A Randomized Placebo-Controlled Study of Vernakalant (Oral) for the
Prevention of Atrial Fibrillation Recurrence Post-Cardioversion

Running title: Torp-Pedersen et al.; Vernakalant to Prevent AF Recurrence

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Journal Subject Codes: [5] Arrhythmias, clinical electrophysiology, drugs
Abstract:

**Background** - Vernakalant, a relatively atrial-selective antiarrhythmic drug, has previously demonstrated efficacy for the acute conversion of atrial fibrillation (AF) to sinus rhythm. This study was designed to determine the most appropriate oral dose of vernakalant for the prevention of AF recurrence post-cardioversion.

**Methods and Results** - Patients with non-permanent AF were randomized to 150, 300, or 500 mg vernakalant or placebo twice daily (BID) for up to 90 days. The efficacy analysis was conducted on 605 of 735 patients who entered the maintenance phase on Day 3 following cardioversion. The time to the first recurrence of symptomatic sustained AF was significantly longer in the 500 mg vernakalant group, with a median of >90 days versus 29 days in the placebo group (hazard ratio 0.735, \( P = 0.0275 \)). No significant effect was seen at the lower doses. The percent of patients in sinus rhythm at Day 90 was 41%, 39%, and 49% in the 150 mg (N=147), 300 mg (N=148), and 500 mg (N=150) vernakalant groups, respectively, compared to 36% in the placebo group (N=160). There were no vernakalant-related proarrhythmic events. Related serious adverse events occurred in two patients in the 150 mg vernakalant group and in one patient in each of the other groups.

**Conclusions** - Vernakalant, 500 mg BID, appears to be effective and safe for the prevention of AF recurrence after cardioversion. The absence of proarrhythmia and favorable safety profile is an important finding for the drug.

**Clinical Trial Registration Information** - Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00526136).

**Key words:** antiarrhythmia agents, arrhythmia, cardioversion, prevention, vernakalant
Maintenance of sinus rhythm is a necessary goal in many patients with paroxysmal or persistent atrial fibrillation (AF). In the Euro Heart Survey, 1 77% of patients with paroxysmal or persistent AF received pharmaceutical rhythm control therapy. Currently available antiarrhythmic drugs have important limitations. The most effective compound, amiodarone, is associated with severe non-cardiac side effects. 2,3 Class 1C antiarrhythmics and sotalol are associated with risks of proarrhythmia which limit their use. 4 Finally, the newly registered dronedarone was significantly inferior to amiodarone for the composite primary endpoint of time to first AF recurrence or premature study drug discontinuation (due to intolerance or lack of efficacy). 5 Thus, there is a continued need to develop safe and efficacious antiarrhythmic drugs.

Vernakalant represents a novel class of antiarrhythmics being developed for conversion as well as maintenance of sinus rhythm after conversion. The electrophysiological properties differ from currently available compounds. Vernakalant has relative atrial specificity and targets early-activating and acetylcholine-activated potassium channels, and also has a weak effect on sodium channels in atria and ventricles. 6-8 Vernakalant slows conduction at rapid pacing rates and prolongs atrial refractoriness. The intravenous formulation has been demonstrated to rapidly convert recent onset AF to sinus rhythm in several clinical trials, 9-14 and has recently been approved by regulatory authorities in Europe. Vernakalant is currently being developed for the maintenance of sinus rhythm in the hope that it may deliver efficacious as well as safe therapy. The current study was designed to select the most appropriate oral dose of vernakalant for the prevention of AF recurrence after successful cardioversion.
Methods

Study Design

This was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose ranging study performed in compliance with the guidelines for good clinical practice and the Declaration of Helsinki. The study was approved by an institutional review board or ethics committee at each site, and written informed consent was obtained from patients prior to enrollment in the study.

