Efficacy and Safety of Celivarone, With Amiodarone as Calibrator, in Patients With an Implantable Cardioverter-Defibrillator for Prevention of Implantable Cardioverter-Defibrillator Interventions or Death

The ALPHEE Study

Peter R. Kowey, MD, FAHA; Harry J.G.M. Crijns, MD; Etienne M. Aliot, MD; Alessandro Capucci, MD; Piotr Kulakowski, MD; David Radzik, MD; Denis Roy, MD; Stuart J. Connolly, MD; Stefan H. Hohnloser, MD; on behalf of the ALPHEE Study Investigators

Background—Celivarone is a new antiarrhythmic agent developed for the treatment of ventricular arrhythmias. This study investigated the efficacy and safety of celivarone in preventing implantable cardioverter-defibrillator (ICD) interventions or death.

Methods and Results—Celivarone (50, 100, or 300 mg/d) was assessed compared with placebo in this randomized, double-blind, placebo-controlled, parallel-group study. Amiodarone (200 mg/d after loading dose of 600 mg/d for 10 days) was used as a calibrator. A total of 486 patients with a left ventricular ejection fraction ≤40% and at least 1 ICD intervention for ventricular tachycardia or ventricular fibrillation in the previous month or ICD implantation in the previous month for documented ventricular tachycardia/ventricular fibrillation were randomized. Median treatment duration was 9 months. The primary efficacy end point was occurrence of ventricular tachycardia/ventricular fibrillation–triggered ICD interventions (shocks or antitachycardia pacing) or sudden death. The proportion of patients experiencing an appropriate ICD intervention or sudden death was 61.5% in the placebo group; 67.0%, 58.8%, and 54.9% in the celivarone 50-, 100-, and 300-mg groups, respectively; and 45.3% in the amiodarone group. Hazard ratios versus placebo for the primary end point ranged from 0.860 for celivarone 300 mg to 1.199 for celivarone 50 mg. None of the comparisons versus placebo were statistically significant. Celivarone had an acceptable safety profile.

Conclusions—Celivarone was not effective for the prevention of ICD interventions or sudden death.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00993382.

Patients surviving an episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) have a risk of recurrence of 10% to 50% within 2 years.1,2 These ventricular arrhythmias are responsible for two thirds of sudden cardiac deaths each year in the United States.3 Implantable cardioverter-defibrillators (ICDs) are now the standard of care for secondary prevention of sudden cardiac death in patients at high risk of life-threatening arrhythmias and are used with even greater frequency for the primary prevention of sudden death in high-risk patients.4 ICDs terminate ventricular arrhythmias but do not prevent them. Accordingly, up to 50% of patients with an ICD will require adjunctive antiarrhythmic drug therapy to prevent frequent ICD shocks for VT/VF or for prevention of inappropriate shocks, mostly caused by atrial fibrillation.5,6 These drugs help patients to avoid the discomfort of frequent device discharges and prevent battery depletion. In addition, frequent shocks are assoc-
aded with a higher mortality and frequent, expensive hospitalizations.6

Clinical Perspective on p 2660

The most frequently used and most effective drug for this purpose is the benzofuran derivative amiodarone.7 Its use, however, is limited by a wide range of organ-toxic side effects, difficult pharmacology, and a host of drug-drug interactions.7,8 Azimilide and sotalol have also been studied and have positive data to support their use, but no pharmacological agent has yet gained regulatory approval for this indication.5,9

Celivarone is a noniodinated benzofuran derivative that has been under development for use in atrial and ventricular arrhythmias. It blocks calcium, sodium, and several potassium channels and inhibits α1- and β1-adrenergic responses and angiotensin II receptor stimulation.10 Like amiodarone and dronedarone, celivarone has class I, II, III, and IV antiarrhythmic effects, but its relative potency for each of these channel and receptor effects distinguishes this drug from its congeners. In addition, the structure and pharmacokinetics of celivarone differ from those of amiodarone and thus may have an improved side-effect profile, faster time to effect and elimination times, and a reduced potential for drug-drug interactions.10,11

Celivarone was studied in a robust and comprehensive phase II program. In 2 studies performed in patients with atrial fibrillation, the drug was not effective for the maintenance of sinus rhythm or for atrial fibrillation conversion to sinus rhythm.12,13

Because preclinical data indicated that the drug had ventricular activity, a randomized, double-blind, placebo-controlled, dose-ranging study (Prevention of Ventricular Arrhythmia-Triggered ICD Interventions [ICARIOS]) was performed in 153 patients with ICDs. Patients were randomized to placebo or celivarone 100 or 300 mg once daily for 6 months, and the primary end point was prevention of VT/VF-triggered ICD interventions.14 There was a positive, but statistically nonsignificant, trend toward a decreased number of events in the celivarone 300-mg group. In addition, post hoc analysis of a subgroup of patients in the celivarone 300-mg group who had recent ICD therapy in the month preceding randomization showed a significant benefit (hazard ratio [HR]=0.46; P=0.032). These results formed the hypothesis that led to the design of this phase IIB clinical trial.

We performed a randomized, placebo-controlled, dose-ranging, phase II study of celivarone, with an amiodarone calibrator arm (Dose Ranging Study of Celivarone With Amiodarone as Calibrator for the Prevention of Implantable Cardioverter Defibrillator Interventions or Death [ALPHEE]), to evaluate the safety and efficacy of celivarone in preventing ICD interventions or death in patients at high risk for a severe ventricular arrhythmia.

Methods

Study Design

ALPHEE (NCT00993382) was conducted at 151 centers in 26 countries from September 2009 to May 2011. The primary objective was to assess the efficacy of celivarone (50, 100, or 300 mg/d) versus placebo, with the use of amiodarone (200 mg/d after a loading dose of 600 mg/d for 10 days) as a calibrator, for the prevention of ICD interventions or sudden death. Secondary objectives were assessment of the safety and tolerability of celivarone and delineation of its pharmacokinetic profile in this relevant patient population.

The study protocol was approved by independent ethics committees or institutional review boards and complied with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice, and local laws, regulations, and any applicable guidelines in each country. Written informed consent was obtained from each patient with the use of a document that was reviewed and certified by each institutional committee.

An independent steering committee of academic physicians and 1 industry representative was responsible for the design and conduct of the study, data analysis, central blinded adjudication of deaths, and reporting of the study. An independent data monitoring committee oversaw the safety of patients. A blinded central adjudication committee reviewed all ICD events. Because we anticipated multiple events in a minority of patients in the trial, we prespecified that only the first 10 ICD events per episode would be recorded and counted to the end point.

