Efficacy and safety of vernakalant in patients with atrial flutter: a randomized, double-blind, placebo-controlled trial

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Aims	Vernakalant is a novel, relatively atrial-selective antiarrhythmic agent for conversion of atrial fibrillation (AF) to sinus rhythm. This study examined the safety and efficacy of vernakalant in converting atrial flutter (AFL) to sinus rhythm.
Methods and results	This was a phase 2/3, randomized, double-blind, placebo-controlled trial. Adults with AFL received either a 10 min infusion of 3.0 mg/kg vernakalant ($n = 39$) or placebo ($n = 15$). If AFL or AF persisted at the end of a 15 min observation period, a second 10 min infusion of 2.0 mg/kg vernakalant or placebo was administered. The primary efficacy outcome was the proportion of patients who had treatment-induced conversion of AFL to sinus rhythm for a minimum duration of 1 min within 90 min after the start of the first infusion. No patient in the placebo group met the primary outcome. Only one patient receiving vernakalant (1 of 39, 3%) converted to sinus rhythm. A reduced mean absolute ventricular response rate occurred within 50 min in patients receiving vernakalant (mean change from baseline −8.2 b.p.m.) vs. patients receiving placebo (−0.2 b.p.m.) ($P = 0.037$). A *post-hoc* analysis revealed that vernakalant increased AFL cycle length by an average of 55 ms, whereas the AFL cycle length was unchanged in the placebo group ($P < 0.001$). There was no occurrence of 1 : 1 atrio-ventricular conduction. Dysgeusia and sneezing were the most common treatment-related adverse events, consistent with previous reports.
Conclusion	Vernakalant did not restore sinus rhythm in patients with AFL. Vernakalant modestly slowed AFL and ventricular response rates, and was well tolerated.
Keywords	Atrial flutter • Antiarrhythmic drugs • Arrhythmia • Vernakalant

Introduction

Atrial flutter (AFL) is a macro re-entrant atrial tachycardia that is characterized by an organized atrial rhythm with a rate usually between 250 and 350 b.p.m.[1] The annual incidence of AFL in the United States is estimated to be 200 000.[2] Compared with patients with atrial fibrillation (AF), patients with AFL may be more likely to have a history of chronic obstructive pulmonary disease, heart failure, and smoking.[2,3]

Atrial tachycardia, AFL, and AF are interrelated and can co-exist in the same patient.[4] Patients presenting with atrial tachycardia or AFL are at risk of developing AF.[5] Atrial flutter often deteriorates into AF, and AF and AFL may switch back and forth to one another.[6]

Most drugs currently used to treat atrial arrhythmias have effects on the entire heart, have limited efficacy, and may induce ventricular proarrhythmia.[7] Those with prominent sodium channel blocking properties but no direct effect on increasing

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atrio-ventricular (AV) nodal refractoriness can increase ventricular rate during AFL indirectly by slowing the atrial rate, which physiologically increases AV conduction.[8]

Vernakalant is a novel, relatively atrial-selective antiarrhythmic agent for the conversion of AF to sinus rhythm that acts by blockade of various potassium currents (e.g. I_{Kur}, I_{to}, I_{KAch}, and I_{Kr}) and frequency-dependent blockade of sodium channels.[9,10] In phase 2 and 3 trials vernakalant rapidly converted AF to sinus rhythm in patients with recent-onset AF[11−13] and in patients with post-operative AF.[14] The present study examined the ability of vernakalant to convert AFL to sinus rhythm, the efficacy of vernakalant in lowering the ventricular response rate, and the safety of vernakalant in patients experiencing AFL. A *post-hoc* analysis assessed vernakalant's effect on AFL cycle length in order to provide insight into the potential risk of 1 : 1 AV conduction.

Methods

Study design

The study was a phase 2/3, prospective, randomized, double-blind, placebo-controlled trial conducted at 24 sites in Denmark, Canada, the United States, and Sweden (Clinical Trial Registration—clinicaltrials.gov. identifier: NCT00476112). The study was approved by an institutional review board at each site and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrolment.

