dosing				0-24 Hours Post Dosing			
	Rate Control Medications		No Rate Control Medications		Rate Control Medications		No Rate Control Medications	
	Placebo n=252	Ver Inj n=537	Placebo n=63	Ver Inj n=200	Placebo n=252	Ver Inj n=537	Placebo n=63	Ver Inj n=200
Any Hypotension Event†	**74 (29.4%)**	**113 (21.0%)**	**21 (33.3%)**	**39 (19.5%)**	**118 (46.8%)**	**201 (37.4%)**	**26 (41.3%)**	**70 (35.0%)**
Adverse events database	3 (1.2%)	35 (6.5%)	0	5 (2.5%)	10 (4.0%)	40 (7.4%)	1 (1.6%)	9 (4.5%)
SBP decrease ≥ 30 mmHg	11 (4.4%)	52 (9.7%)	4 (6.3%)	11 (5.5%)	30 (11.9%)	73 (13.6%)	5 (7.9%)	23 (11.5%)
SBP < 90 mmHg	14 (5.6%)	38 (7.1%)	2 (3.2%)	7 (3.5%)	24 (9.5%)	47 (8.8%)	2 (3.2%)	8 (4.0%)
DBP decrease ≥ 15 mmHg	63 (25.0%)	93 (17.3%)	19 (30.2%)	32 (16.0%)	102 (40.5%)	171 (31.8%)	24 (38.1%)	61 (30.5%)

Ver Inj: vernakalant injection; DBP: diastolic blood pressure; SBP: systolic blood pressure

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

†Within a data source, patients may have experienced more than one hypotension event.

In summary, the incidence of ventricular arrhythmia or hypotension in patients receiving vernakalant compared with patients receiving placebo was not affected by background rate control medications.

8.5.4 Patients with History of Congestive Heart Failure

In the phase 3 studies, the percentage of patients with a history of CHF was 14.9% (110/737) of those who received vernakalant injection and 17.1% (54/315) of those who received placebo. Among patients with a history of CHF, in the first 24 hours, 25.9% (14/54) of patients in the placebo group and 26.4% (29/110) of patients in the vernakalant injection group had any ventricular arrhythmia event [Table 30]. In the 0-2 hour time period post dosing, 3.7% (2/54) of patients in the placebo group and 10.9% (12/110) of patients in the vernakalant injection group had any ventricular arrhythmia event. In the 0-2 hour time period in patients without a history of CHF, 6.9% (18/261) of patients in the placebo group and 4.3% (27/627) of patients in the vernakalant injection group had any ventricular arrhythmia event. None of the ventricular tachycardia events reported was polymorphic. One

event of torsade de pointes and one event of ventricular fibrillation occurred in patients with a history of CHF.

Table 30: Incidence of Ventricular Arrhythmia Events Occurring in the First 24 Hours by History of CHF—All Phase 3 Studies

	0-2 Hours Post Dosing				0-24 Hours Post Dosing			
	With History of CHF		Without History of CHF		With History of CHF		Without History of CHF	
	Placebo n=54	Ver Inj n=110	Placebo n=261	Ver Inj n=627	Placebo n=54	Ver Inj n=110	Placebo n=261	Ver Inj n=627
Any Ventricular Arrhythmia Event†	**2 (3.7%)**	**12 (10.9%)**	**18 (6.9%)**	**27 (4.3%)**	**14 (25.9%)**	**29 (26.4%)**	**38 (14.6%)**	**63 (10.0%)**
Any torsade de pointes	0	0	0	0	0	1 (0.9%)‡	0	0
Any ventricular fibrillation	0	1 (0.9%)	0	0	0	1 (0.9%)	0	0
Any ventricular tachycardia	1 (1.9%)	6 (5.5%)	8 (3.1%)	17 (2.7%)	13 (24.1%)	20 (18.2%)	28 (10.7%)	53 (8.5%)

Ver Inj: vernakalant injection; CHF: congestive heart failure

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

†Within a data source, patients may have experienced more than one ventricular arrhythmia event.

‡ A nine beat run of a ventricular arrhythmia was captured by Holter monitoring.

In the first 24 hours post dosing, the incidence of any hypotensive event was 53.7% (29/54) in patients receiving placebo and 48.2% (53/110) in patients receiving vernakalant injection, which was mostly due to a decrease from baseline in diastolic blood pressure [Table 31].

In the first 2 hours post dosing, there was no difference in the overall incidence of hypotension events in patients with a history of CHF between the placebo group (31.5%, 17/54) and the vernakalant injection group (31.8%, 35/110). However, the incidence of any hypotension event in patients with a history of CHF was greater compared to patients without a history of CHF for both the placebo group (29.9%, 78/261) and the vernakalant injection group (18.7%, 117/627). No hypotension adverse events were reported in patients with a history of CHF who received placebo compared with 12.7% (14/110) of patients with a history of CHF who received vernakalant injection. In the vital sign database, the incidence of hypotension events in patients with a history of CHF was similar between the placebo group (31.5%, 17/54) and the vernakalant injection group (31.8%, 35/110). There were more reports of decrease from baseline systolic blood pressure ≥ 30 mmHg (placebo 1.9%, vernakalant injection 20.0%) and/or a systolic blood pressure <90 mmHg (placebo 5.6%,

vernakalant injection 15.5%) in patients with a history of CHF receiving vernakalant injection compared with placebo.

Table 31: Incidence of Hypotension Events Occurring in the First 24 Hours by History of CHF—All Phase 3 Studies

	0-2 Hours Post Dosing				0-24 Hours Post Dosing			
	With History of CHF		Without History of CHF		With History of CHF		Without History of CHF	
	Placebo n=54	Ver Inj n=110	Placebo n=261	Ver Inj n=627	Placebo n=54	Ver Inj n=110	Placebo n=261	Ver Inj n=627
Any Hypotension Event†	**17 (31.5%)**	**35 (31.8%)**	**78 (29.9%)**	**117 (18.7%)**	**29 (53.7%)**	**53 (48.2%)**	**115 (44.1%)**	**218 (34.8%)**
Adverse events database	0	14 (12.7%)	3 (1.1%)	26 (4.1%)	2 (3.7%)	16 (14.5%)	9 (3.4%)	33 (5.3%)
SBP decrease ≥ 30 mmHg	1 (1.9%)	22 (20.0%)	14 (5.4%)	41 (6.5%)	6 (11.1%)	26 (23.6%)	29 (11.1%)	70 (11.2%)
SBP <90 mmHg	3 (5.6%)	17 (15.5%)	13 (5.0%)	28 (4.5%)	6 (11.1%)	20 (18.2%)	20 (7.7%)	35 (5.6%)
DBP decrease ≥ 15 mmHg	14 (25.9%)	28 (25.5%)	68 (26.1%)	97 (15.5%)	24 (44.4%)	44 (40.0%)	102 (39.1%)	188 (30.0%)

Ver Inj: vernakalant injection; DBP: diastolic blood pressure; SBP: systolic blood pressure

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

† Within a data source, patients may have experienced more than one hypotension event.