Patients

Patients aged ≥21 years were eligible for inclusion if they had an indication for an ICD for primary prevention. To increase the event rate, we further required at least 1 ICD intervention for VT or VF in the previous month. We also enrolled secondary prevention patients who in the previous month had either an ICD implantation for documented VT/VF or at least 1 ICD intervention for VT or VF. All patients had to have significant cardiac dysfunction, defined as a left ventricular ejection fraction ≤40%. ICDs had to have a data-logging function with cumulative counting of device interventions (shock and antitachycardia pacing), electrogram storage capabilities, and ventricular demand pacing.

The main exclusion criteria were the following: recent unstable angina pectoris or myocardial infarction within 4 weeks; history of torsades de pointes or congenital long-QT syndrome; preexcitation syndrome; cardiogenic shock, advanced heart failure, or treatment with intravenous pressor agents; hemodynamically significant primary obstructive valvular disease; hemodynamically significant obstructive cardiomyopathy; a cardiac operation or revascularization procedure within 4 weeks preceding randomization; incessant sustained VT or VF during the 3 days preceding randomization; inappropriate shocks during the month preceding randomization; and treatment with amiodarone (>20 tablets during the 2 months preceding randomization).

The only drugs prohibited during the study were Vaughan-Williams class I and III antiarrhythmic drugs as well as agents known to induce torsades de pointes.

Screening, Randomization, and Therapy

Patients were screened for eligibility up to 7 days before randomization. Screening and baseline evaluations included medical history; prior and concomitant medications; clinical examination; chest x-ray; 2-dimensional echocardiogram; ICD interrogation; 12-lead ECG; and clinical laboratory tests. ICDs were programmed at the randomization visit (day 1) to allow for precise recording and storage of relevant events.

Patients were randomized to receive double-blind, once-daily oral therapy for at least 6 months with celivarone (50, 100, or 300 mg); amiodarone (600 mg for 10 days followed by 200 mg/d thereafter), or placebo. Medication was taken at the end of the patient's main meal of the day because of a previously documented significant food effect with celivarone and amiodarone.

A centralized randomization list was generated with an interactive voice response system or interactive Web response system. Randomization was stratified by the timing of ICD implantation (<1 or >1 month) and country, with a ratio of 2:2:2:2:1 for...
Follow-Up

Follow-up visits were scheduled on days 5 and 14, months 1, 2, 3, 4, 5, and 6, and then every 3 months until the scheduled study end (date of randomization of the last patient + 190 days). Visits included blood pressure measurement, ICD interrogation, 12-lead ECG, and documentation of symptoms and adverse events. Blood samples for general clinical laboratory evaluation were collected at all visits except months 4 and 5 and for pharmacokinetic analyses on day 5 and at months 1, 2, 3, 6, and 12.

A trained electrophysiologist interrogated the ICD at each follow-up visit. Data stored since the last interrogation were printed and reviewed for quality before adjudication by the central committee. Patients were instructed to call the investigator if they received a shock or in case of syncope or dizziness so that they could be seen as soon as possible (within 1 week) for an ICD interrogation. If a patient experienced cluster shocks or electric instability (>3 interventions per day), the patient required a visit and ICD interrogation within 1 day. Data from the ICD were used to count all ICD interventions (shocks and antitachycardia pacing), document arrhythmic events triggering the device up to 10 episodes per patient and until first ICD shock, and classify the ICD interventions as appropriate or inappropriate. Interventions delivered as a result of VT or VF were deemed appropriate, whereas those delivered in response to supraventricular tachycardia or other events, such as oversensing, were deemed inappropriate. If multiple shocks or antitachycardia pacings were delivered by the device to terminate the same episode of arrhythmia, they were considered to be part of 1 event. Patients were followed until the scheduled study end or until recovery or stabilization of an adverse event, whichever came last.

Study End Points

The primary efficacy end point was the occurrence of VT/VF-triggered ICD interventions (shocks or antitachycardia pacing) or sudden death, analyzed with a time to first event approach. A prespecified sensitivity analysis was also conducted, taking into account recurrent arrhythmic episodes as described in the following section. The secondary efficacy end point was occurrence of ICD shocks (appropriate or inappropriate) or death from any cause.

Statistical Assumptions and Analyses

The number of patients needed to assess the primary end point was determined with assumption of an ICD intervention/sudden death rate in the placebo group at 2, 4, 6, 8, 10, 14, and 20 months of 48%, 52%, 60%, 75%, 78%, 78.5%, and 79%, respectively. We powered the study to detect a relative risk reduction of 44% in at least 1 celivarone group versus placebo. With the use of these assumptions, with 85% power, 108 patients would be required in each of the placebo and celivarone groups.

No direct comparison of celivarone and amiodarone was intended, and no statistical power was assigned. The objective of the calibrator arm was to obtain evidence of efficacy in this group versus placebo to validate the study design. Therefore, including half of the number of patients in the amiodarone group compared with the celivarone group was deemed to be adequate.

The main efficacy population included all randomized patients (intention-to-treat population). Each celivarone dose group was compared with the placebo group with a stratified, 2-sided, log-rank asymptotic test according to randomization stratum (timing of ICD implantation ≤30 days/ >30 days). HRs with 95% confidence intervals (CIs) were estimated by the Cox model. Cumulative incidence functions and 95% CIs were calculated with the use of nonparametric Kaplan-Meier estimates and Greenwood’s variance estimation.

A secondary sensitivity analysis of the primary end point was the time from randomization to occurrence of all VT/VF-triggered ICD interventions (up to 10 per patient) or sudden death. HRs for each celivarone dose versus placebo were estimated by the Anderson-Gill mean intensity model and the robust sandwich
The main analysis of the secondary efficacy end point was the time from randomization to the first ICD shock or death from any cause. To address the multiplicity in end points, a closed testing procedure was used. The safety population included all randomized patients who received at least 1 dose of study medication, and safety data were summarized with the use of descriptive statistics.

### Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=109)</th>
<th>Celivarone 50 mg (n=109)</th>
<th>Celivarone 100 mg (n=102)</th>
<th>Celivarone 300 mg (n=113)</th>
<th>Amiodarone 200 mg (n=53)</th>
<th>All (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64.7 (12.0)</td>
<td>65.8 (10.6)</td>
<td>62.8 (10.3)</td>
<td>63.0 (11.5)</td>
<td>66.8 (8.4)</td>
<td>64.4 (10.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98 (89.9)</td>
<td>96 (88.1)</td>
<td>91 (89.2)</td>
<td>97 (85.8)</td>
<td>49 (92.5)</td>
<td>431 (88.7)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (10.1)</td>
<td>13 (11.9)</td>
<td>11 (10.8)</td>
<td>16 (14.2)</td>
<td>4 (7.5)</td>
<td>55 (11.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>101 (92.7)</td>
<td>101 (92.7)</td>
<td>93 (91.2)</td>
<td>106 (93.8)</td>
<td>50 (94.3)</td>
<td>451 (92.8)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (3.7)</td>
<td>3 (2.8)</td>
<td>5 (4.9)</td>
<td>2 (1.8)</td>
<td>1 (1.9)</td>
<td>15 (3.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3.7)</td>
<td>5 (4.6)</td>
<td>3 (2.9)</td>
<td>3 (2.7)</td>
<td>1 (1.9)</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>2 (1.8)</td>
<td>1 (1.9)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>LVEF, mean (SD), %</td>
<td>29.2 (7.5)</td>
<td>28.3 (8.0)</td>
<td>29.8 (6.7)</td>
<td>29.1 (8.0)</td>
<td>29.2 (7.6)</td>
<td>29.1 (7.6)</td>
</tr>
<tr>
<td>LVEF, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35%</td>
<td>73 (67.0)</td>
<td>76 (69.7)</td>
<td>64 (62.7)</td>
<td>70 (61.9)</td>
<td>35 (66.0)</td>
<td>318 (65.4)</td>
</tr>
<tr>
<td>≥35%</td>
<td>36 (33.0)</td>
<td>33 (30.3)</td>
<td>38 (37.3)</td>
<td>43 (38.1)</td>
<td>18 (34.0)</td>
<td>168 (34.6)</td>
</tr>
<tr>
<td>Any congestive heart failure</td>
<td>96 (88.9%)</td>
<td>96 (88.1%)</td>
<td>84 (82.4%)</td>
<td>99 (87.6%)</td>
<td>42 (79.2%)</td>
<td>417 (86.0%)</td>
</tr>
<tr>
<td>NYHA class I*</td>
<td>16 (16.7)</td>
<td>14 (14.6)</td>
<td>13 (15.5)</td>
<td>15 (15.2)</td>
<td>7 (16.7)</td>
<td>65 (15.6)</td>
</tr>
<tr>
<td>NYHA class II*</td>
<td>55 (57.3)</td>
<td>57 (59.4)</td>
<td>52 (61.9)</td>
<td>63 (63.6)</td>
<td>25 (59.5)</td>
<td>252 (60.4)</td>
</tr>
<tr>
<td>NYHA class III*</td>
<td>25 (26.0)</td>
<td>25 (26.0)</td>
<td>19 (22.6)</td>
<td>21 (21.2)</td>
<td>10 (23.8)</td>
<td>124 (25.5)</td>
</tr>
<tr>
<td>Cardiovascular history,† n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>86 (78.9)</td>
<td>78 (71.6)</td>
<td>75 (73.5)</td>
<td>72 (63.7)</td>
<td>36 (67.9)</td>
<td>347 (71.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 (64.2)</td>
<td>69 (63.3)</td>
<td>65 (63.7)</td>
<td>58 (51.3)</td>
<td>27 (50.9)</td>
<td>289 (59.5)</td>
</tr>
<tr>
<td>Ischemic dilated cardiomyopathy</td>
<td>61 (56.0)</td>
<td>54 (49.5)</td>
<td>51 (50.0)</td>
<td>52 (46.0)</td>
<td>28 (52.8)</td>
<td>246 (50.6)</td>
</tr>
<tr>
<td>Syncope</td>
<td>28 (25.7)</td>
<td>33 (30.3)</td>
<td>37 (36.3)</td>
<td>36 (31.9)</td>
<td>22 (41.5)</td>
<td>156 (32.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (27.5)</td>
<td>39 (35.8)</td>
<td>23 (22.5)</td>
<td>34 (30.1)</td>
<td>13 (24.5)</td>
<td>139 (28.6)</td>
</tr>
<tr>
<td>Nonischemic dilated cardiomyopathy</td>
<td>20 (18.3)</td>
<td>30 (27.5)</td>
<td>28 (27.5)</td>
<td>33 (29.2)</td>
<td>13 (24.5)</td>
<td>124 (25.5)</td>
</tr>
<tr>
<td>Nonrheumatic valvular heart disease</td>
<td>21 (19.3)</td>
<td>32 (29.4)</td>
<td>18 (17.6)</td>
<td>21 (23.9)</td>
<td>15 (28.3)</td>
<td>113 (23.3)</td>
</tr>
<tr>
<td>Indication for ICD implantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>34 (31.2)</td>
<td>44 (40.4)</td>
<td>34 (33.3)</td>
<td>43 (38.1)</td>
<td>18 (34.0)</td>
<td>173 (35.6)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>75 (68.8)</td>
<td>65 (59.6)</td>
<td>68 (66.7)</td>
<td>70 (61.9)</td>
<td>35 (66.0)</td>
<td>313 (64.4)</td>
</tr>
<tr>
<td>Time since first ICD implantation, mean (SD), mo</td>
<td>27.3 (38.2)</td>
<td>32.2 (38.9)</td>
<td>28.7 (38.1)</td>
<td>27.8 (35.3)</td>
<td>27.7 (37.5)</td>
<td>28.8 (37.5)</td>
</tr>
<tr>
<td>Time since last appropriate ICD intervention,‡ mean (SD), d</td>
<td>12.4 (9.8)</td>
<td>13.6 (9.6)</td>
<td>13.4 (10.5)</td>
<td>14.4 (13.8)</td>
<td>10.2 (8.4)</td>
<td>13.1 (10.7)</td>
</tr>
<tr>
<td>Prior cardiovascular medications,§ n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>101 (92.7)</td>
<td>96 (88.1)</td>
<td>92 (90.2)</td>
<td>101 (89.4)</td>
<td>43 (81.1)</td>
<td>433 (89.1)</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>90 (82.6)</td>
<td>93 (85.3)</td>
<td>88 (86.3)</td>
<td>100 (88.5)</td>
<td>43 (81.1)</td>
<td>414 (85.2)</td>
</tr>
<tr>
<td>Lipid-modifying agents</td>
<td>82 (75.2)</td>
<td>76 (69.7)</td>
<td>81 (79.4)</td>
<td>81 (71.7)</td>
<td>36 (67.9)</td>
<td>356 (73.3)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>75 (68.8)</td>
<td>74 (67.9)</td>
<td>69 (67.6)</td>
<td>82 (72.6)</td>
<td>36 (67.9)</td>
<td>336 (69.1)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>14 (12.8)</td>
<td>12 (11.0)</td>
<td>12 (11.8)</td>
<td>12 (10.6)</td>
<td>3 (5.7)</td>
<td>53 (10.9)</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; ICD, implantable cardioverter-defibrillator; ACE, angiotensin-converting enzyme; and ARB, angiotensin II receptor blocker.