Patients

Eligible patients were men and non-pregnant women ≥18 years of age with AFL that had been sustained for >3 h and ≤45 days. Atrial flutter included typical AFL defined as an atrial rate between 220 and 320 b.p.m. and a typical sawtooth pattern in electrocardiogram (ECG) leads II and III. Atypical AFL was included in the absence of a typical sawtooth pattern when there was clear evidence of regular, organized atrial activity in other leads (particularly lead V_2) within this range of rates and fixed AV conduction (2 : 1, 3 : 1, etc.). Patients had to have adequate anticoagulant therapy as judged by the investigator, be haemodynamically stable (systolic blood pressure 90−160 mmHg and diastolic blood pressure <95 mmHg at screening and baseline), and have a body weight between 45 and 136 kg.

Patient exclusions were identical to those of previous studies of vernakalant for conversion of AF.[11−13] Briefly, they excluded those at risk of QT prolongation, bradycardia, or other proarrhythmia; haemodynamically unstable patients; and those with reversible causes of AFL or recent use of other antiarrhythmic drugs.

Treatments

Patients were randomly assigned (2 : 1) to receive either a 10 min infusion of 3.0 mg/kg vernakalant or placebo (normal saline solution), followed by a 15 min observation period. If the patient was in AFL or in AF at the end of the observation period, a second 10 min infusion of 2.0 mg/kg vernakalant or placebo was administered. The infusion was discontinued if any of the following were observed: uncorrected QT interval of 550 ms or QT prolongation of >25% of baseline; heart rate between 40 and 50 b.p.m. lasting ≥30 s with symptoms of bradycardia, or <40 b.p.m. lasting ≥30 s with or without symptoms; systolic blood pressure >190 mmHg or <85 mmHg; new bundle-branch block or QRS interval prolongation of 50% of control; any polymorphic ventricular tachycardia; one or more sinus pause of ≥5 s; or any

intolerable side effect or change in cardiac rhythm or AV conduction deemed by the investigator as unsafe.

Study outcomes

The primary efficacy outcome was the proportion of patients who received treatment and converted from AFL to sinus rhythm for a minimum duration of 1 min within 90 min after the start of the first infusion. Patients were assessed for the presence of AFL symptoms at screening, baseline, 90 min post-dose, 24 h post-dose, at a Day 7 follow-up visit, and by telephone on Day 30. Secondary efficacy outcomes included time-to-conversion of AFL to sinus rhythm and absolute reduction (change from baseline) of the ventricular response rate at 50 min after first exposure to treatment.

Conversion of AFL to sinus rhythm was confirmed by members of a Clinical Events Committee (who were blinded to treatment assignment), using the results of the Holter monitor and/or two consecutive 12-lead ECG recordings at least 1 min apart within 90 min of first exposure to study drug. All ECGs through Day 7 were reviewed by the committee.

Analysis of electrocardiogram intervals

The ECG intervals were measured at several time points throughout the first 24 h and again at the Day 7 follow-up visit. The QT intervals were corrected by both Bazett and Fredericia formulae.[15,16]

A separate *post-hoc* analysis was done to assess the effect of vernakalant on AFL cycle length and the potential risk of 1 : 1 AV conduction. The 12-lead ECGs were masked concerning treatment group assignment. The AFL rate was assessed by determination of the average of five FF intervals (interval between atrial depolarizations in AFL; AFL cycle length) per ECG. The FF intervals were determined for the three successive baseline ECGs (recorded between $T = −10$ min and 0) and for the ECGs obtained at 5, 10, 15, and 30 min following the initiation of infusion.

Safety

Safety was assessed by adverse events (AE), serious adverse events (SAE), vital signs, Holter monitor variables (including specifically 1 : 1 AV conduction), laboratory parameters (haematology, serum chemistry, and urinalysis), and physical examination results. Adverse events and SAEs were monitored over a 30-day period following drug administration.