‡ Includes all non-serious adverse events starting after the start of the dose #1 through day 10, and serious adverse events starting after the start of the dose #1 through day 30

In summary, the number of patients with a history of CHF was small, but a trend towards an increased incidence of hypotension during the first 2 hours post dosing was observed in patients receiving vernakalant injection. The incidence of any ventricular arrhythmic event was also increased during this period. There was no difference in the incidence of bradycardia based on history of CHF. Additional studies are required to evaluate the safety of vernakalant injection in patients with CHF.

8.6 Laboratory Profile

Laboratory evaluations including mean changes from baseline in hematology and chemistry parameters in the individual studies did not reveal any findings suggestive of an effect of vernakalant injection. Mean values at post-dose time points were generally within the normal range for both the placebo and vernakalant injection treatment groups or were within clinically acceptable ranges for the study populations. Shifts from baseline to potentially

clinically significant high or low values were small and no clinically important differences were noted between the placebo and vernakalant injection treatment groups.

8.7 12-Lead ECG Data

8.7.1 ECG Findings in Healthy Volunteers

Study 1235-1-04-12-01 was a phase 1, single-blind, placebo-controlled, randomized study conducted to determine the safety of ascending single doses of vernakalant injection and to assess the pharmacokinetic parameters in healthy, normal volunteers. Data from 28 patients were included in the safety analyses. Single doses of vernakalant injection ranging from 0.1 mg/kg to 5 mg/kg were administered over a 10 minute period. 12-lead ECGs were obtained at screening and admission to the study facility, every minute during the 10 minute infusion, every minute for 10 minutes following the infusion, and 15 minutes, 30 minutes, 45 minutes, 60 minutes, 2 hours, 4 hours, 8 hours, 24 hours/discharge following the infusion, and at follow-up.

In patients who received 4 mg/kg and 5 mg/kg, mean heart rate increased slightly from baseline during the infusion (peak increases of 10 ± 8 bpm in the 4 mg/kg group and 14 ± 3 bpm in the 5 mg/kg group near the end of the infusion), resolving by approximately 30 minutes following dosing.

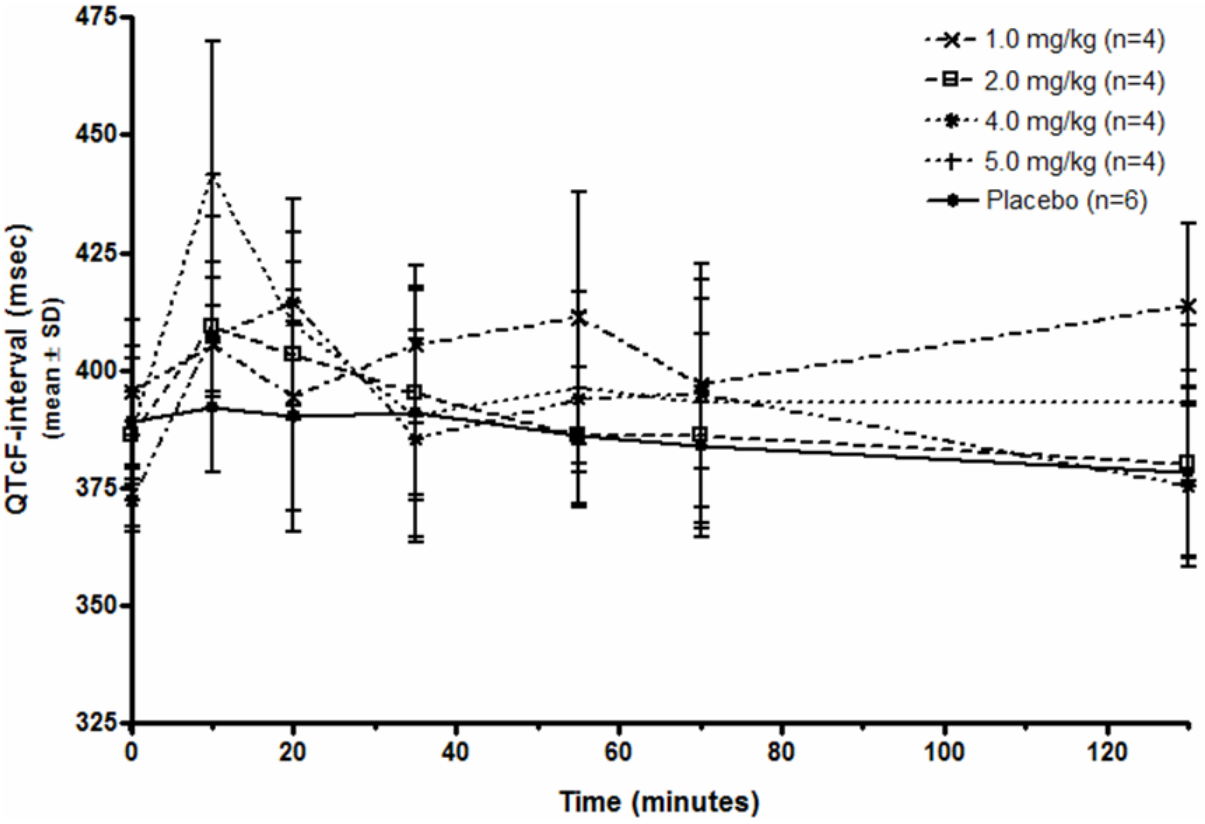
Mean PR intervals for the 4 mg/kg and 5 mg/kg dose groups increased from baseline during infusion and shortly thereafter (peak increases of 23 ± 7 msec for the 4 mg/kg group at 1 minute to the end of the infusion and 28 ± 9 msec for the 5 mg/kg group at 3 minutes following the infusion), with mean values remaining well under the preset upper threshold (>240 msec). The PR interval for one patient ranged from 185-215 msec during and following the infusion. It should be noted that this patient's predose PR interval was 191 msec. No individual PR interval reached the preset upper threshold during the trial.