*Only for patients with congestive heart failure.

†Listing of conditions occurring with a frequency >10% in the overall study population.

‡Only for patients with appropriate ICD intervention between ICD implantation and randomization.

§Medications used by patients 7 d before first dose of study medication.

Data unavailable for 1 patient.
Results

Patients
A total of 486 patients were randomized, of whom 481 received study drug (median treatment duration = 9 months; 28.7% of patients were treated for at least 12 months) and 312 (64.2%) completed treatment (Figure 1). The proportion of patients not completing treatment was similar across the groups. Approximately one third of patients were randomized in the stratum ICD implantation date ≤ 30 days and two thirds in the stratum > 30 days. The majority of patients (87.7%) were followed until the scheduled study end date, with the overall median follow-up of 12.1 months (range, 0.2–19.2). A similar proportion of patients across the groups were followed for at least 9 months (75.7% of patients overall).

The baseline characteristics of patients were similar across the treatment groups. The mean age was 64.4 years (17.3% were aged ≥ 75 years), and 88.7% were male (Table 1). Mean left ventricular ejection fraction was 29.1% overall, and 65.4% of patients had a left ventricular ejection fraction ≤ 35%. Most patients (86.0%) had some degree of congestive heart failure; mean left ventricular ejection fraction and congestive heart failure severity were evenly distributed across the groups (Table 1). The mean time since first ICD implantation was 28.8 months, and secondary prevention was the reason for ICD implantation in 64.4% of patients. Details of prior cardiovascular medications are included in Table 1.

Efficacy

Primary End Point
The cumulative proportion of patients experiencing an appropriate ICD intervention or sudden death was 61.5% in the placebo group; 67.0%, 58.8%, and 54.9% in the celivarone 50-, 100-, and 300-mg groups, respectively; and 45.3% in the amiodarone 200-mg group (Figure 2). The primary end point was driven by the VT/VF component in all groups. There were a total of 6 sudden deaths in the trial: 1 in the placebo group, 1 in the celivarone 300-mg group, and 4 in the amiodarone group. None of the HRs versus placebo for the primary end point, ranging from 0.86 for the celivarone 300-mg group to 1.199 for celivarone 50-mg group, were statistically significant. There was a trend toward a decrease in the incidence of the primary end point in the amiodarone group compared with the placebo group (HR = 0.697; 95% CI, 0.437–1.113; P = 0.13).

Analysis of the first component of the primary end point (VT/VF-triggered ICD intervention alone) showed no statistically significant differences between the celivarone groups and the placebo group (Figure 3A) and did not show any evidence of a dose effect. There was, however, a significant decrease in this component of the primary end point in the amiodarone group compared with the placebo group (HR = 0.595; 95% CI, 0.360–0.982; P = 0.0399).

The number of events for the second component of the primary end point (sudden death) was low, and there was no evidence of a difference between the celivarone groups and the placebo group or of any dose effect (Figure 3B). In the amiodarone group, the HR versus placebo was 4.46 (P = 0.0207).

The proportion of patients with multiple ICD interventions (up to 10) is shown in Figure 4A. The HRs versus placebo were 1.045, 0.839, and 0.681 for the celivarone 50-, 100-, and 300-mg groups, respectively. Mean cumulative number of occurrences (up to 10 arrhythmic episodes or sudden death per patient) is shown in Figure 4B. These findings were not statistically significant when analyzed with the use of the Hochberg correction for multiplicity of comparisons.

Secondary End Point
In this analysis of time to first event, the proportion of patients experiencing an ICD shock or death was 44.0% in the placebo group; 45.0%, 37.3%, and 41.6% in the celivarone 50-, 100-, and 300-mg groups, respectively; and 26.4% in the amiodarone 200-mg group (Figure 5). The secondary end point was driven by shock in all of the celivarone groups; in the amiodarone group, 6 of the 14 events were death. HRs for the celivarone groups versus placebo ranged from 0.797 for the celivarone 100-mg group to 1.023 for the celivarone
50-mg group, but none were statistically significant, and there was no evidence of a dose effect. Consistent with the primary analysis, there was a non–statistically significant reduction in the secondary end point with amiodarone compared with placebo (HR \(0.556; P=0.503\)).

Analysis of the first component of the secondary end point (ICD shocks alone) showed no statistically significant differences between the celivarone and placebo groups and no evidence of a dose effect (Figure 6A). However, there was a significant decrease in ICD shocks in the amiodarone group compared with placebo (HR=0.333; 95% CI, 0.157–0.706; \(P=0.0026\)).

The number of events for the second component of the secondary end point (death from any cause) was low, and there was no evidence of a difference between the celivarone groups and placebo or of any dose effect (Figure 6B). In the amiodarone group, the HR versus placebo was 3.327 (95% CI, 1.182–9.367; \(P=0.0158\)); this was contributed to by a difference in the number of sudden deaths.

**Pharmacokinetic Data**

With follow-up to 12 months of repeated administration, mean steady state values of celivarone C\(_{\text{max}}\) were 103, 215, and 763 ng/mL at 50, 100, and 300 mg, respectively. At steady state, mean C\(_{\text{trough}}\) values were 48.1 ng/mL at 50 mg, 99.6 ng/mL at 100 mg, and 290 ng/mL at 300 mg.

**Safety**

Five patients in the intention-to-treat population (3 in the celivarone groups and 2 in the amiodarone group) did not receive a dose of study medication and were therefore excluded from the safety analysis. A similar proportion of
patients experienced treatment-emergent adverse events in each of the treatment groups, and approximately half of these were serious treatment-emergent adverse events (Table 2). There was no evidence of a dose effect in the celivarone groups for treatment-emergent adverse events, serious treatment-emergent adverse events, or treatment-emergent adverse events leading to discontinuation of treatment. The percentage of patients discontinuing treatment because of a treatment-emergent adverse event was higher in the amiodarone group than in the placebo group (31.4% versus 16.5%).