Eligible patients were males and females 18-85 years of age and weighing 45-113 kg, with symptomatic AF (sustained for 72 hours to 6 months) for which cardioversion was indicated. Patients were required to be hemodynamically stable (systolic blood pressure >100 mmHg but <190 mmHg) at screening and prior to dosing, and adequately anticoagulated in accordance with guidelines.2

Patients with any of the following criteria were excluded from the study: known prolonged QT syndrome, QTcB interval >500 msec, familial long QT syndrome, previous torsades de pointes (TdP), ventricular fibrillation, or sustained ventricular tachycardia (VT); QRS interval >140 msec; second or third degree atrioventricular block; clinically significant persistent bradycardia with heart rate <50 beats per minute, sick sinus syndrome, or pacemaker; clinically significant moderate or severe aortic valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis; New York Heart Association Class III or IV congestive heart failure or hospitalization for heart failure in the previous 6 months; myocardial infarction, cardiac surgery, angioplasty, unstable angina, or acute coronary syndrome within 30 days prior to enrollment; serious or end-stage disease states; known temporary secondary causes of AF; uncorrected electrolyte imbalance; digoxin toxicity;
concurrent participation in another drug study; or receipt of an investigational drug within
30 days prior to screening. Women were not pregnant or nursing, and if premenopausal, were
using birth control. Patients were also excluded if they had received Class I or III antiarrhythmic
drugs (including sotalol) within 3 days (or oral amiodarone within 4 weeks) of randomization, or
intravenous Class I or III antiarrhythmics or amiodarone within 24 hours prior to dosing.

Eligible patients were randomly allocated (in a 1:1:1:1 ratio) to placebo or 1 of 3 doses of
oral vernakalant: 300, 600, or 1000 mg daily (150, 300, or 500 mg twice daily [BID]). Patients
were stratified according to the use of angiotensin converting enzyme inhibitors (ACEIs) and/or
angiotensin receptor blockers (ARBs) versus non-use of these drugs.

Patients were monitored in hospital for at least 3 days from the beginning of treatment.
If sinus rhythm was not restored after 3 days of drug exposure, electrical cardioversion was
performed. Successfully cardioverted patients (sinus rhythm maintained for >90 minutes) entered
the maintenance phase of the study and treatment was continued for up to 90 days. Rate control
medications were withheld on the day of electrical cardioversion until after the cardioversion
procedure and the establishment of an adequate heart rate. Patients were not permitted to receive
Class I or III antiarrhythmics until at least 48 hours after the completion of dosing.

Study drug was to be discontinued if any of the following occurred: failed electrical
cardioversion on Day 3; recurrence of AF (or other atrial tachyarrhythmia) documented by
two 12-lead electrocardiograms (ECGs) taken 90 minutes apart (all of these events were to be
recorded as adverse events [AEs] or serious adverse events [SAEs]); ventricular fibrillation;
sustained monomorphous VT (duration >30 seconds), incessant VT (recurrent VT episodes lasting
≤30 seconds), or polymorphous VT (e.g., TdP); symptomatic or clinically significant bradycardia
(persistent heart rate <45 beats per minute); QTcB prolongation (>550 msec); persistent systolic
blood pressure >190 mmHg or <85 mmHg; use of prohibited concomitant medications; seizures; syncope; any changes in cardiac rhythm or atrioventricular conduction that compromised the patient’s safety; or any intolerable side effects.

Study visits in the outpatient clinic were scheduled on Days 10, 17, 28, 56, and 90 after randomization. A final follow-up telephone call was performed 30 days after the last dose of study drug for all patients. Safety assessments included 12-lead ECGs, vital signs, clinical laboratory parameters, and physical examinations. Adverse events were recorded through the final follow-up visit and SAEs were recorded through the final follow-up telephone call. Patients recorded their cardiac rhythm each day until the end of the study using a transtelephonic monitor (TTM), and were also instructed to record the presence or absence of symptoms related to AF in a daily diary.

**Study Endpoints**

This study had multiple “time-to-event” endpoints that were assessed through 12-lead ECGs taken at scheduled visits and TTM devices used daily by patients to record a single lead 30-second ECG tracing. Multiple cardiologists (both the treating physician and the core lab cardiologist, who were blinded to treatment assignment) assessed the recurrence of AF through the 12-lead ECG and TTM data. Symptoms were assessed through a diary completed by patients on a daily basis; the recurrence of AF was only considered symptomatic if the patient diary was dated the day of or the day before the ECG and/or TTM showing AF.