Mean QRS intervals increased from baseline for the 4 mg/kg and 5 mg/kg groups near the end of the infusion (peak increases of 8 ± 6 msec at 2 minutes to the end of the infusion and 11 ± 3 msec at the end of the infusion, respectively). At the same time, mean QT intervals increased for the 4 mg/kg and 5 mg/kg groups, with peak increases of 35 ± 15 msec at 1 minute following the infusion for the 4 mg/kg group and 39 ± 8 msec at the end of the infusion for the 5 mg/kg group.

Mean QTcB intervals gradually increased from infusion onset, with peak increases of 56 ± 34 msec at 2 minutes to the end of the infusion for the 4 mg/kg group and 76 ± 16 msec at the end of the infusion for the 5 mg/kg group. Mean QTcF increased during the infusion, with peak increases of 48 ± 6 msec at 3 minutes to the end of the infusion for the 4 mg/kg group and 63 ± 10 msec at the end of the infusion for the 5 mg/kg group [Figure 11]. One patient in the 5 mg/kg group exceeded the preset QTc protocol threshold during the infusion, with QTcB values of 512 msec and 509 msec at 4 minutes to the end of infusion and the end of the infusion, respectively. This patient's QT interval was within normal range at these

same time points (418 msec and 426 msec, respectively), as was the QTcF (479 msec at both time points).

Figure 11: Mean QTcF Over Time in Study 1235-1-04-12-01 in Healthy Volunteers



8.7.2 ECG Findings in All Patients in Phase 2 and Phase 3 Studies

In the phase 2 and phase 3 studies, 12-lead ECGs were recorded frequently (every 5 minutes in the primary studies) in the first 50 minutes and at hour 2, hour 4, and hour 8 post dosing. ECGs were also recorded at the time of conversion to sinus rhythm, in the event of a serious adverse event, at discharge/24 hours and at the follow-up visit.

It should be noted for interpretation of ECG findings that other interventions (including electrical cardioversion, other antiarrhythmic drugs for conversion and/or maintenance of sinus rhythm) were permitted 2 hours after administration of study drug. It should also be noted that the data presented include patients in atrial fibrillation and sinus rhythm.

The ECG results document the direct effects of vernakalant injection on the ECG and the indirect effects due to conversion to sinus rhythm, which was associated with a large decrease in heart rate. This decrease in heart rate had substantial effects on QT interval measurements irrespective of any direct pharmacologic effect of treatment. There are a number of formulas to correct for heart rate when assessing the QT interval, with recognized

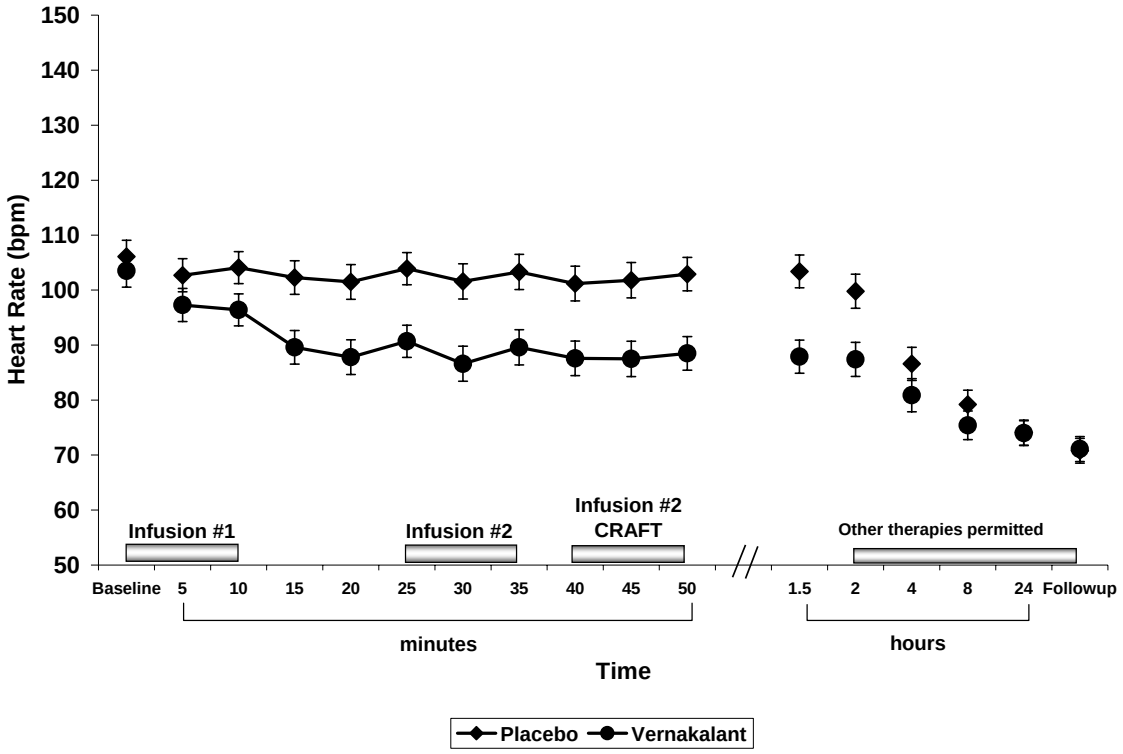
limitations (Malik, 2001). In reviewing the QT interval changes in the vernakalant injection studies, it is useful to keep in mind the following established relationships of heart rate and QT interval (Pritchett et al, 2002; Funck-Brentano et al, 1993):

- when heart rate decreases, the QT interval increases,
- when heart rate decreases, the QTcB interval decreases, and
- when heart rate decreases, QTcF is generally unchanged.

The peak direct effect of vernakalant injection on ECG parameters was usually recorded at or near the time when the infusion of dose 1 finished at minute 10, and a secondary peak was recorded at minute 35.

In the pooled population of all phase 2 and phase 3 studies, baseline mean heart rate was similar in the placebo group (106.1 ± 26.23 bpm) and vernakalant injection group (103.5 ± 27.05 bpm). Small decreases in mean heart rate (range -0.8 to -6.4 bpm) in the placebo group occurred at all time points through hour 2. Larger decreases in mean heart rate (range -4.0 to -16.0 bpm) occurred in the vernakalant injection group. From hour 4 through follow-up, larger mean decreases in heart rate occurred in the placebo group (-19.0 to -34.8) compared with the vernakalant injection group (-22.7 to -32.2). The mean heart rate at all time points is depicted in Figure 12.

