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Efficacy and Safety of Vernakalant for Cardioversion of Recent-onset Atrial Fibrillation in the Asia–Pacific Region: A Phase 3 Randomized Controlled Trial

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Abstract: Atrial fibrillation (AF) is a common clinically significant cardiac arrhythmia. This phase 3 randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of vernakalant hydrochloride for the pharmacological conversion of AF to sinus rhythm in patients with recent-onset (>3 hours to ≤7 days) symptomatic AF from the Asia–Pacific region. Patients received an infusion of vernakalant (3 mg/kg) or placebo for 10 minutes. If AF had not been terminated 15 minutes later, a second infusion of vernakalant (2 mg/kg) or placebo for 15 minutes was administered. The primary efficacy end point was conversion of AF to sinus rhythm for >1 minute within 90 minutes. The study was terminated early for administrative reasons; 123 patients from Korea, Taiwan, and India were randomized to receive vernakalant (n = 55) or placebo (n = 56). A greater proportion of patients who received vernakalant (52.7%) than placebo (12.5%) met the primary end point ($P < 0.001$), and cardioversion was faster in the vernakalant group than in the placebo group ($P < 0.001$). Vernakalant was generally well tolerated; the incidence of treatment-emergent adverse events was similar between the groups. We conclude that vernakalant is efficacious in the rapid cardioversion of recent-onset AF in patients from the Asia–Pacific region.

Key Words: atrial fibrillation, sinus rhythm, vernakalant hydrochloride, cardioversion, antiarrhythmic

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common clinically significant cardiac arrhythmias; it has been predicted that 5–16 million adults in the United States and >1 million adults in Japan will be affected by AF by 2050.[1] Available data indicate that the prevalence of AF may be lower in Asian countries than in Western countries. In individuals more than 80 years of age, the estimated prevalence is 2%–3% in Japan compared with 7%–14% in Western countries.[1] The prevalence in the same age group has been reported as 5.8% and 4.0% in Singapore[2] and Korea,[3] respectively; the prevalence has been estimated to be 5.9% in individuals 80–84 years old in China.[4] There are also potential differences between cultures in treatment practices (including the use of background medications, such as pilsicainide) and illness reporting, and in genetics, such as cytochrome P450 2D6 (CYP2D6) genotype, that could lead to dissimilarities in the response to vernakalant. Despite these differences, AF-related epidemiological factors in Western and Asian populations could be similar.[5]

AF is associated with an increased risk of embolic stroke, heart failure, and cardiovascular morbidity, and symptoms include palpitations, dizziness, breathlessness, and chest pain.[6,7] The management of AF is focused on preventing complications associated with arrhythmia and reducing symptoms. Treatment includes conversion to sinus rhythm (SR); rapid cardioversion is preferable because delays of more than 12 hours for patients with short-duration (<48 hours) AF may increase the risk of cerebral ischemic attacks in the 30 days after conversion.[8,9] Pharmacological treatment strategies include the use of antiarrhythmic agents; however, many of these agents are only partially effective in achieving rapid and durable conversion of AF to SR and have been associated with proarrhythmic effects and significant noncardiac toxicity.[10–12]

Vernakalant is an atrial-selective compound that is available in European countries and elsewhere for the cardioversion of recent-onset AF.[13] To date, the efficacy and safety of this compound have been investigated in studies conducted predominantly in North America and Europe. Three randomized placebo-controlled phase-3 trials, one randomized active-controlled trial, and a phase-4 open-label study of vernakalant have been reported.[14–18] In the Arrhythmia Conversion Trial (ACT) I and ACT III, intravenous vernakalant was found to be more effective than placebo in achieving cardioversion of recent-onset (>3 hours to ≤7 days) AF ($P < 0.001$ in both

trials).[16,17] Vernakalant was also reported to be more effective than amiodarone in achieving cardioversion of short-duration (3–48 hours) AF within 90 minutes of drug infusion.[14]

The objective of this randomized controlled trial was to investigate the safety and efficacy of vernakalant hydrochloride for the conversion of symptomatic recent-onset AF to SR in patients from the Asia–Pacific region.