Efficacy endpoints included the time to the first documented recurrence of 1) symptomatic sustained AF per TTM or investigator decision (sustained AF required two positive TTM recordings taken at least 20 hours apart, and symptoms as defined above); 2) AF determined by investigator assessment only; 3) symptomatic AF based on 12-lead ECG (required
two 12-lead ECGs showing AF recorded at least 75 minutes apart, and symptoms as defined above); and 4) any AF recurrence (also required two 12-lead ECGs showing AF recorded at least 75 minutes apart).

Additional efficacy endpoints included the proportion of patients in sinus rhythm at Day 90, improvement in AF symptoms as assessed by an AF symptom checklist, and improvement in quality of life as measured by the Short Form (SF)-36 Health Survey.

**Statistical Analyses**

Sample size calculation was based on the hypothesis of an AF recurrence rate of 60% on placebo at 90 days and a 40% relative reduction in recurrence rate on at least one dose of vernakalant, assessed using a two-sided log-rank test with a 5% significance level and 80% power. This resulted in an estimated sample size of 500 patients (125 per group) entering the maintenance phase of the study. Assuming a 20% to 25% dropout rate during the first 3 days as a result of failure to achieve sinus rhythm, a minimum of 670 patients was planned.

Two interim analyses were performed to assess the safety and tolerability of the study drug, but did not result in modification or early termination of the study.

There were two analysis populations defined in this study. The safety population was used for the safety analyses and consisted of all randomized patients who took at least one dose of study drug. The modified intent-to-treat population was used for the efficacy analyses and consisted of all randomized patients who took at least one dose of study drug and were discharged in sinus rhythm (by Day 3) into the maintenance phase of the study.

Time to event was compared with a log-rank test stratified for ACEI/ARB use. A Cox proportional hazards model, with factors for ACEI/ARB use and treatment group, was used to
estimate the hazard ratio and respective 95% confidence interval for each pair-wise comparison with placebo.

Treatment group comparisons of the change from baseline for the severity and frequency domains of the symptom checklist and the 8 domains of the SF-36 were based on an analysis of covariance model with treatment group, ACEI/ARB use, and baseline score as covariates.

As this was a phase 2 dose ranging study, all analyses were considered exploratory and no adjustment for multiplicity was performed.

Results

Patient Characteristics

From April 2007 to July 2008, 735 patients were enrolled into the study at 152 centers in 24 countries. There were 732 patients who received study drug, and 605 patients were discharged in sinus rhythm and were available for efficacy analyses (Figure 1). All 4 treatment groups were well balanced in regards to baseline characteristics (Table 1).

Efficacy

A summary of the endpoints used to assess the time to first recurrence of AF is presented in Table 2. There was a statistically significant reduction in the recurrence of symptomatic sustained AF with vernakalant 500 mg BID compared to placebo (Figure 2). This effect was not significant at the lower doses. The median time to the first recurrence of symptomatic sustained AF was 29 days in the placebo group and >90 days in the vernakalant 500 mg group (hazard ratio 0.735, \( P = 0.028 \)).

Based on the investigator’s assessment, vernakalant 500 mg BID resulted in a 26% reduction in the rate of AF recurrence (irrespective of symptoms) (hazard ratio 0.743,
Based on the 12-lead ECG assessment, there was a 45% reduction in the rate of symptomatic AF recurrence with vernakalant 500 mg BID (hazard ratio 0.553, \( P = 0.023 \)). The 150 and 300 mg BID doses did not provide a benefit in reducing the rate of sustained or symptomatic AF recurrence as compared to placebo. There was not a statistically significant reduction in the rate of recurrence of any AF (symptomatic or asymptomatic).

Patients who received vernakalant and in whom sinus rhythm was restored were more likely to be in sinus rhythm after 90 days of treatment than patients who received placebo. There were 57/160 patients (36%) in the placebo group, 61/147 patients (41%) in the 150 mg group (P=0.296 vs placebo), 57/148 patients (39%) in the 300 mg group (P=0.603 vs placebo), and 73/150 patients (49%) in the 500 mg group (P=0.021 vs placebo) still in sinus rhythm at Day 90. Considering the intent-to-treat population of all randomized patients, a post-hoc analysis demonstrated that 57/184 patients (31%) in the placebo group were in sinus rhythm at Day 90 compared to 73/183 patients (40%) in the vernakalant 500 mg BID group, demonstrating that patients in the 500 mg group were 1.29 times more likely to be in sinus rhythm after 90 days compared to placebo (P=0.074).