Figure 12: Mean Heart Rate Over Time—All Phase 2 and Phase 3 Studies



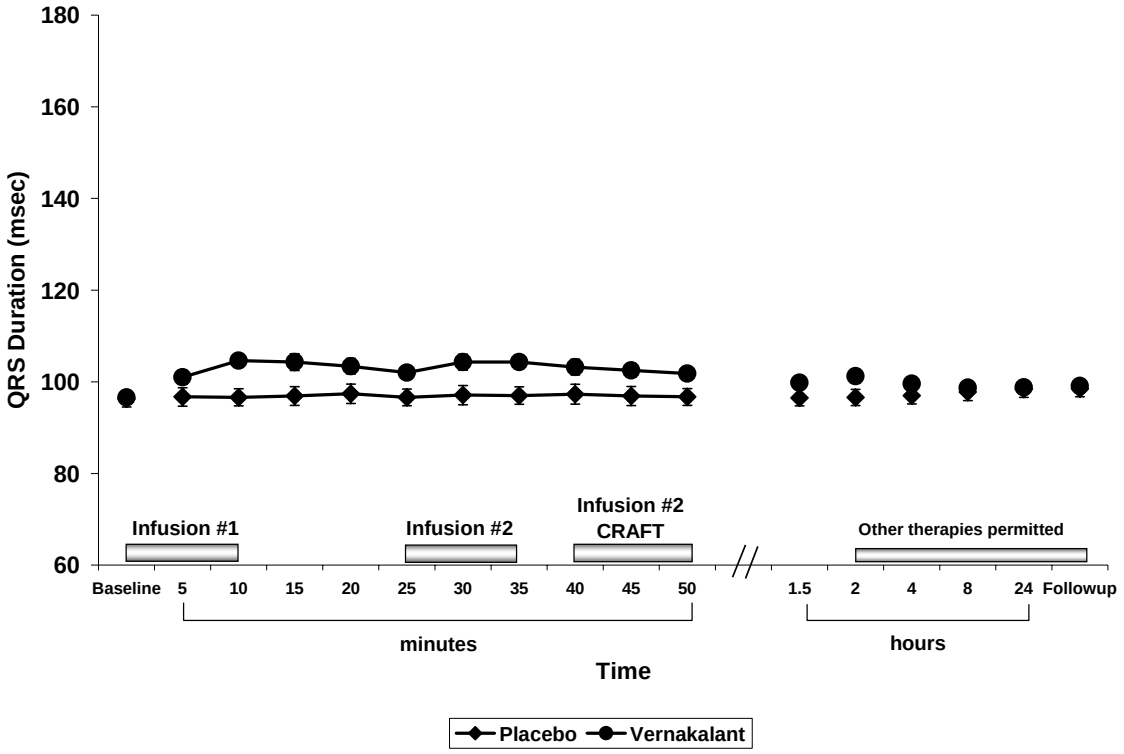
All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

Note: The observation period in CRAFT was 30 minutes, not 15 as in other studies.

Bars around the means represent the 95% confidence intervals. Statistically significant difference vernakalant injection group compared to placebo group at all time points minute 5 through hour 8 ($P<0.001$ through hour 2, $P=0.001$ at hour 4, $P=0.022$ at hour 8)

In the pooled population of all phase 2 and phase 3 studies, baseline mean QRS duration was 96.3 ± 15.67 in placebo patients and 96.6 ± 15.55 msec in the vernakalant injection patients. The QRS duration was essentially unchanged in the placebo group from baseline through hour 8, with small mean increases of 1.7 msec and 2.1 msec observed at hour 24 and follow-up, respectively. In the vernakalant injection group, the QRS duration increased to a maximum mean of 104 msec with each infusion, with peak placebo-subtracted changes of 7.6 msec and 6.9 msec. The increase in QRS duration contributed to increases in QT interval measures. Mean QRS duration at all time points is depicted in Figure 13.

Figure 13: Mean QRS Duration Over Time—All Phase 2 and Phase 3 Studies



All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

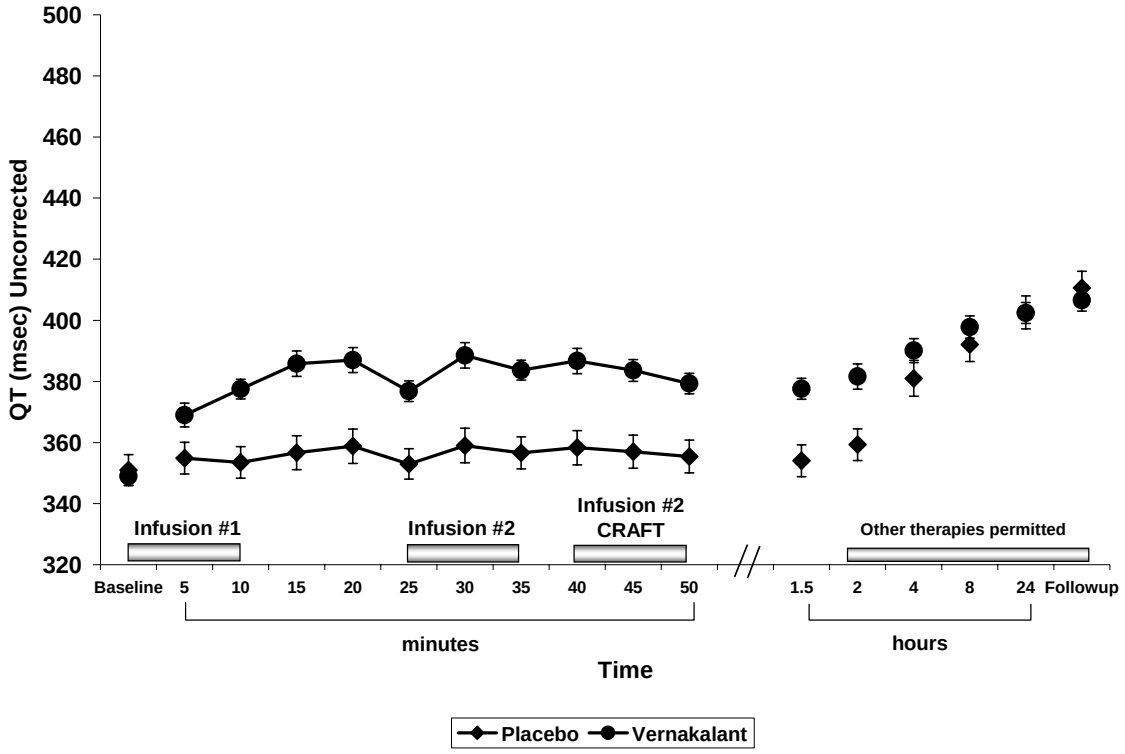
Note: The observation period in CRAFT was 30 minutes, not 15 as in other studies.