METHODS

Study Design

This multicenter, randomized, double-blind, placebo-controlled, phase-3 clinical trial assessed the efficacy and safety of vernakalant in patients with recent-onset AF from the Asia–Pacific region (ClinicalTrials.gov identifier: NCT01174160). The study protocol and amendments were reviewed and approved by an independent ethics committee or institutional review board at each study site. The study was overseen by the sponsors and an independent clinical events committee (CEC) and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All included patients gave written informed consent. The study was designed to enroll 615 patients from Taiwan, Korea, India, China, and Hong Kong.

Patient Screening and Selection

Eligible patients were adults (aged 18–85 years, weighing 45–136 kg) with recent-onset AF (>3 hours to ≤7 days) and dysrhythmic symptoms. Patients must have been hemodynamically stable for more than 12 hours before screening, adequately hydrated, and receiving sufficient anticoagulant therapy, as determined by the investigator. Figure 1 shows the key exclusion criteria. The proportion of patients with structural heart disease was limited to 20%–60%.

Treatment Plan

Patients were randomized in a 1:1 ratio to receive vernakalant or placebo. Patients were assigned an allocation number and randomized into the study by an unblinded pharmacist using an Interactive Voice Response System. Participants received a 10-minute intravenous infusion of vernakalant (3 mg/kg) or an equivalent volume of placebo (normal saline). If after a 15-minute observation period, patients were in AF or atrial flutter, a second 10-minute infusion of vernakalant (2 mg/kg) or equivalent volume of placebo was administered, unless any dose-stopping criteria had been met (Table 1).

All time points given are relative to the first exposure to study drug. Electrical cardioversion was not permitted until 2 hours after the start of infusion, unless the investigator deemed it necessary before this time. Vital signs were recorded at screening; baseline; the start of infusion; discharge; 10, 20, 25, 35, 45, 65, and 90 minutes; 2, 4, and 24 hours; and 7 days after the start of drug infusion. Twelve lead electrocardiograms (ECGs) were obtained at screening, at baseline, at discharge, on conversion to SR; and at 10, 25, 35, 45, 65, and 90 minutes, and 2, 4, and 24 hours, and 7 days after the start of infusion [The following ECG parameters were recorded: ventricular rate, RR interval, PR interval, QRS interval, QT interval, QTc interval corrected according to the Bazett formula (QTcB), and QTc interval corrected according to the Fridericia's formula (QTcF)]. Patients were confirmed to be in AF at baseline by independent CEC assessment of