Cardiovascular events were the most frequently reported treatment-emergent adverse events, with VT being the most commonly reported. There was no evidence of a dose effect for cardiovascular events across the celivarone groups. One case of torsades de pointes was reported in the celivarone 300-mg group in a male patient who had several risk factors for the development of torsades de pointes.

There was no difference in the proportion of patients with increased QTc intervals (QTc Fridericia or QTc Bazett) across the celivarone groups. In the amiodarone group, the proportion of patients with a QTc Fridericia interval ≥ 500 ms (46.0%) or with an increase from baseline of ≥ 60 ms (56.0%) was higher than in the placebo group.

The frequency of organ-toxic side effects was the same across all celivarone dose groups. Likewise, there was no evidence of an effect of celivarone on clinical laboratory test
results, including hepatic and renal parameters, or on the thyroid gland. As expected, serum creatinine levels were increased in the amiodarone group compared with placebo, and there were more cases of hypothyroidism.

There were 43 all-cause deaths during the study (placebo, n=6; celivarone 50 mg, n=9; celivarone 100 mg, n=8; celivarone 300 mg, n=11; amiodarone 200 mg, n=9). The principal cause of death was cardiovascular. There was no apparent dose effect in the celivarone groups, but the number of deaths in the amiodarone group was notably higher than in the placebo group (17.0% versus 5.5%).

**Discussion**

The ALPHEE study did not demonstrate efficacy of celivarone at any of the doses studied for the prevention of ICD intervention or death in a relevant patient population. Although none of the results in the celivarone groups versus placebo were statistically significant after correction for multiplicity, in the 300-mg group, HRs of 0.86 and 0.681 in the primary analysis and the sensitivity analysis of the primary end point, respectively, could be in favor of a modestly reduced number of events in this group. The drug was well tolerated at all 3 doses, and serious adverse events and deaths were not seen at a rate different from placebo. Amiodarone, as expected, demonstrated superior efficacy compared with placebo but was not well tolerated and was associated with more sudden and nonsudden cardiovascular deaths. Pharmacokinetic data were consistent with the dose of celivarone administered in the different groups.

Antiarrhythmic drugs have been poorly and inadequately studied for ventricular indications. Surrogates are unreliable, and it is unethical to expose placebo-assigned patients to the risk of a malignant arrhythmia. Consequently, double-blind, placebo-controlled, dose-ranging studies have been conducted mainly in patients with ICDs. However, these patients are difficult to recruit and follow, interrogation and interpretation of the ICD can be complex, and, as a result, studies in this population are uncommon.

The efficacy of antiarrhythmic drugs in preventing shocks in patients with ICDs has been investigated in a few published studies. Sotalol reduced the risk of death from any cause or the delivery of a first shock for any reason, death from any cause, or the delivery of a first appropriate shock in a 12-month, double-blind, placebo-controlled multicenter study.9 A dose-ranging study of azimilide (Shock Inhibition Evaluation With Azimilide [SHIELD]; n=633) demonstrated equally significant reductions in the incidence of all appropriate ICD interventions at daily doses of 75 and 125 mg.5 In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients study (OPTIC; n=412), amiodarone plus a β-blocker significantly reduced the risk of ICD shock compared with a β-blocker alone or sotalol alone.7 Finally, 11 of 12 patients refractory to antiarrhythmic drugs treated with ranolazine had significantly reduced VT and remained free of ICD shock after a follow-up of 6 months.15 Although the data from these trials were compelling, none of the drugs have undergone successful regulatory review, and thus none are approved in the United States for the precise indication of prevention of ICD therapy or mortality reduction. Each suffers the major limitation of inadequate dose exploration and/or small number of patients and events.

There continues to be an unmet need. The number of ICD implants has risen dramatically, mainly for primary prevention purposes. With the inclusion of older patients with more comorbidities, we anticipate an increase in the number of patients who will require adjuvant therapy. The emergence of better ICD programming techniques and ablation procedures in this population will have a positive effect but will not be applicable to the broader population.

We believed that celivarone was an excellent candidate for this purpose. Preclinical information indicated that the drug would have a broad spectrum of antiarrhythmic effect, sup-
pressing both atrial and ventricular arrhythmias, and that it would be well tolerated. As a once-daily drug, we anticipated good patient adherence, and a paucity of safety signals presaged excellent tolerance.

Furthermore, we were buoyed by the results of the previous randomized, double-blind, placebo-controlled, dose-ranging study (ICARIOS), which evaluated celivarone 100 and 300 mg. ICARIOS showed a statistically insignificant trend toward a decreased number of arrhythmia-triggered ICD interventions in the celivarone 300-mg group over 6 months. Especially compelling was a positive post hoc finding in patients who had an ICD intervention within 30 days of randomization (HR = 0.46; P = 0.032).

The larger ALPHEE study was designed to explore this observation further with the following design improvements. ALPHEE prospectively investigated the population of patients who seemed to derive the greatest benefit from celivarone treatment based on the observations of ICARIOS, specifically patients with an ICD intervention within 30 days before randomization or implanted within the month preceding randomization for VT/VF.

A high dose of celivarone (300 mg) was chosen because of the trend toward efficacy for the prevention of ICD interventions and good tolerance in the ICARIOS study. A 50-mg dose was chosen as the lowest dose because it had shown little effect on 12-lead ECG parameters for documentation of the lowest effective dose. A broader investigation of dose effect was considered particularly important given the reverse dose effect observed for dronedarone, the precursor of celivarone, in the Dronedarone Atrial Fibrillation Study After Electrical Cardioversion (DAFNE).

Finally, patients received treatment over a longer period to permit a better assessment of safety as well as durability of clinical efficacy.
Most importantly, ALPHEE incorporated an amiodarone calibrator arm. This allowed us to establish the validity of the study methods and the sensitivity of the design. Amiodarone behaved as expected, lowering the number of ICD shocks compared with placebo. By so doing, it facilitated the interpretation of the results for the celivarone groups while increasing the total number of patients by 10%. The amiodarone results are interesting in that they corroborate data from other clinical trials that have suggested a lack of survival benefit and a safety signal in patients with advanced heart failure who receive ICDs. Given the small number of events

in this trial, the results need to be interpreted with caution, but they should encourage further evaluation of this drug in future studies of this indication.