Statistical analysis

All statistical tests were two-sided and conducted at the 0.05 significance level. All patients in each treatment group who received any amount of study drug (full analysis set) were analysed for efficacy and safety. Sample size calculation was based on the assumption that the conversion to sinus rhythm in the placebo group would be 20% and the conversion rate in the vernakalant group would be 60%. Thus, a sample size of 60 patients with AFL, 20 patients in the placebo group, and 40 in the vernakalant group would provide 86% power using a two-sided test with a 5% significance level.

Demographics and baseline characteristics were compared using a one-way analysis of variance with a fixed effect for treatment for continuous variables (a Wilcoxon test was used for the duration of AFL) and a χ^2 test for categorical variables (a Fisher test was used where appropriate). The primary outcome was analysed by the Cochran−Mantel−Haenszel test stratified by country. Time to conversion of AFL to sinus rhythm was analysed by the product-limit method to obtain estimates of the median time to conversion, the associated 95% confidence intervals (CIs), and the survival curves associated with each treatment group. The two treatment groups were compared using a log rank test. Absolute reduction of the ventricular response rate was analysed by analysis of
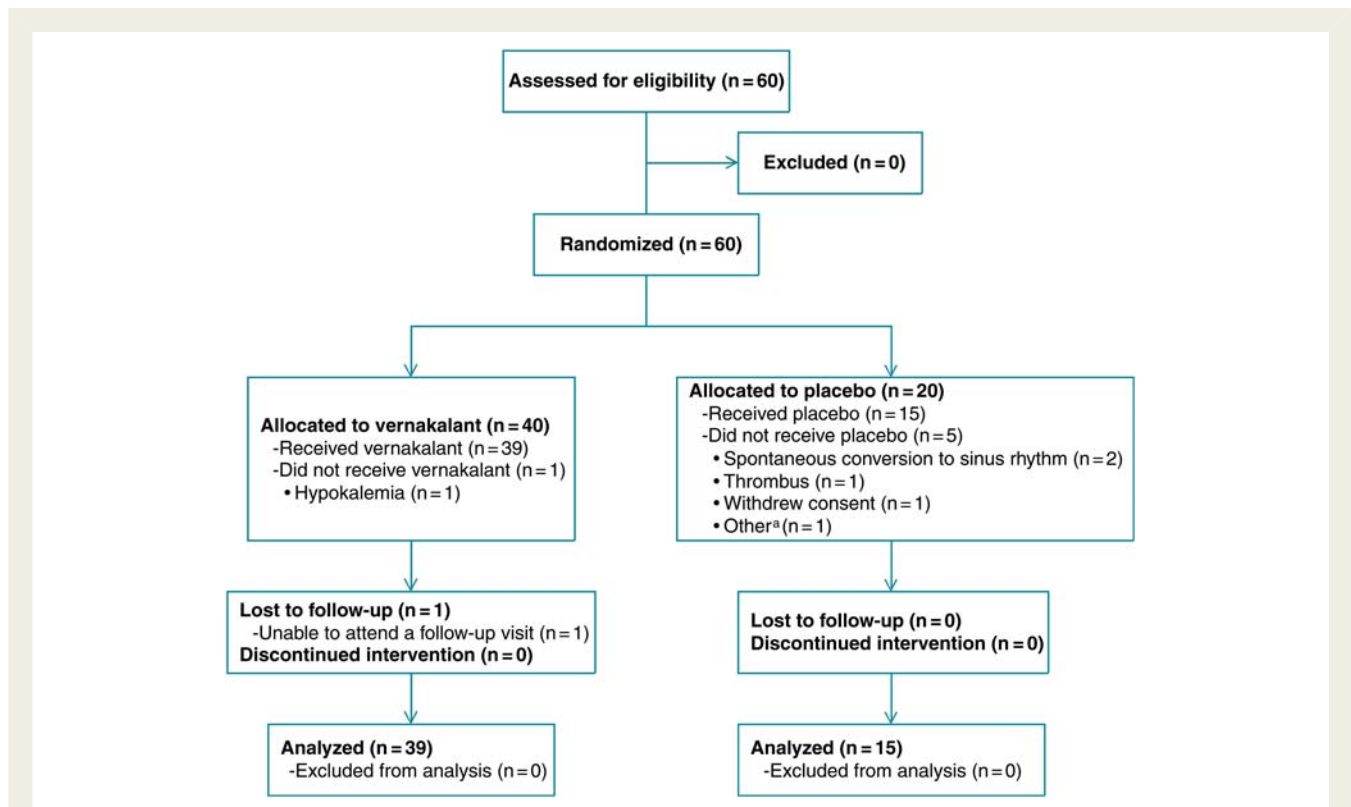
Figure 1 Disposition of patients. [a]The reason for 'other' in the placebo group was that the site personnel were unable to obtain a second intravenous line.