No significant differences between treatment groups were observed for the frequency or severity scores of the symptom checklist, or in any of the 8 domains of the SF-36. An exploratory analysis of the frequency and severity scores from the symptom checklist showed that patients (regardless of treatment) experienced fewer and less severe symptoms when in sinus rhythm compared to when in AF.
Safety

Table 3 outlines the incidence of treatment-emergent AEs, SAEs, and discontinuations due to AEs for the safety population. Four deaths were reported in this study (none of which were considered to be related to treatment): two in the placebo group and one each in the 150 and 300 mg vernakalant groups. The two placebo deaths consisted of a 58-year-old male who died following myocardial infarction and a 70-year-old male who died following an ischemic stroke.

In the 150 mg group, a 70-year-old female died of cervical cancer, which was undiagnosed prior to entering the study. In the 300 mg group, a 59-year-old female died of pneumonia and pulmonary embolism following mitral valvuloplasty and annuloplasty, approximately 4 weeks after her last dose of study drug.

The incidence of SAEs was similar among treatment groups. The most common SAE was hospitalization associated with the recurrence of AF, reported in 11 of 184 patients (6.0%) in the placebo group, 7 of 183 patients (3.8%) in each of the 150 and 300 mg groups, and 9 of 182 patients (4.9%) in the 500 mg group. Five patients (1 placebo, 4 vernakalant) had SAEs that were considered by the investigator to be related to treatment: ventricular tachycardia prior to electrical cardioversion (during the induction of anesthesia) in the placebo group; angina pectoris and conduction disorder in the 150 mg BID group; atrial flutter in the 300 mg BID group; and sinus arrest at the time of electrical cardioversion in the 500 mg BID group.

The most frequent related AE was bradycardia, occurring in 5 patients (2.7%) in the 500 mg group, and in 2 patients (1.1%) in each of the other groups. Most of the discontinuations due to AEs were for the recurrence of AF, which occurred more frequently in the placebo group. There were 8 (1.5%) vernakalant patients who discontinued study drug due to related AEs (other
than AF recurrence or atrial flutter). In the placebo group, there was one (0.5%) premature discontinuation for a related AE of AF recurrence.

In terms of cardiovascular side effects, no treatment-related proarrhythmic events (including TdP) were reported with vernakalant. In addition to the aforementioned related SAE of VT in the placebo group, an unrelated episode of VT (7-beat monomorphic run) was reported two days after discontinuation of vernakalant 500 mg BID.

There was no effect of vernakalant on QRS duration; however, the QTcF interval showed a mean prolongation of 5.8 msec (95% confidence interval 3.54-7.96) in the vernakalant 500 mg group compared to placebo after steady state was reached. No significant increases were observed in the 150 or 300 mg groups. The proportion of patients with a QTcF interval >500 msec at Day 10 was 0.7% (1 patient), 0.8% (1 patient), 2.3% (3 patients), and 1.5% (2 patients) in the placebo, 150, 300, and 500 mg groups, respectively. On subsequent visits, there was only one patient in each of the placebo and 300 mg groups with a QTcF interval >500 msec.

There were no clinically significant trends over time or differences between treatment groups in vital signs, laboratory parameters, or physical examination findings.

Discussion

Main Study Findings

The results of this study demonstrate that after conversion to sinus rhythm, vernakalant at a dose of 500 mg BID significantly delayed the time to first AF recurrence when compared to placebo. The drug was safe and well tolerated during exposure up to 90 days, and no proarrhythmic reactions were observed.
Antiarrhythmic Efficacy

Vernakalant at a dose of 500 mg BID prolonged the time to the first recurrence of symptomatic sustained AF by >3-fold compared to placebo, from a median of 29 to >90 days. This was associated with a sinus rhythm maintenance rate at 90 days of 49% in vernakalant-treated patients, compared to the placebo rate of 36%. Consistent with other post-cardioversion studies,15,16 our study population appears to be at a high risk for AF recurrences. The efficacy analyses were based on relatively frequent hospital visits in conjunction with a daily recording on a TTM device and a daily symptom diary, allowing for robust detection of early symptomatic and sustained AF recurrences.