In addition to providing protection to patients during antiarrhythmic trials, ICDs are a valuable tool for studying ventricular arrhythmias because they allow for precise delineation of events during the course of the trial, many of which may not be overt or appropriate. In ALPHEE, a central adjudication committee reviewed the arrhythmia episodes recorded in >6000 ICD printouts and confirmed whether the ICD intervention was appropriate or inappropriate, thus

Table 2. Number and Percentage of Patients With Selected Treatment-Emergent Adverse Events (Safety Population; n=481)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Placebo (n=109)</th>
<th>Celivarone 50 mg (n=107)</th>
<th>Celivarone 100 mg (n=101)</th>
<th>Celivarone 300 mg (n=113)</th>
<th>Amiodarone 200 mg (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>92 (84.4)</td>
<td>92 (86.0)</td>
<td>87 (86.1)</td>
<td>98 (86.7)</td>
<td>44 (86.3)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>53 (48.6)</td>
<td>45 (42.1)</td>
<td>53 (52.5)</td>
<td>49 (43.4)</td>
<td>23 (45.1)</td>
</tr>
<tr>
<td>Any TEAE leading to death*</td>
<td>4 (3.7)</td>
<td>2 (1.9)</td>
<td>5 (5.0)</td>
<td>6 (5.3)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Discontinued because of TEAE</td>
<td>18 (16.5)</td>
<td>29 (27.1)</td>
<td>24 (23.8)</td>
<td>24 (21.2)</td>
<td>16 (31.4)</td>
</tr>
</tbody>
</table>

TEAEs occurring in ≥5% of patients in any group

Neurological event
- Dizziness 6 (5.5) 13 (12.1) 8 (7.9) 7 (6.2) 9 (17.6)
- Syncope 6 (5.5) 9 (8.4) 7 (6.9) 12 (10.6) 0
- Headache 8 (7.3) 4 (3.7) 6 (5.9) 2 (1.8) 1 (2.0)

Cardiovascular event
- Ventricular tachycardia 19 (17.4) 25 (23.4) 25 (24.8) 20 (17.7) 7 (13.7)
- Heart failure 4 (3.7) 12 (11.2) 6 (5.9) 8 (7.1) 1 (2.0)
- Ventricular fibrillation 6 (5.5) 11 (10.3) 3 (3.0) 9 (8.0) 2 (3.9)
- Congestive heart failure 8 (7.3) 2 (1.9) 10 (9.9) 9 (8.0) 5 (9.8)
- Atrial fibrillation 10 (9.2) 10 (9.3) 9 (8.9) 4 (3.5) 2 (3.9)
- Hypertension 1 (0.9) 1 (0.9) 1 (1.0) 0 4 (7.8)

Gastrointestinal event
- Nausea 10 (9.2) 12 (11.2) 5 (5.0) 6 (5.3) 6 (11.8)
- Diarrhea 7 (6.4) 6 (5.6) 4 (4.0) 4 (3.5) 2 (3.9)

Pulmonary event
- Cough 4 (3.7) 4 (3.7) 6 (5.9) 5 (4.4) 1 (2.0)
- Dyspnea 4 (3.7) 6 (5.6) 5 (5.0) 5 (4.4) 1 (2.0)

Infections
- Pneumonia 3 (2.8) 2 (1.9) 4 (4.0) 4 (3.5) 3 (5.9)
- Sinusitis 1 (0.9) 1 (0.9) 2 (2.0) 1 (0.9) 3 (5.9)
- Nasopharyngitis 4 (3.7) 6 (5.6) 4 (4.0) 6 (5.3) 2 (3.9)

Endocrine disorders
- Hypothyroidism 1 (0.9) 3 (2.8) 1 (1.0) 1 (0.9) 4 (7.8)

Musculoskeletal disorders
- Back pain 3 (2.8) 0 5 (5.0) 3 (2.7) 5 (9.8)

Other
- Increased serum creatinine† 3 (2.8) 5 (4.7) 2 (2.0) 5 (4.4) 9 (17.6)
- Fatigue 1 (0.9) 7 (6.5) 4 (4.0) 5 (4.4) 0
- Sudden death‡ 0 0 0 1 (0.9) 3 (5.9)
- Fall 2 (1.8) 2 (1.9) 3 (3.0) 3 (2.7) 3 (5.9)

TEAE indicates treatment-emergent adverse event.
* A total of 43 deaths (all included in the intention-to-treat efficacy analysis) occurred when pretreatment and posttreatment periods were taken into account.
† As reported by the investigator.
‡ Based on adverse events reported by the investigator before adjudication.
adjudicating the primary and secondary end points. This central review, in which a prospectively defined procedure validated by the Steering Committee was used, reduced variability in interpretation. This is particularly important in a dose-ranging study in which variability engendered by small patient numbers can easily reduce sensitivity.

ALPHEE enrolled a relevant patient population with reduced left ventricular function and the expected comorbid conditions and concomitant medications. The Steering Committee believed that it was important to study an advanced patient population at an intermediate stage of clinical development to confirm the safety of a new drug and to precisely define an optimal dose before wider administration in a large, confirmatory, efficacy trial. To accomplish this, we relied on a Data Monitoring Committee experienced in the interpretation of interim data and used prospectively defined procedures to avoid any bias in the conduct of the study. Although not powered to detect significant differences in overall or sudden death rates, these end points were analyzed regularly by the Data Monitoring Committee to maximize safety and to permit completion of the trial without bias.

In the ICARIOS study, we noted that many patients had large numbers of VT/VF-triggered ICD interventions. Patients with >27 events were censored at the date of their 27th event (equivalent to the 95th percentile of the distribution of events), but all ICD interventions up to the 27th were analyzed as the primary efficacy end point. To avoid confounding by a small number of patients contributing many events, the ALPHEE study, designed by the same Steering Committee as ICARIOS, used time to the first event as the primary analysis. Cumulative events were analyzed in a sensitivity analysis but were prospectively restricted to the first 10 events.

To conclude, the ALPHEE study has shown that doses of celivarone at 50, 100, and 300 mg are not effective in preventing ventricular arrhythmia–triggered ICD interventions. The study design has, however, been shown to be sensitive and valid for evaluating the effects of antiarrhythmic agents on VT/VF-triggered ICD interventions. In particular, the presence of the amiodarone calibrator arm has proven to greatly facilitate the interpretation of results with limited impact on the overall study size. As such, it serves as a valuable model for studies of new antiarrhythmic agents.