covariance with treatment as a fixed effect and baseline heart rate as a covariate. A three-parameter sigmoid model was fit to the cycle length data, allowing each parameter to vary by patient, and fitting different average maximal values for each treatment.

Results

Patient disposition

Sixty patients were randomized and 53 (88%) completed the study (*Figure 1*). Six patients (five in the placebo group, one in the vernakalant group) did not receive any study drug. In the placebo group, two patients spontaneously converted to sinus rhythm, one patient withdrew at baseline due to a thrombus (left atrium) observed during a transoesophageal echocardiogram, one patient withdrew consent, and site personnel were unable to obtain a second intravenous access line for one patient. In the vernakalant group, one patient had a serum potassium level of 3.0 mmol/L at baseline and failed to meet screening criteria.

The full analysis set was defined as all randomized patients who received any amount of study drug (placebo, $n = 15$; vernakalant, $n = 39$) and was designated as the primary analysis set for all efficacy and safety analyses.

Demographic and baseline clinical characteristics (*Table 1*) were similar between the two groups. Although mean diastolic blood pressure was higher ($P < 0.05$) in the placebo group (84 ±

Table 1 Demographic and baseline characteristics

Parameter	Treatment group	
	Placebo ($n = 15$)	**Vernakalant** ($n = 39$)
Male, n (%)	12 (80)	26 (67)
White, n (%)	15 (100)	36 (92)
Age, years, mean ± standard deviation	69 ± 11	67 ± 11
Body mass index, kg/m², mean ± standard deviation	29.7 ± 7.0	29.3 ± 5.3
Current smoker, n (%)	2 (13)	6 (15)
Any AFL symptom at baseline, n (%)	10 (67)	28 (72)
AFL symptom duration, h, median (range)	178 (32–760)	98 (5–784)
Systolic blood pressure, mmHg, mean ± standard deviation	129 ± 13	126 ± 15
Diastolic blood pressure, mmHg, mean ± standard deviation	84 ± 12	76 ± 13*
Heart rate, b.p.m., mean ± standard deviation	106 ± 28	100 ± 33

AFL, atrial flutter; b.p.m., beats per minute.
*$P = 0.03$ vs. placebo.

12 mmHg) compared with the vernakalant group (76 ± 13 mmHg), this difference was not considered to be clinically meaningful.

Efficacy

One of 39 (3%) vernakalant patients and 0 of 15 (0%) placebo patients converted to sinus rhythm within 90 min [2.6% difference in treatment success (95% CI −2.4 to 7.5%); $P = 0.45$]. The Clinical Events Committee assessed the screening and baseline ECG data for this patient as AF. The time to conversion in the one vernakalant patient who met the primary efficacy outcome was 11 min, and sinus rhythm was maintained at all subsequent time points through to the Day 7 follow-up visit.

Heart rate and AFL cycle length were analysed from 46 patients (11 placebo, 35 vernakalant) with full sets of ECGs. A significantly ($P = 0.037$) reduced mean absolute ventricular response rate occurred within 50 min in patients receiving vernakalant [mean (standard deviation) change from baseline −8.2 (17.7) b.p.m.] compared with patients receiving placebo [−0.2 (9.0) b.p.m.].

Vernakalant was associated with an average 55 ms increase in AFL cycle length (FF interval) ($P < 0.001$; 95% CI 39−71 ms), with 50% of the effect occurring within 4 min (*Figure 2*). There were no occurrences of 1 : 1 AV conduction.