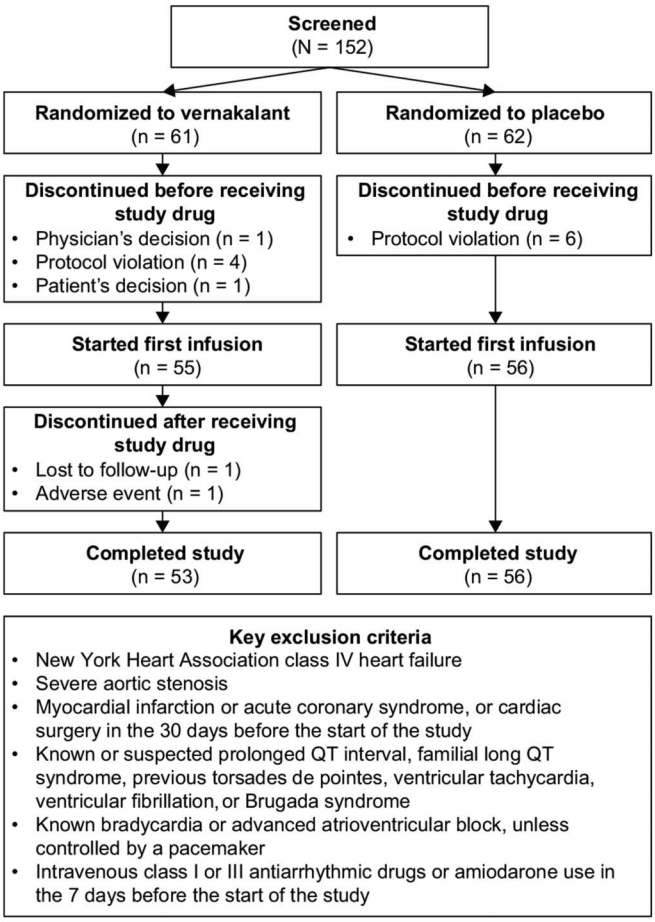

FIGURE 1. Study population.

TABLE 1. Dose-stopping Criteria

Dose-stopping Criteria
Clinically significant hypotension as assessed by the investigator
Any ventricular tachycardia lasting more than 30 s
Polymorphic ventricular tachycardia
Systolic blood pressure <85 or >190 mm Hg
QRS prolongation by >50% compared with the baseline value
An uncorrected QT interval of 0.55 s or QT prolongation by >25% compared with the baseline value
Heart rate between 40 and 50 bpm alongside symptoms of bradycardia
Heart rate <40 bpm for 30 s or longer
Sinus pause of 5 s or longer
New bundle branch block
Intolerable side effects or changes in cardiac rhythm or atrioventricular conduction that in the investigator's opinion were a threat to patient safety

bpm, beats per minute.

12-lead ECG recordings. Continuous telemetry was performed from baseline to 2 hours postexposure, and Holter monitoring was performed from screening to 24 hours postexposure. All ECGs, including 12-lead Holter monitoring, were adjudicated by blinded members of the CEC.

Study Outcomes

The primary efficacy end point was the proportion of patients with treatment-induced conversion of AF to SR for a minimum of 1 minute in the 90 minutes after first exposure to study drug. Secondary efficacy end points included time to conversion to SR within 24 hours, the proportion of patients reporting AF symptoms at 90 minutes, and the proportions of patients who both met the primary end point and were still in SR at 24 hours and 7 days after first exposure. Tertiary efficacy end points included: 1) time to conversion within 90 minutes and 2) time to conversion within 4 hours.

Treatment-emergent adverse events (TEAEs) comprised those that began in the 10 days after the start of the first infusion of study drug, or serious adverse events (SAEs), AF, or atrial flutter starting in the 30 days after the first infusion. Events that were not treatment emergent contributed to listings only.

"Bradycardia", clinically significant hypotension, and "ventricular arrhythmia" were predefined as events of clinical interest, regardless of severity, and were captured for up to 10 days postinfusion. Bradycardia included all TEAEs of bradycardia, sinus bradycardia, and sinus arrest captured up to day 10, and CEC-adjudicated bradycardia events identified from Holter monitoring data collected in the 24 hours after infusion. Ventricular arrhythmia included TEAEs of idioventricular rhythm, accelerated idioventricular rhythm, ventricular tachycardia, ventricular fibrillation, and torsades de pointes captured up to day 10, and CEC-adjudicated ventricular arrhythmia events (excluding supraventricular tachycardia) identified from ECG monitoring data collected in the 24 hours after infusion. Hypotensive events included any TEAEs of clinically significant hypotension as determined by the investigator and neurogenic shock captured until day 10.

Statistical Analysis

The original plan was to enroll 615 patients from Taiwan, Korea, India, China, and Hong Kong; 7%–10% of the randomized patients were expected to withdraw before receiving the study drug, leaving approximately 560 evaluable patients. Based on the results of ACT I, conversion rates were estimated to be 51.7% for vernakalant and 4.0% for placebo.[17] With 280 evaluable patients per group, the study would have had 90% power (one-sided, $\alpha = 0.025$) to detect a 7.2% difference in the primary end point between the 2 groups.