Safety

There was no evidence for vernakalant-associated proarrhythmia in this study. Importantly, no cases of TdP were observed, which is consistent with vernakalant’s relatively atrial-selective electrophysiological profile.6-8 The effect of vernakalant on the QTc interval was small at the highest dose. Vernakalant also proved to be hemodynamically well tolerated. The incidence of related SAEs was very low (0.5% at 500 mg BID), with no dose relationship or target organ system.

Other Antiarrhythmics

It has been estimated that over 50% of patients have a recurrence of AF within one year of restored sinus rhythm on most currently available antiarrhythmics.17 Of the various Class I and III antiarrhythmics that have been studied in controlled trials for the maintenance of sinus rhythm,15 amiodarone has shown the highest rate of efficacy.16 However, amiodarone has numerous side effects and has reported discontinuation rates due to side effects in up to 23% of patients over the course of 1-2 years.3 Dronedarone appeared to have a better safety profile
compared to amiodarone in patients with persistent AF; however, dronedarone was significantly less effective than amiodarone in decreasing the recurrence of AF.\textsuperscript{5} In the large outcome study, ATHENA,\textsuperscript{18} dronedarone reduced all-cause mortality and cardiovascular hospitalization compared to placebo in AF patients at risk for a cardiovascular event; however, questions still remain about dronedarone’s place in the treatment of AF.\textsuperscript{19}

**Study Limitations**

The relatively small sample size was a limitation. The 90-day treatment and assessment period was too short to assess any long term benefit or difficulties that patients with AF could expect from vernakalant treatment. Using time to first relapse and having a single relapse result in treatment termination does not capture the potential benefits or futility that additional cardioversions and treatment courses may have in influencing a patient’s AF burden over time. Another limitation was that no adjustments for multiplicity were performed.

**Conclusions**

This dose ranging study demonstrated that vernakalant was safe and well tolerated in patients with symptomatic sustained AF, and that 500 mg BID was effective for the maintenance of sinus rhythm following cardioversion. The favorable safety profile associated with vernakalant appears to be a significant advancement in the treatment of AF.

**Acknowledgments:** Cardiome Pharma Corp (Vancouver, British Columbia, Canada) sponsored the study, and is indebted to the staff of the participating hospitals for their care and assistance in conducting the study. A list of the institutions where the work was performed is available in the supplemental material.

**Funding Sources:** This study was funded and supported by Cardiome Pharma Corp.
Conflict of Interest Disclosures: Christian Torp-Pedersen, MD, has received consultant fees, honoraria, and speaker’s fees from Cardiome Pharma Corp and Merck, and has been an advisory board and steering committee member for Cardiome Pharma Corp and Merck. Dimitar H. Raev, MD, PhD, was a principal investigator in this clinical trial. Garth Dickinson, MD, is a paid consultant for Cardiome Pharma Corp. Noam N. Butterfield, PhD, Brian Mangal, MSc, and Gregory N. Beatch, PhD, are full time employees of Cardiome Pharma Corp.

References:


Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=184)</th>
<th>150 mg BID (N=183)</th>
<th>300 mg BID (N=183)</th>
<th>500 mg BID (N=182)</th>
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<tr>
<td>Male, n (%)</td>
<td>128 (69.6)</td>
<td>116 (63.4)</td>
<td>127 (69.4)</td>
<td>121 (66.5)</td>
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<td>White, n (%)</td>
<td>182 (98.9)</td>
<td>180 (98.4)</td>
<td>179 (97.8)</td>
<td>181 (99.5)</td>
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<tr>
<td>Age (years), mean (SD)</td>
<td>62.8 (10.2)</td>
<td>63.7 (10.1)</td>
<td>61.9 (11.1)</td>
<td>64.2 (10.5)</td>
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<td>Number of Prior AF Episodes, n (%)</td>
<td></td>
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<tr>
<td>0</td>
<td>92 (50.0)</td>
<td>96 (52.5)</td>
<td>91 (49.7)</td>
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<td>1-3</td>
<td>61 (33.2)</td>
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<td>60 (32.8)</td>
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<td>&gt;3</td>
<td>31 (16.8)</td>
<td>34 (18.6)</td>
<td>32 (17.5)</td>
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<td>Duration of Current AF Episode (days)</td>
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<td>Mean (SD)</td>
<td>81.1 (46.6)</td>
<td>76.2 (48.7)</td>
<td>74.9 (48.1)</td>
<td>74.4 (47.0)</td>
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<td>Median</td>
<td>76.0</td>
<td>66.0</td>
<td>68.0</td>
<td>66.5</td>
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<td>Last Attempt at Electrical Cardioversion Prior to Study Enrollment, n (%)</td>
<td>15 (8.2)</td>
<td>4 (2.2)</td>
<td>6 (3.3)</td>
<td>3 (1.6)</td>
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<tr>
<td>Failure</td>
<td>79 (42.9)</td>
<td>83 (45.4)</td>
<td>87 (47.5)</td>
<td>86 (47.3)</td>
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<td>Success</td>
<td>90 (48.9)</td>
<td>96 (52.5)</td>
<td>90 (49.2)</td>
<td>93 (51.1)</td>
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<td>Medical History, n (%)</td>
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<td>Hypertension</td>
<td>145 (78.8)</td>
<td>142 (77.6)</td>
<td>142 (77.6)</td>
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<td>Ischemic heart disease</td>
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<td>Diabetes</td>
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<td>Valvular heart disease</td>
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<td>Myocardial infarction</td>
<td>15 (8.2)</td>
<td>9 (4.9)</td>
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<td>Congestive heart failure</td>
<td>83 (45.1)</td>
<td>72 (39.3)</td>
<td>64 (35.0)</td>
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<td>NYHA Class I</td>
<td>21 (11.4)</td>
<td>13 (7.1)</td>
<td>17 (9.3)</td>
<td>18 (9.9)</td>
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<tr>
<td>NYHA Class II</td>
<td>62 (33.7)</td>
<td>59 (32.2)</td>
<td>47 (25.7)</td>
<td>45 (24.7)</td>
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<tr>
<td>LADD and LVEF, mean (SD)</td>
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<tr>
<td>LADD (mm)</td>
<td>45.9 (6.4)</td>
<td>44.9 (6.6)</td>
<td>45.4 (6.2)</td>
<td>45.1 (6.1)</td>
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<tr>
<td>LVEF (%)</td>
<td>54.0 (9.6)</td>
<td>54.7 (10.0)</td>
<td>54.6 (10.2)</td>
<td>54.7 (9.5)</td>
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<tr>
<td>Medications Used Within 7 Days Prior to the First Dose of Study Drug, n (%)</td>
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<tr>
<td>Any rhythm control†</td>
<td>6 (3.3)</td>
<td>6 (3.3)</td>
<td>9 (4.9)</td>
<td>11 (6.0)</td>
</tr>
<tr>
<td>Class I antiarrhythmics†</td>
<td>4 (2.2)</td>
<td>3 (1.6)</td>
<td>5 (2.7)</td>
<td>4 (2.2)</td>
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<tr>
<td>Class III antiarrhythmics†</td>
<td>2 (1.1)</td>
<td>3 (1.6)</td>
<td>4 (2.2)</td>
<td>8 (4.4)</td>
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<tr>
<td>Any rate control‡</td>
<td>160 (87.0)</td>
<td>170 (92.9)</td>
<td>155 (84.7)</td>
<td>166 (91.2)</td>
</tr>
<tr>
<td>Beta blockers†</td>
<td>146 (79.3)</td>
<td>161 (88.0)</td>
<td>127 (69.4)</td>
<td>151 (83.0)</td>
</tr>
<tr>
<td>Calcium channel blockers†</td>
<td>17 (9.2)</td>
<td>12 (6.6)</td>
<td>28 (15.3)</td>
<td>17 (9.3)</td>
</tr>
<tr>
<td>Cardiac glycosides‡</td>
<td>33 (17.9)</td>
<td>47 (25.7)</td>
<td>40 (21.9)</td>
<td>33 (18.1)</td>
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<tr>
<td>ACEI/ARB Use‡</td>
<td>125 (67.9)</td>
<td>125 (68.3)</td>
<td>123 (67.2)</td>
<td>123 (67.6)</td>
</tr>
</tbody>
</table>

ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BID: twice daily; LADD: left atrial diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SD: standard deviation.