Bars around the means represent the 95% confidence intervals.

Statistically significant difference vernakalant injection group compared to placebo group at all time points minute 5 through hour 8 (P<0.001 through hour 4, P=0.002 at hour 8)

The baseline mean QT interval (uncorrected for heart rate) was 351.0 ± 43.88 msec in the placebo group and 349.0 ± 42.48 msec in the vernakalant injection group. In the placebo group, small mean increases in the QT interval occurred up to hour 2 (range +1.1 to +9.8 msec), and larger increases occurred from hour 2 to follow-up (+29.8 msec to +58.1 msec). The QT interval increased from baseline in the vernakalant injection group with a peak placebo-subtracted change from baseline of +30.5 msec at minute 15 (mean 356.7 ± 44.69 msec in the placebo group and 385.8 ± 44.45 msec in the vernakalant injection group) . At minute 35, the placebo-subtracted change was 28.2 msec (mean 356.6 ± 43.58 msec in the placebo group and 383.7 ± 40.97 msec in the vernakalant injection group). From hour 4 through the follow-up visit, the placebo-subtracted change decreased from +9.5 msec to -2.8 msec, respectively. Mean QT interval values at all time points are depicted in Figure 14.

Figure 14: Mean QT (uncorrected) Interval Over Time— All Phase 2 and Phase 3 Studies



All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

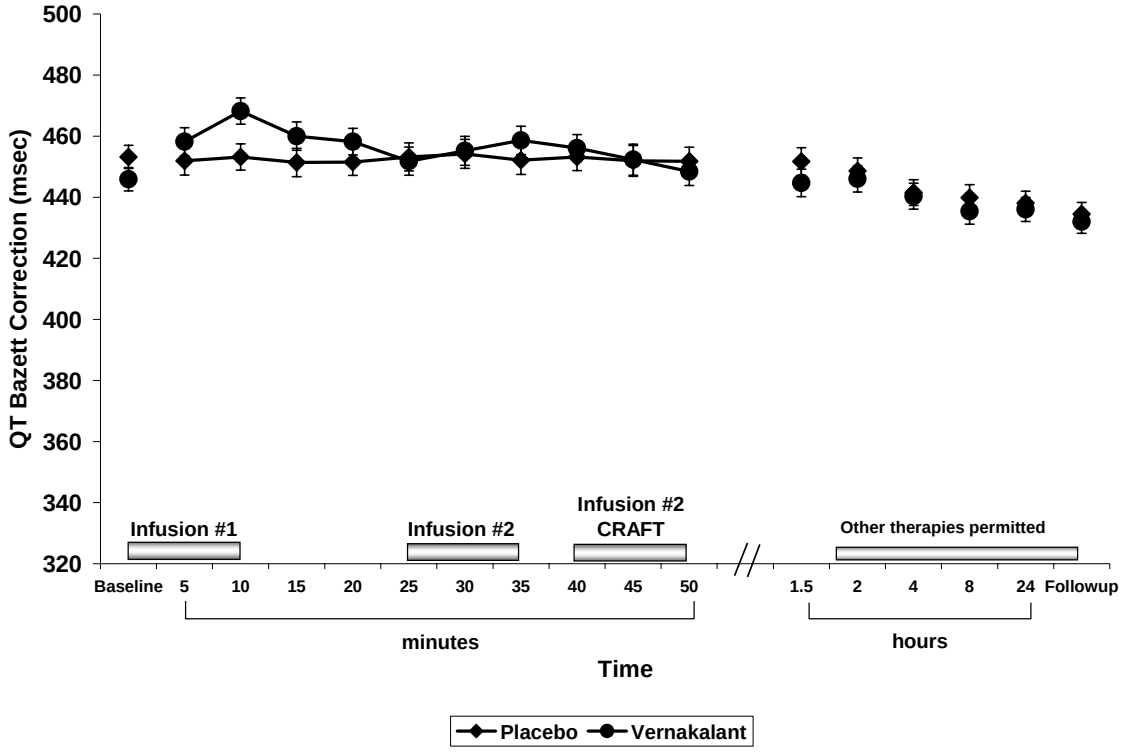
Note: The observation period in CRAFT was 30 minutes, not 15 as in other studies.

Bars around the means represent the 95% confidence intervals.

Statistically significant difference vernakalant injection group compared to placebo group at all time points minute 5 through hour 8 ($P<0.001$ through hour 4, $P=0.005$ at hour 8)

The baseline mean QT interval corrected for heart rate using Bazett's formula was similar in the placebo patients (453.2 ± 33.57 msec) and vernakalant injection patients (445.9 ± 31.98 msec). The mean QTcB interval increased following administration of vernakalant injection and the peak placebo-subtracted changes from baseline of +19.8 msec (minute 10) and +11.8 msec (minute 35). The placebo-subtracted change from baseline in the QTcB interval fell to -2.3 msec at minute 90, when the mean QTcB was 451.7 ± 39.31 msec in the placebo group and 444.7 ±36.77 msec in the vernakalant injection group. Mean QTcB interval values at all time points are depicted in Figure 15.