Owing to early termination of the study for administrative reasons, only 123 patients (from Taiwan, Korea, and India) were randomized to receive vernakalant or placebo. Assuming the same 7%–10% withdrawal rate, it was anticipated that 112 patients would be evaluable. With 56 evaluable patients per group, this study had 90% power (one-sided, $\alpha = 0.025$) to detect a 21.5% difference between the 2 groups for the primary end point.

All randomized patients who received any amount of study drug were included in the efficacy and safety analyses. Baseline demographics and patient characteristics were summarized by treatment group. For continuous data, summaries included the number of observations, mean, and SD; frequency counts and percentages are presented for categorical data.

Asymptotic 95% confidence intervals (CIs) and the Wald test were used to assess differences between treatment groups in the proportions of patients meeting the primary efficacy end point. The secondary end point of time to conversion to SR within 24 hours was tested at a 2-sided 5% α-level if there was a statistically significant positive finding for the primary end point. Patients who received electrical cardioversion or withdrew were censored at the corresponding time. The product-limit method was used to obtain estimates of the median time to conversion, and the 95% CIs and survival curves associated with each treatment group. The groups were compared using the log-rank test.

Safety events of clinical interest that were identified a priori were subject to statistical testing; *P* values and 95% CIs were calculated for between-group comparisons.

RESULTS

This study involved 35 sites, 25 of which enrolled at least 1 patient (15 in Korea, 9 in Taiwan, and 1 in India). A total of 123 participants were randomized in a 1:1 ratio to receive vernakalant or placebo; of these, 111 (vernakalant: n = 55; placebo, n = 56) received any amount of study drug and were included in the efficacy and safety analyses. Figure 1 shows the study population.

Baseline Demographics and Characteristics

Demographics, characteristics of AF, and cardiovascular assessments were similar in the 2 treatment groups (Table 2). Most patients were men (60%) and from Korea (81%). Patients had a mean age of 59.9 (±12.8) years and a mean weight of 66.1 (±9.2) kg. Nearly all patients had a CYP2D6 genotype that classified them as extensive (63%) or intermediate (36%) metabolizers. Proportions of patients with structural heart disease were similar in the vernakalant (20%) and placebo (23%) groups. The mean duration of the current AF episode was similar in the vernakalant and placebo groups (48 ± 43 and 48 ± 35 hours, respectively); 58% of patients had AF lasting 48 hours or less at study entry.

Efficacy

The study met all primary and secondary efficacy end points. A significantly greater proportion of patients in the vernakalant group than in the placebo group converted from AF to SR for at least 1 minute in the 90 minutes after the first drug exposure [52.7% (29 of 55) vs. 12.5% (7 of 56), respectively; $P < 0.001$].

The time to cardioversion in the first 90 minutes after infusion was significantly shorter in the vernakalant group than in the placebo group ($P < 0.001$; Fig. 2A); in the subset of patients who converted to SR in the first 90 minutes, the median time to conversion was 11.0 minutes (n = 29) in the

TABLE 2. Baseline Patient Demographics and Characteristics

Demographics and Characteristics	Vernakalant (n = 55)	Placebo (n = 56)
Sex, n (%)		
Men	37 (67)	30 (54)
Women	18 (33)	26 (46)
Mean age, yr (SD)	60.7 (13.7)	59.2 (12.0)
Mean weight, kg (SD)	66.3 (9.4)	65.8 (9.0)
Race, n (%)		
American Indian or Alaskan native	0	1 (2)
Asian	55 (100)	55 (98)
Ethnicity, n (%)		
Hispanic or Latino	1 (2)	0
Not Hispanic or Latino	54 (98)	56 (100)
Japanese ancestry		
Yes	0	0
No	55 (100)	56 (100)
Country, n (%)		
India	0	1 (2)
Korea	42 (76)	48 (86)
Taiwan	13 (24)	7 (13)
Classification based on CYP2D6 genotype, n (%)	n = 53	n = 52
Extensive metabolizer	37 (70)	29 (56)
Intermediate metabolizer	15 (28)	23 (44)
Poor metabolizer	1 (2)	0
NYHA functional classification, n (%)		
None	50 (91)	53 (95)
Class I	1 (2)	1 (2)
Class II	2 (4)	2 (4)
Class III	2 (4)	0
Structural heart disease, n (%)		
None	44 (80)	43 (77)
Congestive heart failure	5 (9)	3 (5)
Ischemic heart disease	4 (7)	7 (13)
Myocardial infarction	1 (2)	0
Valvular heart disease	2 (4)	3 (5)
Mean duration of current AF episode, h (SD)	48 (43)	48 (35)
Duration of AF episode, n (%)		
48 h or less	33 (60)	31 (55)
More than 48 h	22 (40)	25 (45)