†A patient may have been taking more than one rhythm or rate control medication.
‡Beta blockers included intravenous or oral non-selective and selective beta blockers (excluding sotalol) and alpha- and beta-blocking agents; calcium channel blockers included diltiazem and verapamil; and cardiac glycosides included digitalis glycosides (digoxin and digitalis) and strophanthus glycosides.
§Patients were stratified according to the use of ACEIs and/or ARBs.
Table 2. Summary of Endpoints to Assess the Time to First AF Recurrence

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vernakalant (oral) (BID)</th>
<th>Placebo (N=160)</th>
<th>150 mg (N=147)</th>
<th>300 mg (N=148)</th>
<th>500 mg (N=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic* Sustained† AF Recurrence Per TTM or Investigator Decision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to event (days)</td>
<td></td>
<td>29</td>
<td>26</td>
<td>24</td>
<td>&gt;90</td>
</tr>
<tr>
<td>KM estimate of patients in SR at Day 90 (%)</td>
<td></td>
<td>38</td>
<td>45</td>
<td>43</td>
<td>51</td>
</tr>
<tr>
<td>Hazard ratio for each dose versus placebo‡</td>
<td></td>
<td>0.904</td>
<td>0.996</td>
<td>0.735</td>
<td></td>
</tr>
<tr>
<td>P-value§</td>
<td></td>
<td>0.404</td>
<td>0.798</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>AF Recurrence Per Investigator’s Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to event (days)</td>
<td></td>
<td>36</td>
<td>26</td>
<td>26</td>
<td>&gt;90</td>
</tr>
<tr>
<td>KM estimate of patients in SR at Day 90 (%)</td>
<td></td>
<td>39</td>
<td>46</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td>Hazard ratio for each dose versus placebo‡</td>
<td></td>
<td>0.906</td>
<td>1.009</td>
<td>0.743</td>
<td></td>
</tr>
<tr>
<td>P-value§</td>
<td></td>
<td>0.438</td>
<td>0.859</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Symptomatic* AF Recurrence Per ECGŒ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to event (days)</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td>KM estimate of patients in SR at Day 90 (%)</td>
<td>62</td>
<td>76</td>
<td>77</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio for each dose versus placebo‡</td>
<td>0.802</td>
<td>0.792</td>
<td>0.553</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value§</td>
<td>0.416</td>
<td>0.283</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AF Recurrence Per ECG¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to event (days)</td>
<td>50</td>
<td>29</td>
<td>51</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>KM estimate of patients in SR at Day 90 (%)</td>
<td>34</td>
<td>47</td>
<td>41</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio for each dose versus placebo‡</td>
<td>0.920</td>
<td>1.002</td>
<td>0.793</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value§</td>
<td>0.534</td>
<td>0.832</td>
<td>0.103</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; BID: twice daily; ECG: electrocardiogram; KM: Kaplan Meier; SR: sinus rhythm; TTM: transtelephonic monitor.

*Based on symptoms recorded in the patient diary.
†Based on two consecutive TTMs showing AF, recorded ≥20 hours apart.
‡Placebo or lower doses are the denominator of hazard ratios.
§P-value comparing the distribution of the Kaplan Meier curves based on a two-sided log-rank test.
ŒRequired two ECGs ≥75 minutes apart.
### Table 3. Safety Overview