Figure 15: Mean QTcB Interval Over Time— All Phase 2 and Phase 3 Studies



All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

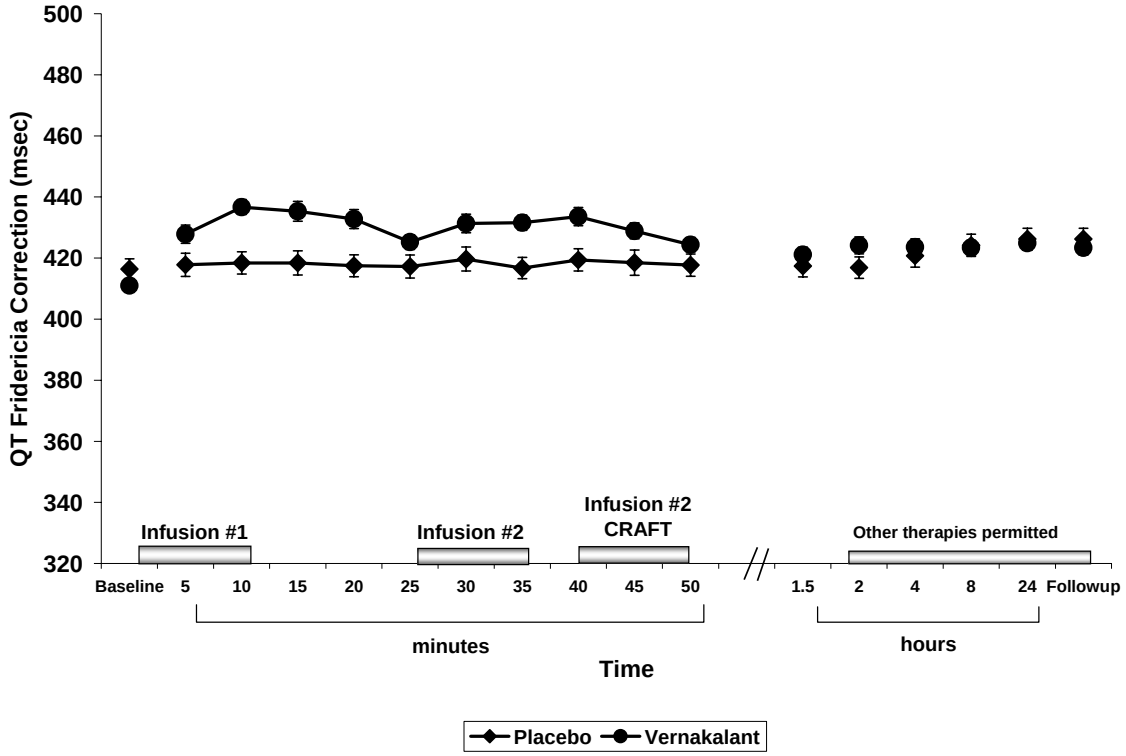
Note: The observation period in CRAFT was 30 minutes, not 15 as in other studies.

Bars around the means represent the 95% confidence intervals.

Statistically significant difference vernakalant injection group compared to placebo group at minute 5, minute 10, minute 15 ($P<0.001$), minute 20 ($P=0.001$), minute 35 ($P<0.001$), minute 40 ($P=0.021$), minute 45 ($P=0.0038$).

The baseline mean QT interval using Fridericia's correction formula was 416.4 ± 28.77 in the placebo group and 411.0 ± 27.41 msec in the vernakalant injection group. The QTcF interval increased following administration of vernakalant injection with peak placebo-subtracted increases observed at or near the end of the first infusion (+22.6 msec at minute 10 and +20.1 msec at minute 15) and at minute 35 (+19.1). At minute 90, the mean QTcF was 417.4 ± 31.86 msec in the placebo group and 421.1 ± 29.98 msec in the vernakalant injection group. Mean QTcF values at all time points are depicted in Figure 16.

Figure 16: Mean QTcF Interval Over Time— All Phase 2 and Phase 3 Studies



All phase 2 and phase 3 studies include the following: CRAFT, ACT I, Scene 2, ACT III, ACT II, ACT IV.

Note: The observation period in CRAFT was 30 minutes, not 15 as in other studies.

Bars around the means represent the 95% confidence intervals.

Statistically significant difference vernakalant injection group compared to placebo group at all time points minute 5 through hour 8 ($P<0.001$ through hour 2, $P=0.003$ at hour 4, $P=0.022$ at hour 8)

Shifts from baseline in QTcF were evaluated for patients in the phase 3 studies. A total of 4.3% of patients in the placebo group and 8.9% of patients in the vernakalant injection group shifted from QTcF ≤ 500 msec at baseline to >500 msec at any time point [Table 32]. The peak occurrence of QTcF >500 msec in the vernakalant injection group was at the end of the first infusion. The incidence of shifts in QTcF ≤ 550 msec at baseline to >550 msec at any time point was similar in the placebo group (0.7%) and the vernakalant injection group (1.0%).

Table 32: Shifts in QTcF Interval from ≤ 500 msec and ≤ 550 msec at Baseline to >500 msec and >550 msec—All Phase 3 Studies

Time	>500 msec†		>550 msec‡	
	Placebo N=300	Vernakalant Inj N=707	Placebo N=300	Vernakalant Inj N=707
Any Post-dose Time Point	12 (4.3%)	61 (8.9%)	2 (0.7%)	7 (1.0%)
Minute 5	3 (1.1%)	11 (1.6%)	0	1 (0.1%)
Minute 10	1 (0.4%)	17 (2.5%)	0	1 (0.1%)
Minute 15	3 (1.1%)	13 (1.9%)	0	1 (0.1%)
Minute 20	0	11 (1.6%)	0	1 (0.1%)
Minute 25	1 (0.4%)	7 (1.0%)	0	0
Minute 30	3 (1.1%)	0	0	1 (0.1%)
Minute 35	1 (0.4%)	9 (1.3%)	0	0
Minute 40	1 (0.4%)	6 (0.9%)	0	0
Minute 45	3 (1.1%)	6 (0.9%)	0	0
Minute 50	1 (0.4%)	11 (1.6%)	1 (0.4%)	1 (0.1%)
Minute 90	2 (0.7%)	5 (0.7%)	0	0
Hour 2	4 (1.4%)	6 (0.9%)	0	0
Hour 4	2 (0.7%)	3 (0.4%)	0	0
Hour 8	3 (1.1%)	2 (0.3%)	0	1 (0.1%)
Hour 24	3 (1.1%)	9 (1.3%)	0	2 (0.3%)
Follow-up	3 (1.1%)	9 (1.3%)	1 (0.4%)	2 (0.3%)

All phase 3 studies include the following: ACT I, Scene 2, ACT III, ACT II, ACT IV.

2 hours after administration of study drug, interventions which could have included electrical cardioversion and/or administration of antiarrhythmic drugs for conversion and/or maintenance of sinus rhythm were permitted

† Subjects shifted from ≤ 500 msec at baseline to >500 msec at the specified time point.

‡ Subjects shifted from ≤ 550 msec at baseline to >550 msec at the specified time point.

In summary, a prolongation of the QRS complex and QT interval corrected for heart rate (using both the Bazett and Fridericia formulas) was observed after vernakalant injection administration. The maximal placebo-subtracted changes from baseline were 8 msec for QRS, 20 msec for QTcB, and 23 msec for QTcF. The peak effect was seen at the end of the first infusion, with a second peak at the end of the second infusion. The QRS and QTcB returned to baseline within 2 hours. The placebo-corrected QTcF change from baseline was <5 msec within 4 hours. The incidence of shifts in QTcF ≤ 550 msec at baseline to >550 msec at any time point was similar in the placebo group (0.7%) and the vernakalant injection group (1.0%). These electrocardiographic changes suggest that, at therapeutic concentrations, vernakalant injection exhibits electrophysiological effects on ventricular repolarization. However, despite the QT prolongation, the incidence of ventricular arrhythmia after administration of vernakalant injection was similar to or less than after placebo.