NYHA, New York Heart Association.

vernakalant group compared with 19.2 minutes (n = 7) in the placebo group. Likewise, time to conversion to SR in the 24 hours after infusion was significantly shorter in the vernakalant group than in the placebo group (P = 0.008; Fig. 2B). Median times for those who converted were 17.3 minutes (n = 35) and 300.7 minutes (n = 27), respectively. A high proportion of patients who met the primary end point and received vernakalant were still in SR at 24 hours (89%) and 7 days (82%). It should be noted that 12 patients who received placebo and 6 who received vernakalant received electrical cardioversion and were censored at the time of the shock. By including patients who received electrical cardioversion as nonresponders, there was a 15% absolute and 32% relative improvement in the conversion rate within 24 hours versus placebo.

The proportion of patients reporting AF symptoms was reduced in both treatment groups at 90 minutes relative to baseline. A greater proportion of patients in the vernakalant group than in the placebo group reported no AF symptoms at 90 minutes (62% vs. 43%, respectively). At later time points, the proportion of patients meeting this end point was similar in the vernakalant and placebo groups (Fig. 3).

Safety

Overall, the vernakalant and placebo groups were similar with respect to the incidence of TEAEs, including those that were drug related or serious (Table 3). One or more TEAE was experienced by 42% (23 out of 55) of patients in the vernakalant group and 41% (23 out of 56) of those in the placebo group. Approximately half of the patients who experienced TEAEs did so within 24 hours of the infusion. The incidence of the most frequently reported AEs was similar in the 2 groups, but sneezing occurred more frequently in patients who received vernakalant.

Six patients in each group reported one or more SAE. Only one SAE was considered to be drug related: the patient experienced dyspnea starting 14 minutes after initiation of vernakalant infusion but converted to SR and recovered the same day. It is noteworthy that 2 patients in the placebo group (none in the vernakalant group) experienced cerebral infarctions: both patients had had AF for longer than 12 hours at the time of dosing.

The events of clinical interest tended to occur within 24 hours of drug exposure. Seven patients in the vernakalant group experienced bradycardia compared with 4 in the placebo group [difference (95% CI): 6% (−6%, 18%); P = 0.327]; in 3 of the 7 patients receiving vernakalant and 1 of the 4 patients receiving placebo, the events were not reported as AEs but were identified through CEC review of Holter ECGs. Three patients in the vernakalant group and 9 in the placebo group experienced ventricular arrhythmia [difference (95% CI): −11% (−23%, 1%); P = 0.073]; in 2 of those receiving vernakalant and 5 receiving placebo, events were identified solely through CEC review of Holter ECGs (1 patient in the placebo group experienced nonsustained polymorphic ventricular tachycardia, the other 6 patients experienced nonsustained monomorphic ventricular tachycardia). One patient in the vernakalant group experienced hypotension compared with 3 in the placebo group [difference (95% CI): −4% (−13%, 5%); P = 0.319]. Two events of clinical interest in the vernakalant group were considered serious: 1 SAE of hypotension and 1 SAE of bradycardia. Both occurred on day 2 and neither was considered drug related by the investigator.