Safety

At least one treatment-emergent AE was reported by 73% of patients in the placebo arm and 87% of patients in the vernakalant arm (*Table 2*). Most of the AEs were transient and mild to moderate in severity. The most frequently reported AEs associated with vernakalant included sneezing (15 of 39, 38%), dysgeusia (15 of 39, 38%), and paraesthesia (6 of 39, 15%). Treatment-emergent AEs that resulted in discontinuation of study drug occurred in three (8%) patients in the vernakalant group: dysgeusia and a feeling of suffocation in one patient, hypotension in one patient, and QRS prolongation in one patient. No patients in the placebo group had a treatment-emergent AE that led to discontinuation of study drug.
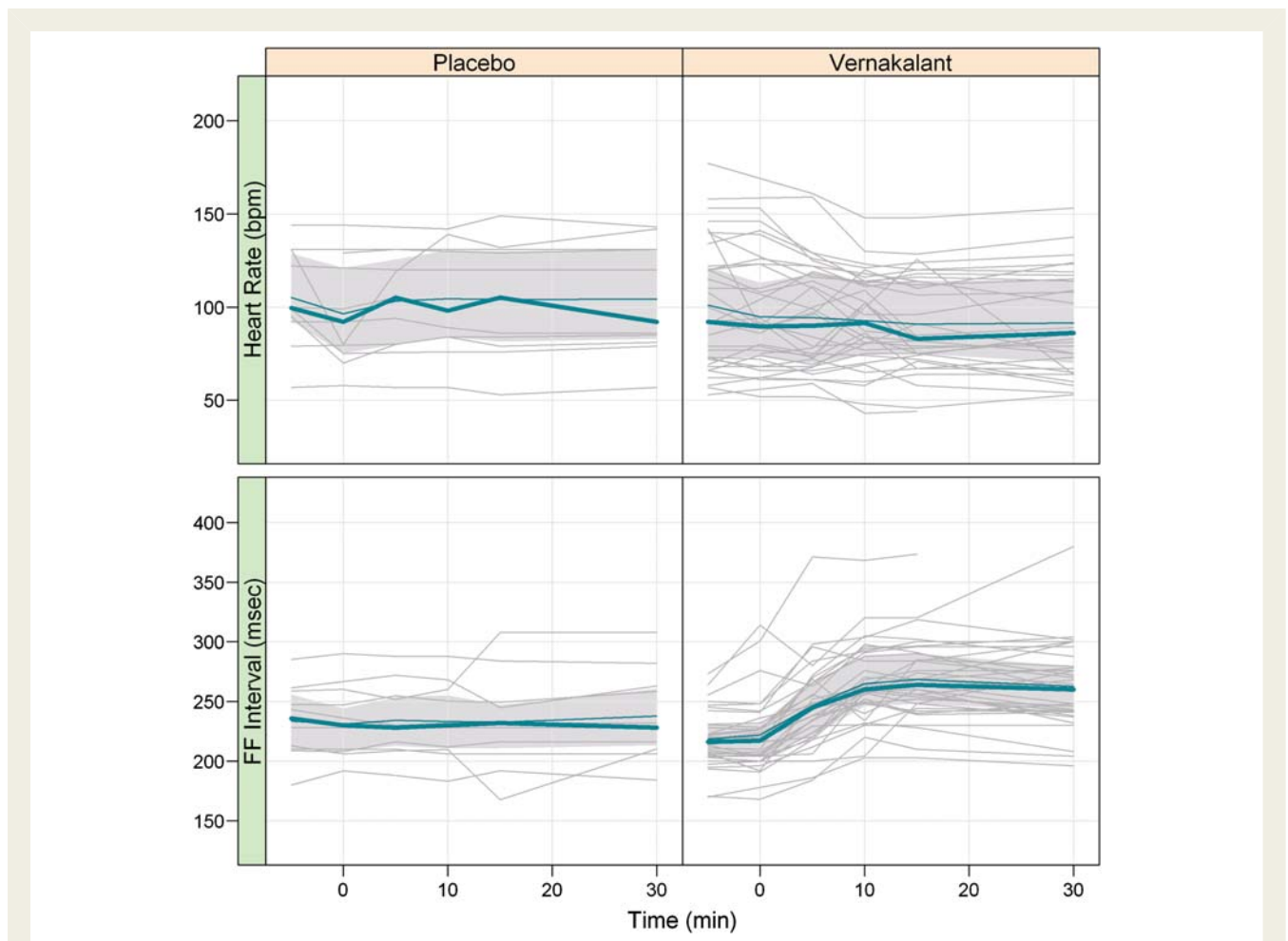