Acknowledgments

The authors would like to thank the investigators who participated in this clinical trial, the Data Monitoring Committee, and the Central Adjudication Committee of ICD events. A full list of investigators and committee members can be found in the Appendix in the online-only Data Supplement. We also thank the following individuals for their contributions to the study: Urszula Wisniewska (Study Director), Aline Cuvilliez (Clinical Trial Manager), Melanie Espinasse-Lorendeau (Statistician), and Aurelie Brunet (Pharmacokinetics). Editorial assistance with copyediting and journal formatting was provided by PAREXEL International and funded by Sanofi.

Sources of Funding

The ALPHEE study was sponsored by Sanofi.

Disclosures

Dr Kowey has received consulting and lecture fees from Sanofi and honoraria from Sanofi. Dr Crijns has received consulting fees and honoraria/travel reimbursement from Sanofi. Dr Aliot has received consulting fees from Bayer, Biotronik, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Meda Pharma, Medtronic, Pfizer, Sanofi, and St. Jude Medical and honoraria from Sanofi. Dr Capucci has received consulting fees from Sanofi. Dr Kulakowski has received consulting fees and honoraria from Sanofi. Dr Hohnloser has received consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Sanofi and honoraria and lecture fees from Bristol-Myers Squibb, Boehringer Ingelheim, Cardiome, Medtronic, Sanofi, and St. Jude Medical.

References


---

**CLINICAL PERSPECTIVE**

Sudden cardiac death is preventable with implantable cardioverter-defibrillators. These devices can now be placed not only in patients who have had a sustained arrhythmia, but also in those deemed high risk for whom a mortality benefit can also be derived. Unfortunately, a sizable percentage of patients who receive these devices may have frequent or inappropriate shock therapy. We have learned that these events are psychologically devastating, cause frequent hospitalizations, and predispose to morbid and mortal events. Although antiarrhythmic drugs are frequently used to prevent frequent device discharges, no drug has gained US regulatory approval for this indication. On the basis of favorable data obtained in a small phase IIa trial, we studied the efficacy and safety of celivarone, a novel benzofuran derivative and congener of amiodarone and dronedarone, for the prevention of device activation and sudden death. In a multinational, multicenter, prospective, double-blind, randomized parallel-group trial, we compared 3 doses of celivarone with placebo and included an amiodarone calibrator arm to confirm the adequacy of the design and the study population. Although it proved to be well tolerated and safe, we found no significant benefit for celivarone for this indication at any dose. Amiodarone, as expected, reduced device activations, including shocks, but was associated with a higher mortality than placebo, whereas celivarone was mortality neutral. The search for drugs to prevent device activation and death in implantable cardioverter-defibrillator patients will continue. The Dose Ranging Study of Celivarone With Amiodarone as Calibrator for the Prevention of Implantable Cardioverter Defibrillator Interventions or Death (ALPHEE), although a negative trial, provides a precedent for the study of new drugs for ventricular indications.
Efficacy and Safety of Celivarone, With Amiodarone as Calibrator, in Patients With an Implantable Cardioverter-Defibrillator for Prevention of Implantable Cardioverter-Defibrillator Interventions or Death: The ALPHEE Study

Peter R. Kowey, Harry J.G.M. Crijns, Etienne M. Aliot, Alessandro Capucci, Piotr Kulakowski, David Radzik, Denis Roy, Stuart J. Connolly and Stefan H. Hohnloser

_Circulation_. 2011;124:2649-2660; originally published online November 14, 2011; doi: 10.1161/CIRCULATIONAHA.111.072561

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/24/2649

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2011/11/17/CIRCULATIONAHA.111.072561.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
Appendix {Online only supplement}