No clinically important changes in laboratory parameters or vital signs occurred in the vernakalant group versus the placebo group. Vernakalant was associated with transient prolongations of the QTc interval relative to placebo; based on 12-lead ECG recordings taken between 10 minutes and 4 hours after the start of the first infusion, 10%–17% of patients

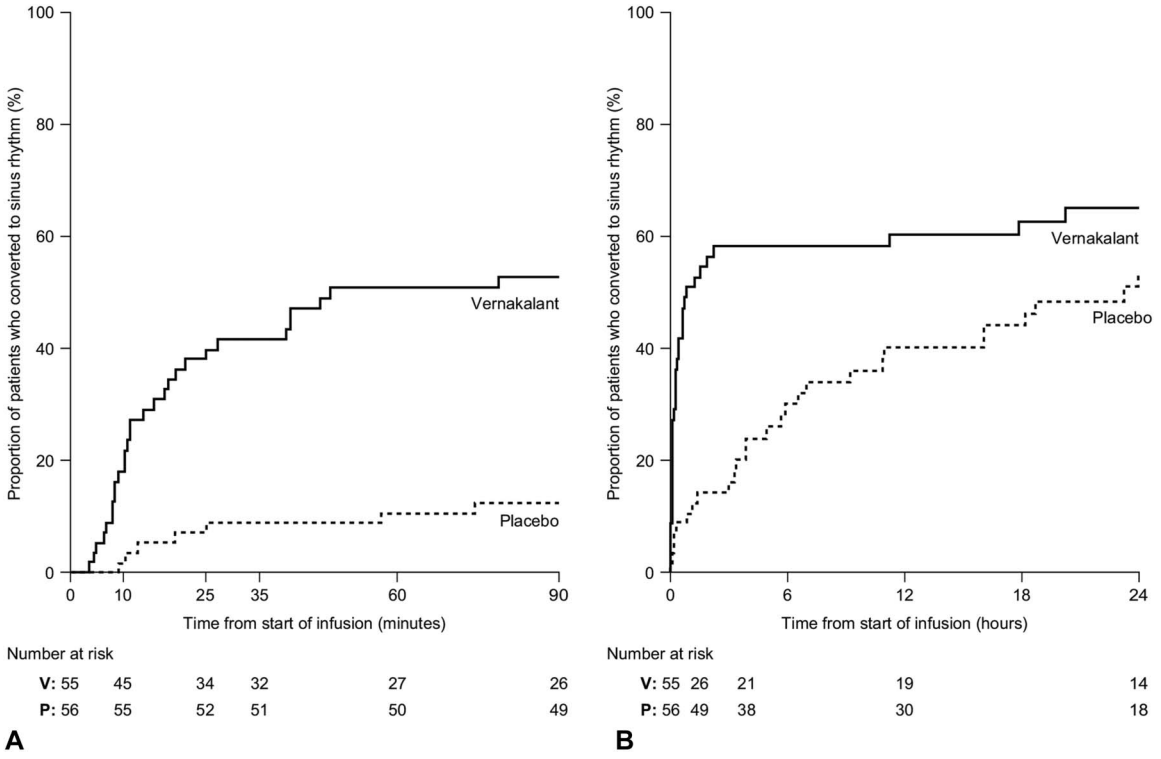

FIGURE 2. Survival curves for time to conversion from atrial fibrillation to sinus rhythm in the (A) 90 minutes and (B) 24 hours after the start of infusion of placebo (P) or vernakalant (V). Patients who received electrical cardioversion or withdrew were censored at the corresponding time.

in the vernakalant group had QTcF interval prolongations of at least 30 milliseconds compared with 0%–6% of patients who received placebo.