Figure 2 Atrial flutter cycle length (FF interval) and heart rate from baseline to 30 min. Vernakalant was given at time 0. $n = 11$ placebo and 35 vernakalant patients; data were not available for eight patients (four placebo and four vernakalant). The grey lines represent individual patient data, the thin blue line represents the mean, and the bold blue line represents the median. The shaded grey region is the sample interquartile range. b.p.m., beats per minute.

Table 2 Adverse events occurring in ≥5% of patients within a treatment group

Adverse event	Treatment group	
	Placebo (*n* = 15)	Vernakalant (*n* = 39)
Any adverse event	11 (73)	34 (87)
Dysgeusia	0	15 (38)
Paraesthesia	0	6 (15)
Dizziness	0	5 (13)
Headache	0	3 (8)
Syncope	1 (7)	1 (3)
Sneezing	0	15 (38)
Cough	0	5 (13)
Dyspnea	1 (7)	2 (5)
Bradycardia	0	4 (10)
Nausea and vomiting	1 (7)	9 (23)
Hypotension	1 (7)	5 (13)
Hyperhidrosis	0	4 (10)
Infusion site pain	0	3 (8)
Pain in extremity	0	2 (5)

Values are patients, *n* (%).

There were no deaths during this study. Serious adverse events were reported in 11 of 54 (20%) patients overall: 4 of 15 (27%) patients in the placebo group and 7 of 39 (18%) patients in the vernakalant group. Most SAEs were not considered by the investigator to be related to study drug. Two SAEs reported for patients receiving vernakalant were considered by the investigator to be probably or definitely related to study drug and began during the 0–24 h time period: hypotension (1 of 39, 3%) and a feeling of suffocation (1 of 39, 3%).

A nine-beat asymptomatic run of TdP was captured by Holter monitoring ~2 h after the infusion of vernakalant and immediately following an infusion of ibutilide. The event was not observed or reported as an AE by the investigator.

Discussion

Vernakalant did not restore sinus rhythm in patients with AFL with duration >3 h and ≤45 days. Only 1 of 39 patients receiving vernakalant injection had sinus rhythm restored. This result agrees with previously reported studies in which vernakalant failed to convert AFL to sinus rhythm in patients with short-duration AFL (one conversion out of 14 patients)[13] or in patients with AFL after cardiac surgery (zero conversions out of six patients).[14]

Vernakalant is effective in converting AF to sinus rhythm in patients with recent onset AF (51% conversion rate)[11,13] and in patients with AF following heart surgery (47% conversion rate).[14] The explanation for its lack of effect in converting AFL to sinus rhythm is unclear. It is possible that more selective and potent blockade of the rapidly activated delayed rectifier potassium current (I_{Kr}), as seen with ibutilide[17–19] or dofetilide,[20,21] is required for effective conversion of AFL to normal sinus rhythm.

Slowing excessively rapid heart rates is an important step in managing AF and AFL.[22] Vernakalant was associated with a significant absolute reduction in atrial rate and ventricular response rate; however, these reductions were modest. Vernakalant has rate-related blocking effects on sodium channels (I_{Na}), which is the probable explanation for the modest effect on AFL rate. Other antiarrhythmic agents (such as flecainide) with more potent sodium channel blocking properties can markedly slow the flutter rate or convert AF to slow AF often with a widened QRS.[23] Marked slowing of atrial rate can result in haemodynamically unstable 1 : 1 AV conduction indirectly with a high ventricular rate and often aberrant conduction (widened QRS).[24–26] This rhythm can sometimes be confused with ventricular tachycardia and is an important safety issue with these drugs.