8.8 Electrical Cardioversion in All Phase 2 and Phase 3 Studies

Within the first 24 hours, 58.4% (184/315) of subjects in the placebo group and 36.6% (270/737) of subjects in the vernakalant injection group underwent electrical cardioversion. Vernakalant injection 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 injection group. The median number of shocks and the median number of joules required for successful cardioversion was the same in both treatment groups (1 shock, 200 joules).

9 SUMMARY OF RISK BENEFIT

9.1.1 Limitations of Existing Treatments

While electrical cardioversion remains an important treatment option for patients with atrial fibrillation, particularly in hemodynamically unstable patients, the requirement for conscious sedation or anesthesia increases the risk of the procedure and makes it inappropriate for patients in a fed state, or those with impaired respiratory function. Electrical cardioversion has associated adverse cardiovascular effects, risk of pulmonary edema, and local complications, and may prolong recovery of normal atrial contraction compared with pharmacological conversion (Gallagher et al, 2007; Grönefeld, 2003;Manning et al, 1989; Mattioli et al, 1998; Harjai et al, 1997; Fatkin et al, 1994; Morris et al, 1965). Furthermore, although electrical cardioversion has been demonstrated to be effective at conversion of atrial fibrillation to sinus rhythm, these effects can be short lived, with immediate recurrence of atrial fibrillation (IRAF) within 1 to 10 minutes of electrical cardioversion in 9 to 12% of patients, and maintenance of sinus rhythm 24 hours and 1 week following cardioversion ranging from 71 to 95%, and 61 to 70%, respectively (Fuster et al, 2006; Ozdemir, 2006; Korantzopoulos et al, 2005; Sticherling et al, 2005; Ehrlich et al, 2003; Oral et al, 2003; Berry et al, 2001; Daoud et al, 2000; Van Gelder et al, 1999; Tieleman et al, 1998; Bianconi et al, 1996). Finally, electrical cardioversion is not desirable in a post-cardiac surgery population.

Pharmacologic cardioversion is a simpler treatment and avoids the risks of conscious sedation or anesthesia; however, existing agents are less efficacious than electrical cardioversion and have risks associated with their use. Only intravenous ibutilide and oral dofetilide are approved in the US for pharmacological conversion of atrial fibrillation. Both of these agents are associated with torsade de pointes (4% with ibutilide; 1 to 3.3% with dofetilide) and are more effective in converting atrial flutter than atrial fibrillation; conversion rates for atrial fibrillation ranged from 6 to 30% for dofetilide and from 25 to 38% for ibutilide, and in the case of dofetilide, may take days or longer for conversion (Fuster et al, 2006; (Corvert [ibutilide], Pharmacia, 2002; Tikosyn [dofetilide], Pfizer, 2004).).

9.1.2 Overview of the Vernakalant Injection Development Program

The vernakalant injection development program evaluated the efficacy and safety of vernakalant injection with the recommended dosing in patients with atrial fibrillation and atrial flutter ≤ 45 days of duration, stratified on the basis of atrial fibrillation duration; >3 hours to ≤ 7 days and >3 days to ≤ 45 days. The dosing regimen utilized in all phase 3 studies was an initial infusion of 3 mg/kg over 10 minutes. If conversion to sinus rhythm did not occur during a 15-minute observation period after the end of the initial infusion, a second 10-minute infusion of 2 mg/kg was administered. The primary efficacy endpoint for both pivotal trials was the proportion of patients with atrial fibrillation of > 3 hours to ≤ 7 days duration who converted to sinus rhythm within 90 minutes of first exposure to vernakalant injection for a minimum duration of 1 minute. Symptomatic relief of atrial fibrillation and the maintenance of sinus rhythm were also evaluated.

Nine clinical studies have been completed with vernakalant injection, including five studies in the target atrial fibrillation patient population. A total of 1164 adult subjects received treatment, of whom 823 received vernakalant injection and 341 received placebo. Of the 823 subjects who received vernakalant injection, 50 were healthy subjects and 773 had a history of atrial fibrillation or flutter.

The majority patients in the phase 2/phase 3 development program were male (68%), with a mean age of 63 years. Most vernakalant injection-treated patients received background rate control agents (72%, 554/773) with 20% (151/773) receiving rhythm control agents. Most patients (> 80%) presented with atrial fibrillation symptoms at baseline. A substantial proportion of patients had associated cardiovascular conditions: hypertension (52%), CHF (15%), low ejection fraction (25%), and ischemic heart disease (including history of myocardial infarction (24%). The incidence of these associated conditions is comparable to that in the target population (Gentile, 2002; Benjamin, 1998; Levy, 1999), suggesting the subjects enrolled into the vernakalant injection program are representative of patients seen in clinical practice.

Data from vernakalant injection studies demonstrate that, in patients with recent onset atrial fibrillation, the benefits of vernakalant injection outweigh its risks. Vernakalant injection rapidly restored sinus rhythm in approximately 50% of patients and was generally safe and well-tolerated. The development program has demonstrated that vernakalant injection provides a meaningful alternative to the current treatment options for conversion of atrial fibrillation to sinus rhythm.

9.1.3 Risks of Vernakalant Injection

Adverse events observed were generally transient, rarely treatment-limiting, and manageable in the clinical setting for which vernakalant injection is intended. The most common reported adverse events were dysgeusia, sneezing, paresthesia, nausea, and hypotension. Clinically important adverse events that were observed included ventricular arrhythmia,

bradycardia, and hypotension, which are not unexpected with converting therapies and in this patient population.

Ventricular arrhythmias are a major adverse effect of antiarrhythmic drugs. The incidence of any ventricular arrhythmia in the vernakalant injection treatment group was comparable to that of placebo (vernakalant injection 5.3%; placebo 6.3%) in the first 2 hours following infusion. A prolongation of the QRS complex and QT interval corrected for heart rate (using both the Bazett and Fridericia formulas) was observed after vernakalant injection administration. The maximal placebo-subtracted changes from baseline were 8 msec for QRS, 20 msec for QTcB, and 23 msec for QTcF. The peak effect was seen at the end of the first infusion, with a second peak at the end of the second infusion. The QRS and QTcB returned to baseline within 2 hours. The placebo-corrected QTcF change from baseline was < 5 msec within 4 hours. These electrocardiographic changes suggest that, at therapeutic concentrations, vernakalant injection exhibits electrophysiological effects on ventricular repolarization. However, despite the QT prolongation, the incidence of ventricular arrhythmia after vernakalant injection was similar to or less than after placebo. Three cases of torsade de pointes in patients who received vernakalant injection, compared to one case in the placebo group, were observed. One of these events was reported within 24 hours of vernakalant injection administration and immediately following an infusion of ibutilide. The rest occurred more than 24 hours after administration, at a time when plasma concentrations of vernakalant are close to the lower limit of detection. It is recommended that ibutilide be withheld for at least 24 hours after dosing with vernakalant injection.