There was 1 death in the vernakalant group, which was not considered to be drug related by the investigator. An 82-year-old man with a history of abdominal aortic aneurysm,

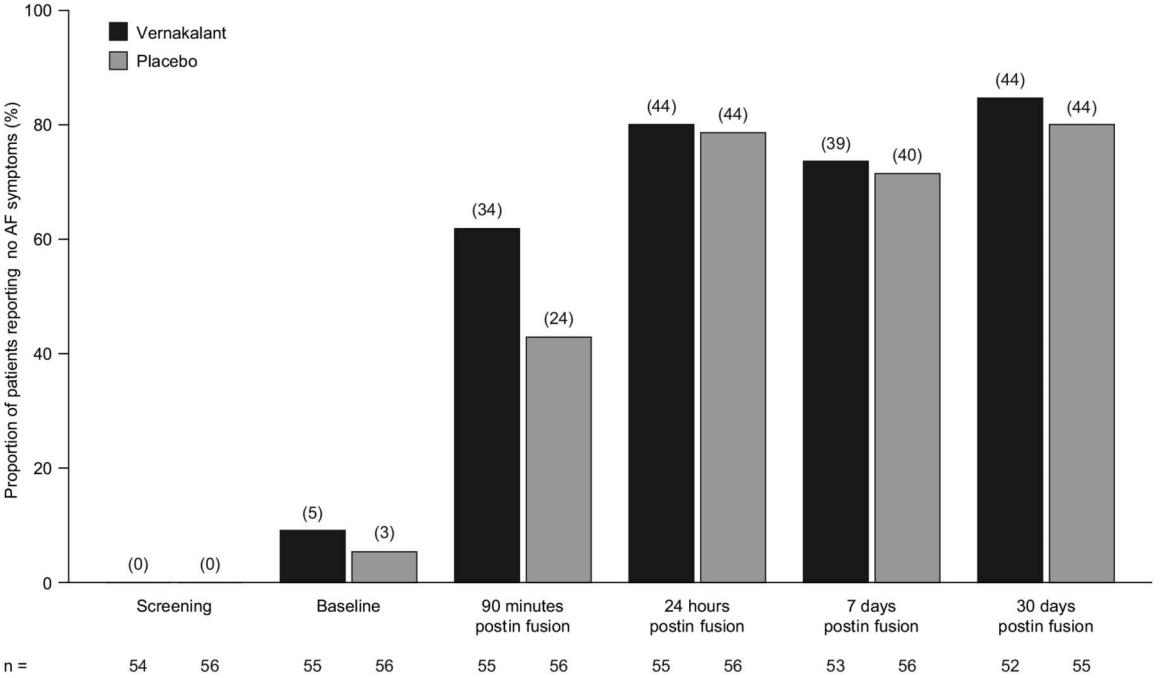

FIGURE 3. Proportion of patients reporting no symptoms of atrial fibrillation (AF) at different time points after administration of vernakalant and placebo. Patient numbers are shown in parentheses.

TABLE 3. TEAEs That Were Considered by the Investigator to be Related to Study Drug and Serious TEAEs in Patients Who Received Vernakalant or Placebo

TEAE, n (%)	Vernakalant (n = 55)	Placebo (n = 56)
TEAEs considered to be related to study drug		
Cardiac disorders		
Ventricular tachycardia	1 (2)	4 (7)
Bradycardia	1 (2)	0
Sinus arrest	1 (2)	0
Respiratory, thoracic and mediastinal disorders		
Sneezing	2 (4)	0
Dyspnea	1 (2)	0
Eye disorders		
Lacrimation increased	1 (2)	0
Gastrointestinal disorders		
Diarrhea	0	1 (2)
Nervous system disorders		
Dysgeusia	1 (2)	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	1 (2)	0
Serious TEAEs		
Cardiac disorders		
Arrhythmia	1 (2)	0
Congestive heart failure	0	1 (2)
Sick sinus syndrome	1 (2)	0
General disorders and administration site conditions		
Chest pain	0	2 (4)
Death	1 (2)	0
Nervous system disorders		
Cerebral infarction	0	2 (4)
Dizziness	0	1 (2)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	2 (4)	0
Infections and infestations		
Urinary tract infection	0	1 (2)
Investigations		
Prothrombin time prolonged	0	1 (2)
Renal and urinary disorders		
Acute renal failure	1 (2)	0
Vascular disorders		
Neurogenic shock	1 (2)	0