In the present study of AFL, and also in prior clinical trial experience, no 1 : 1 AV conduction with rapid ventricular response (>200 b.p.m.) was observed with vernakalant. The observed effect on atrial rate was modest and vernakalant slightly prolonged AV nodal refractoriness at higher doses, tending to slightly prolong AV nodal and His Purkinje conduction as well as intraventricular conduction.[10] This combination of effects probably explains the lack of 1 : 1 AV conduction. In this particular respect, there is no apparent safety concern over rapid conduction to the ventricles when using vernakalant for pharmacologic cardioversion.

Vernakalant was generally well tolerated. Transient dysgeusia and sneezing were the most common treatment-related AEs, which is consistent with previous reports.[11,13]

Conclusion

Vernakalant is well tolerated, but does not restore sinus rhythm in patients with AFL. Vernakalant modestly slows AFL and ventricular response rates.

Conflict of interest: A.J.C. was a member of the Data and Safety Monitoring Board for this and other vernakalant studies; has been an advisor and member of a speakers' bureau for Cardiome, Astellas, and Merck; and has been a consultant to Sanofi, Gilead, Menarini, Servier, Sention, Daiichi, and BMS. E.T., C.T.-P., S.J.-M., and D.G.W were steering committee members for this clinical trial, and P.V. and J.I. were principal investigators in this clinical trial. C.T.-P. has also received consultant fees, honoraria, and speaker's fees from Cardiome and Merck, and has been an advisory board and steering committee member for Cardiome and Merck. S.J.-M. is also a consultant to Merck. D.G.W. is also participating in studies sponsored by Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Sanofi Aventis, BIOTRONIK, Boston Scientfic/ Guident (Europe), Medtronic, and Merck, and has been a consultant to Merck. G.N.B. is a full time employee of Cardiome and G.D. is a consultant to Cardiome.

Appendix: List of centres and investigators

Centre, city, investigator—Canada: Hamilton Health Sciences Centre, Hamilton General Hospital, Hamilton, Connolly; Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montreal, Coutu; Rockyview General Hospital and Heart Health Institute, Calgary, Ma; Centre Hospitalier de l'Université de Montréal Hôtel Dieu, Montreal, Phaneuf; Walter Mackenzie Health Science Center, University of Alberta, Edmonton, Rowe; Montreal Heart Institute, Montreal, Roy; The Ottawa Hospital (Civic and General Campuses) and Clinical Epidemiology Unit, Ottawa, Stiell; Heritage Medical Research Clinic, Calgary, Wyse; Denmark: Gentofte Amtssygehus, Hellerup, Hassager; Centralsygehuset Esbjerg Varde, Esbjerg, Nielsen; Holstebro Centralsygehus, Holstebro, Nyvad; Bispebjerg Hospital, København, Torp-Pedersen; Hjørring-Brønderslev Sygehus, Hjørring, Petersen; Hvidovre Hospital, Hvidovre, Rasmussen; Glostrup Amtssygehus, Glostrup, Rokkedal; Herlev Amtssygehus, Herlev, Skagen; Aalborg Sygehus Syd, Aalborg, Toft; Sweden: Centrallasarettet, Västerås Hjärtmottagningen, Västerås, Bandh; Universitetssjukhuset Mas, Malmö, Juul-Möller; United States: Virginia Commonwealth University Health System, Richmond, Ellenbogen; Thoracic and Cardiovascular Institute and Ingham Regional Medical Center, Lansing, Ip; Regional Cardiology Associates and Mercy General Hospital, Sacramento, O'Neill; Marshfield Clinic and Saint Joseph's Hospital, Marshfield, Vidaillet; McGuire Veterans Affairs Medical Center, Richmond, Vijayaraman.