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (N=184)</th>
<th>150 mg BID (N=183)</th>
<th>300 mg BID (N=183)</th>
<th>500 mg BID (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent AE</td>
<td>135 (73.4)</td>
<td>126 (68.9)</td>
<td>117 (63.9)</td>
<td>118 (64.8)</td>
</tr>
<tr>
<td>Any non-AF/AFL/SVT AE</td>
<td>60 (32.6)</td>
<td>67 (36.6)</td>
<td>48 (26.2)</td>
<td>72 (39.6)</td>
</tr>
<tr>
<td>Any related AE</td>
<td>9 (4.9)</td>
<td>16 (8.7)</td>
<td>13 (7.1)</td>
<td>15 (8.2)</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>0</td>
<td>1 (0.5)</td>
<td>2 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>3 (1.6)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5)</td>
<td>2 (1.1)</td>
<td>0</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0</td>
<td>0</td>
<td>3 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Any SAE</td>
<td>18 (9.8)</td>
<td>13 (7.1)</td>
<td>17 (9.3)</td>
<td>16 (8.8)</td>
</tr>
<tr>
<td>Discontinuation of study drug due to an AE</td>
<td>98 (53.3)</td>
<td>83 (45.4)</td>
<td>88 (48.1)</td>
<td>73 (40.1)</td>
</tr>
<tr>
<td>Discontinuation of study drug due to an AE of AF recurrence</td>
<td>94 (51.1)</td>
<td>76 (41.5)</td>
<td>78 (42.6)</td>
<td>70 (38.5)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.1)</td>
<td>1 (0.5)</td>
<td>3 (1.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

AE: adverse event; AF: atrial fibrillation; AFL: atrial flutter; BID: twice daily; SAE: serious adverse event; SVT: supraventricular tachycardia.

### Figure Legends:

**Figure 1.** Patient Disposition Reasons for “other” included electrical cardioversion not performed (2 patients), atrial flutter (2 patients), and mistakenly randomized (1 patient) in the placebo group; atrial thrombus (2 patients) in the 150 mg vernakalant group; electrical cardioversion not performed (1 patient), inclusion/exclusion criteria not met (1 patient), and wrong dosing (1 patient) in the 300 mg vernakalant group; and atrial thrombus (1 patient) in the 500 mg vernakalant group.

ECV: electrical cardioversion; IRAF: immediate recurrence of atrial fibrillation.

**Figure 2.** Kaplan Meier Curve of Time to First Documented Recurrence of Symptomatic Sustained Atrial Fibrillation
Randomized (N=735)

- Placebo (N=184)
- Vernakalant 150 mg (N=184)
- Vernakalant 300 mg (N=184)
- Vernakalant 500 mg (N=183)
- Not Treated (N=3)
  - Use of prohibited medication, N=1
  - QRS interval >140 msec, N=1
  - Hemodynamically unstable, N=1

Treated (Safety Analyses) (N=732)

- Placebo (N=184)
- Vernakalant 150 mg (N=184)
- Vernakalant 300 mg (N=184)
- Vernakalant 500 mg (N=183)

24 Patients Discontinued Study During Days 1-3
- Failed ECV, N=16 (IRAF, 2)
- Withdrew consent, N=2
- Adverse event, N=1
- Other*, N=5

37 Patients Discontinued Study During Days 1-3
- Failed ECV, N=29 (IRAF, 3)
- Withdrew consent, N=1
- Adverse event, N=1
- Not treated, N=1
- Not in sinus rhythm, N=1
- Other*, N=2

36 Patients Discontinued Study During Days 1-3
- Failed ECV, N=29 (IRAF, 5)
- Withdrew consent, N=2
- Adverse event, N=1
- Not treated, N=1
- Other*, N=3

33 Patients Discontinued Study During Days 1-3
- Failed ECV, N=30 (IRAF, 2)
- Withdrew consent, N=1
- Not treated, N=1
- Other*, N=1

Entered Maintenance Phase (Efficacy Analyses) (N=605)

- Placebo (N=160)
- Vernakalant 150 mg (N=147)
- Vernakalant 300 mg (N=148)
- Vernakalant 500 mg (N=150)
A Randomized Placebo-Controlled Study of Vernakalant (Oral) for the Prevention of Atrial Fibrillation Recurrence Post-Cardioversion
Christian Torp-Pedersen, Dimitar H. Raev, Garth Dickinson, Noam N. Butterfield, Brian Mangal and Gregory N. Beatch

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