heart failure, idiopathic pulmonary fibrosis, rectal cancer, and pulmonary tuberculosis died on day 6. He was receiving concomitant medication including aspirin, carvedilol, furosemide, hydrochlorothiazide with spironolactone, flecainide acetate, enoxaparin sodium, warfarin, potassium chloride, and heparin. The patient was in AF for 7 days before randomization. He received 2 infusions of vernakalant but did not convert to SR. Hospitalization was recommended because of the risk of anticoagulation-related bleeding, but the patient opted to go home on day 3. He attended a follow-up consultation on day 4, and no AEs were observed. His family notified the site that the patient had died while sleeping on day 6. An autopsy was not performed and the cause of death was not ascertained.

DISCUSSION

This phase-3 study evaluating the safety and efficacy of intravenous vernakalant in patients with recent-onset symptomatic AF from Korea, Taiwan, and India expands on previous trials conducted predominantly in Northern America and Europe. The study met its primary efficacy end point, demonstrating that vernakalant rapidly and effectively converts recent-onset AF to SR.

Treatment with vernakalant resulted in 52.7% of patients converting from AF to SR for at least 1 minute in the 90 minutes after the start of infusion compared with 12.5% of those in the placebo group. Patients who received vernakalant and met the primary end point experienced a faster conversion rate and fewer symptoms of AF at 90 minutes than those given placebo. Vernakalant reduced the need for electrical cardioversion and associated sedation/anesthesia, with half as many patients undergoing this procedure in the vernakalant group compared with those in the placebo group in the first 24 hours. The response rate and speed of conversion were largely consistent with results reported in previous trials in other countries.[14–18] Furthermore, the durability of conversion was similar to that reported previously; 89% of patients in this study, and 99% and 98% of patients in ACT I and ACT II, respectively, who received vernakalant and met the primary end point showed sustained conversion to SR at 24 hours.

Vernakalant was generally well tolerated; similar proportions of patients in the 2 groups experienced TEAEs that were serious or that were considered to be related to the study drug. Two cerebral infarctions occurred in the placebo group in patients who had AF lasting longer than 12 hours. This finding is interesting considering the recent report that a delay of 12 hours or longer from AF symptom onset to electrical cardioversion is associated with a 4-fold higher risk of thromboembolic complications compared with AF lasting less than 12 hours.[9] However, further studies are required to confirm this and to establish whether the same risks apply to patients undergoing pharmacological cardioversion.

Rates of events of clinical interest were low, and events tended to be more common in patients who received placebo than in those who received vernakalant. There were minor differences between this and previous placebo-controlled clinical trials; specifically, the proportions of patients experiencing TEAEs of dysgeusia, ventricular arrhythmia, and hypotension were lower than those reported in ACT I and ACT III.

The population studied here was similar to that of previous phase-3 trials in terms of sex and age; most patients were men, and the mean age was approximately 60 years. However, only one patient (<1%) in this study was classified as a poor CYP2D6 metabolizer compared with approximately 7%–10% of European populations.[19] Although the elimination half-life of vernakalant is prolonged from approximately 3 hours to 5–8.5 hours in poor metabolizers; CYP2D6

genotype is unlikely to play a role in the pharmacokinetics of acute exposure to intravenous vernakalant because these are largely determined by redistribution rather than metabolism.[20] There were few other differences in patient demographics and characteristics between this and previous studies of vernakalant. Several other factors could have influenced the results, including cultural differences between Western and Asian populations in attitudes toward illness.[21] However, too few patients were included in this study to investigate why the vernakalant safety profile reported here is slightly better than in previous studies. Further investigation is needed to determine which factors affect TEAE reporting in Western and Asian populations.

CONCLUSIONS

This phase-3 study demonstrated that vernakalant rapidly and effectively converted recent-onset AF to SR in patients from the Asia–Pacific region. Vernakalant was generally well tolerated, and fewer safety events were observed in this study than in previous phase-3 trials.

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