References

1. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. *Circulation* 2003;**108**:1871−909.
2. Granada J, Uribe W, Chyou PH, Maassen K, Vierkant R, Smith PN et al. Incidence and predictors of atrial flutter in the general population. *J Am Coll Cardiol* 2000;**36**: 2242−6.
3. Mareedu RK, Abdalrahman IB, Dharmashankar KC, Granada JF, Chyou PH, Sharma PP et al. Atrial flutter versus atrial fibrillation in a general population: differences in comorbidities associated with their respective onset. *Clin Med Res* 2010;**8**:1−6.
4. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. *J Am Coll Cardiol* 2008;**51**:779−86.
5. Ng DW, Altemose GT, Wu Q, Srivathsan K, Scott LR. Typical atrial flutter as a risk factor for the development of atrial fibrillation in patients without otherwise demonstrable atrial tachyarrhythmias. *Mayo Clin Proc* 2008;**83**:646−50.
6. Estes NA III, Halperin JL, Calkins H, Ezekowitz MD, Gitman P, Go AS et al. ACC/AHA/Physician Consortium 2008 clinical performance measures for adults with nonvalvular atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and the Physician Consortium for Performance Improvement. *Circulation* 2008;**117**:1101−20.
7. Dobrev D, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet* 2010;**375**:1212−23.
8. Chimienti M, Cullen MT Jr, Casadei G. Safety of flecainide versus propafenone for the long-term management of symptomatic paroxysmal supraventricular tachyarrhythmias. Report from the Flecainide and Propafenone Italian Study (FAPIS) Group. *Eur Heart J* 1995;**16**:1943−51.
9. Fedida D, Orth PM, Chen JY, Lin S, Plouvier B, Jung G et al. The mechanism of atrial antiarrhythmic action of RSD1235. *J Cardiovasc Electrophysiol* 2005;**16**: 1227−38.
10. Dorian P, Pinter A, Mangat I, Korley V, Cvitkovic SS, Beatch GN. The effect of vernakalant (RSD1235), an investigational antiarrhythmic agent, on atrial electrophysiology in humans. *J Cardiovasc Pharmacol* 2007;**50**:35−40.
11. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518−25.
12. Roy D, Rowe BH, Stiell IG, Coutu B, Ip JH, Phaneuf D et al. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004;**44**:2355−61.
13. Pratt CM, Roy D, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S et al. Usefulness of vernakalant hydrochloride injection for rapid conversion of atrial fibrillation. *Am J Cardiol* 2010;**106**:1277−83.
14. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ et al. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**:652−9.
15. Bazett HC. An analysis of time relations of electrocardiograms. *Heart* 1920;**7**: 353−70.
16. Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 1920;**53**:469−86.
17. Glatter K, Yang Y, Chatterjee K, Modin G, Cheng J, Kayser S et al. Chemical cardioversion of atrial fibrillation or flutter with ibutilide in patients receiving amiodarone therapy. *Circulation* 2001;**103**:253−7.
18. VanderLugt JT, Mattioni T, Denker S, Torchiana D, Ahern T, Wakefield LK et al. Efficacy and safety of ibutilide fumarate for the conversion of atrial arrhythmias after cardiac surgery. *Circulation* 1999;**100**:369−75.
19. Volgman AS, Carberry PA, Stambler B, Lewis WR, Dunn GH, Perry KT et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. *J Am Coll Cardiol* 1998; **31**:1414−9.
20. Bianconi L, Castro A, Dinelli M, Alboni P, Pappalardo A, Richiardi E et al. Comparison of intravenously administered dofetilide versus amiodarone in the acute termination of atrial fibrillation and flutter. A multicentre, randomized, double-blind, placebo-controlled study. *Eur Heart J* 2000;**21**:1265−73.
21. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation* 2000;**102**: 2385−90.
22. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. *Europace* 2006;**8**:651−745.
23. Hellestrand KJ, Bexton RS, Nathan AW, Spurrell RA, Camm AJ. Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man. *Br Heart J* 1982;**48**:140−8.
24. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. *Europace* 2011;**13**:161−73.
25. Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. *Ann Intern Med* 1992;**117**:141−50.
26. Kawabata M, Hirao K, Horikawa T, Suzuki K, Motokawa K, Suzuki F et al. Syncope in patients with atrial flutter during treatment with class Ic antiarrhythmic drugs. *J Electrocardiol* 2001;**34**:65−72.