An increase in the incidence of bradycardic events, such as sinus arrest, sinus bradycardia, and bradycardia, was observed in the vernakalant injection group in the 2 hours following infusion. Bradycardia is associated with any method of conversion to sinus rhythm (Gallagher et al, 2007). When the incidence of bradycardia is analyzed only using patients remaining in atrial fibrillation, there is no evidence of an increased risk of drug-related bradycardia in the vernakalant injection group.

An increased incidence of hypotension adverse events was observed in patients receiving vernakalant injection (5.4%; 40/737) compared to placebo (1.0%; 3/315) in the first 2 hours following infusion. These events were peri-infusional, generally mild or moderate, and responded to cessation of dosing and administration of fluids. Hypotension was considered a serious adverse event or resulted in discontinuation of study medication in 10 patients receiving vernakalant injection. In these cases, hypotension occurred during the infusion or within 15 minutes after the end of the infusion and responded to Trendelenburg position and fluid administration.

There was an increase in the incidence of hypotension in patients with a history of CHF. In patients with a history of CHF, adverse events of hypotension were reported in 12.7% (14/110) of patients receiving vernakalant injection and 0% of patients receiving placebo (0/54). In patients with no history of CHF, adverse events of hypotension were reported in 4.1% (26/627) of patients receiving vernakalant injection and 1.1% (3/261) of patients receiving placebo. No increase in the incidence of hypotension was seen in patients with a

history of ischemic heart disease. Additional studies are required to evaluate the safety of vernakalant injection in patients with CHF.

Five deaths occurred in patients who received vernakalant injection. The cause of death was unique in each patient (hypotension/ventricular fibrillation in a patient with severe aortic stenosis; inoperable lung cancer, dissecting aortic aneurysm; heart failure/pulmonary edema; and breast cancer/GI hemorrhage) and showed neither a temporal relationship, nor a common pathophysiological or pharmacological cause that may have contributed to their deaths. One of these deaths was in a patient with severe aortic stenosis, acute coronary syndrome and a decreased ejection fraction and was related to vernakalant injection. This patient presented with chest pain and was in atrial fibrillation with rapid ventricular response for about 4 hours before receiving medical care and presented to the hospital in heart failure. His ECG showed changes consistent with myocardial injury with serum troponin levels 6 times the upper limit of normal prior to administration of vernakalant injection. This patient became hypotensive following administration of metoprolol and vernakalant injection and subsequently developed a fatal ventricular rhythm.

The safety profile of vernakalant injection was similar when stratified by age, sex, or the prior use of rate and rhythm control medications. During the development program, certain patient populations were excluded. These include:

- Severe aortic stenosis
- Unstable heart failure
- Hemodynamically unstable
- Acute myocardial infarction

Therefore, appropriate clinical precautions should be taken in these patients.

9.1.4 Benefits of Vernakalant Injection

Vernakalant injection effectively converted atrial fibrillation of duration >3 hours to ≤ 7 days to sinus rhythm (51.1%). In the patients who converted to sinus rhythm, the median time to conversion was 10 minutes. This effect was consistent (50.9% to 52.9%) across all phase 2 and phase 3 trials. Vernakalant injection was effective at converting atrial fibrillation to sinus rhythm (47.0%) in the post-cardiac surgery population, a population in whom electrical cardioversion is not desirable.

In the clinical program, vernakalant injection provided rapid symptomatic relief associated with the conversion to sinus rhythm (34.5% reduction of atrial fibrillation symptoms within 90 minutes). Sinus rhythm was maintained after atrial fibrillation conversion (100% at 24 hours in patients not receiving additional anti-arrhythmic medication).

Vernakalant injection was safe and effective in a broad atrial fibrillation population, including new or recurrent atrial fibrillation and in patients with a variety of co-morbidities such as hypertension and ischemic heart disease. The co-administration of oral rate and rhythm control agents did not affect the safety or the effectiveness of vernakalant injection.

Of note is that vernakalant injection did not affect the effectiveness of electrical cardioversion in patients who failed to convert. Electrical cardioversion was attempted in 72% of patients in the placebo group and 41% of patients in the vernakalant injection group and was successful in 89.2% and 90% of subjects who had received vernakalant injection and placebo, respectively.

Plasma concentrations of vernakalant decrease sharply following the end of infusion with an alpha half-life of 3 to 6 minutes and a mean elimination half-life of approximately 2 hours. The pharmacokinetics of vernakalant are not significantly affected by age, sex, renal function, or a history of CHF. Although no formal pharmacokinetic studies were conducted in subjects with hepatic impairment, drug distribution appears to be the primary mechanism responsible for termination of the pharmacologic effect and the compound is intended for acute use. Thus, significant accumulation is not expected and it is unlikely dosing adjustments will be necessary in subjects with hepatic impairment. Significant drug-drug interactions are not expected based on a population pharmacokinetic analysis and clinical experience from the development program.

9.1.5 Conclusions

Given the limitations of current pharmacological agents used to acutely convert atrial fibrillation and the necessity for conscious sedation or anesthesia for electrical cardioversion, there is a need for better agents to convert atrial fibrillation. The vernakalant injection clinical development program demonstrated that vernakalant injection was safe and effective in patients with new or recurrent atrial fibrillation, including those with post-operative atrial fibrillation. Vernakalant injection restored sinus rhythm and provided relief of symptoms in approximately 50% of patients and further demonstrated a low rate of adverse cardiac events, including arrhythmia. Other clinically relevant adverse events, bradycardia (generally associated with conversion) and hypotension were generally transient and responded to discontinuation of study drug and appropriate medical management.

In conclusion, the data from vernakalant injection studies indicate that, in most patients with recent onset atrial fibrillation for whom rapid cardioversion is indicated, the benefits of vernakalant injection outweighs its risks.

Vernakalant injection provides an important treatment option to physicians and their patients for the rapid pharmacological conversion of atrial fibrillation to sinus rhythm.

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