The participants in the ALPHEE study are as follows: **Steering Committee:** Kowey P.R. (USA), Aliot E.M. (France), Capucci A. (Italy), Connolly S.J. (Canada), Crijns H.J.G.M., (The Netherlands), Hohnloser S.H. (Germany), Kulakowski P. (Poland), Roy D. (Canada), Singh B.M. (USA). **Data Monitoring Committee:** Seltzer J. (USA), Knight B.P. (USA), Kadish A.H. (USA), Smith A. (USA). **ICD Central Adjudication Committee:** Crijns H.J.G.M. – Chair (The Netherlands), Blaauw J. (The Netherlands), Van Opstal J. (The Netherlands), Vernooy K. (The Netherlands), Van Empel V. (The Netherlands), Smid-Ter Bekke R. (The Netherlands), Guedon L. (France), Kouakam C. (France), Sadoul N. (France), Blangy H. (France), Freysz L. (France), Mabo P. (France), Leclercq C. (France). **We acknowledge the investigators in the ALPHEE study: Argentina:** Giniger A. (PI), Albina G. (CI), Sammartino V. (CI), Instituto Cardiovascular Buenos Aires; Reyes I. (PI), Manzolillo H. (CI), Pantich R. (CI), Ruveda S.M. (CI), Pozzer D.L. (CI), Instituto De Cardiología De Corrientes; Aguinaga L. (PI), Paterlini G. (CI), Edouardo H. (CI), Veronica L. (CI), Centro Privado De Cardiologia – Sanatorio, Tucumán. **Australia:** Hill J. (PI), Yeshwant S. (CI), Butterfly S. (CI), Indrajith M. (CI), Cox S. (CI), Perel R. (CI), Finn H. (CI), Princess Alexandra Hospital, Brisbane; Heddle W. (PI), Burdeniuk. C (CI), Singleton C. (CI), McGavigan A. (CI), Benjamin P. (CI), Robert M. (CI), Judd J. (CI), Flinders Medical Centre, Bedford Park; Martin P. (PI), Ange N. (CI), Chao C.Y. (CI), Preston S. (CI), Camuglia A. (CI), Starmer G. (CI), Hillier S. (CI), Hunter J. (CI), Armugum D. (CI), Perel R. (CI), Gomes R.F. (CI), Royal Brisbane and Women’s Hospital, Herston; Pavia S. (PI), Pearson A. (CI), Armstrong C.G. (CI), The Wesley Research Institute, Auchenflower; Paul V. (PI), Catanchin A. (CI), Shah A. (CI), Stoyanov N. (CI), Yeow W. (CI), Gattorna T. (CI), Royal Perth Hospital, Department of Cardiology, Nedlands; Stobie P. (PI), Cooke P. (CI), Di Camillo C. (CI), Thompson A. (CI), Anderson H. (CI), Ng J. (CI), Camuglia A. (CI), Starmer G. (CI), Hillier S. (CI), Hunter J. (CI), Sir Charles Gairdner Hospital, Heart Research Institute, Nedlands; Leitch J. (PI), Barlow M. (CI), Collins N. (CI), John Hunter Hospital, New Lambton Heights; William M. (PI), Choong W.-P. (CI), Wilsmore B. (CI), Wong T. (CI), Renganathan T. (CI), Jackson N. (CI), Gosford Hospital, Gosford; Bradley J. (PI), Mahar L. (CI), Worthley M. (CI), Worthley S. (CI), Ashby D. (CI), Royal Adelaide Hospital; Tan R. (PI), McGill D. (CI), Canberra Hospital, Garran; Kilborn M. (PI), IIsar R. (CI), Royal Prince Alfred Hospital, Department of Cardiology, Camperdown. **Belgium:** Brugada I.T.P. (PI), Chierchia G.-B. (CI), De Asmundis C. (CI), Sarkozy A. (CI), UZ Brussel; Leroy J. (PI), Hausman P. (CI), Grand Hôpital de Charleroi Site Saint-Joseph, Gilly; Goethals M. (PI), Pollet P. (CI), H-Hartziekens Campus Roeselare-Men vzw Campus Wilgenstr, Roeselare; Vijgen J. (PI), Dilling-Boer D. (CI), Virga Jesse Ziekenhuis, Hasselt; Geelen P. (PI), De Potter T. (CI), Peytchev P. (CI), O.L Vrouwziekenhuis Campus
Aalst; Tavernier R. (PI), Duytschaever M. (CI), Vandekerckhove C. (CI), AZ Sint-Jan, Brugge. **Canada:** Coutu B. (PI), Costi P. (CI), Greiss I. (CI), Raymond J.-M. (CI), Mansour F. (CI), Santagata P. (CI), CHUM Hotel Dieu, Montreal; Dorian P. (PI), Ahmad K. (CI), Al-Hesaniyah S. (CI), Korley V. (CI), Mangat I. (CI), Pinter A. (CI), Van Herendaal H. (CI), Van Der Akker-Bermane L. (CI), St. Michael’s Hospital, Toronto; Klein G. (PI), Leong-Sit P. (CI), Skanes A. (CI), Krahn A. (CI), Gula L. (CI), Yee R. (CI), London Health Science Centre, London; Champagne J. (PI), O’Hara G. (CI), Blier L. (CI), Nault I. (CI), Molin F. (CI), Philippson F. (CI), Sarrazin J.-F. (CI), Marcel G. (CI), Institut universitaire de cardiologie et de pneumologie, Sainte-Foy; Kerr C. (PI), Chakrabarti S. (CI), Tung S. (CI), Yeung-Lai-Wah J. (CI), Bennet M. (CI) St Pauls Hospital, Vancouver; Sterns L. (PI), Agarwal S. (CI), Ayou R. (CI), Cromie N. (CI), Jones M. (CI), Leather R. (CI), Novak P. (CI), Sultan O. (CI), Tang A. (CI), Victoria Cardiac Arrhythmia Trials Inc.; Talajic M. (PI), Dubuc M. (CI), Gagné P. (CI), Macle L. (CI), Denis R. (CI), Bernard T. (CI), Paul K. (CI), Peter G. (CI), Léna R. (CI), Montreal Heart Institute; Mitchell L. (PI), Duff H. (CI), Exner D. (CI), Gillis A. (CI), Kavanagh K. (CI), Quinn R. (CI), Sheldon R. (CI), Sumner G. (CI), Veenhuyzen G. (CI), Foothills Hospital, Calgary; Divakaramenon S. (PI), Connolly S. (CI), Healey J. (CI), Mirillo C. (CI), Nair G. (CI), Hamilton Health Sciences. **Chile:** Asenjo R. (PI), Cerceda M. (CI), Herrera E. (CI), Morris R. (CI), Hospital Clinico Universidad De Chile, Santiago. **Czech Republic:** Kucera P. (PI), Belza T. (CI), Polasek R. (CI), Krajska nemocnice Liberec; Tousek F. (PI), Karpianus D. (CI), Osmera O. (CI), Rehouskova K. (CI), Nemocnice Ceske Budejovice As; Heinc P. (CI), Doupal V. (CI), Fedorco M. (CI), Fakultni nemocnice Olomouc; Novak M. (PI), Dvorak I. (CI), Lipoldova J. (CI), Vykytel T. (CI), Fakultni Nemocnice U Sv. Anny V Brne, Brno; Parizek P. (PI), Haman L. (CI), Tauchman M. (CI), Fakultni Nemocnice Hradec Kralove; Sediva L. (PI), Janotka M. (CI), Petru J. (CI), Nemocnice Na Homolce, Praha. **Denmark:** Brandes A. (PI), Odense Universitetshospital; Nielsen J. (PI), Kirkfeldt R. (CI), Aarhus Universitetshospital Skejby; Johannessen A. (PI), Thomsen P.E.B. (CI), Gentofte Hospital, Hellerup; Svendsen J. (PI), Køber L. (Assoc PI), Ersbøll M. (CI), Hassager C. (CI), Larsen L. (CI), Rigshospitalet, Kardiologisk Laboratorium 2013, København. **Finland:** Toivonen L. (PI), Lehto M. (CI), Pakarinen S. (CI), Helsingin Yliopistollinen Keskussairaala, Helsinki; Virtanen V. (PI), Inkovaara J. (CI), Mäkynen H. (CI), Raatikainen P. (CI), TAYS Sydänkeskus Oy, Tampere. **France:** Le Heuzey J.-Y. (PI), Fiorina L. (CI), Marijon E. (CI), Hôpital Pompidou, Paris; Davy J.M. (PI), Cung T.T. (CI), Pasquie J.-L. (CI), Raczka F. (CI), Hôpital Arnaud De Villeneuve, Montpellier; Aliot E. (PI), Blangy H. (CI), Sadoul N. (CI), Zinzius P.-Y. (CI), CHU Brabois, Service de Cardiologie, Vandœuvre-lès-Nancy; Blanc J.J. (PI), Fatemi M. (CI), Hôpital Cavale Blanche, Brest; Kacet S. (PI), Guedon-Moreau L. (CI), Kouakam C. (CI), Marquie C. (CI), CHR Hôpital Cardiologique, Lille; Defaye P. (PI), Jacon P. (CI), Mondesert B. (CI), Cassagneau R. (CI), CHU de Grenoble – Hôpital Nord; Mabo P.
(PI), Bodi S. (CI), Grezis S.G. (CI), Leclercq C. (CI), Pavlin D. (CI), Solnon A. (CI), CHRU Pontchaillou, Rennes. **Germany:** Hohnloser S. (PI), Duray G. (CI), Ehrlich J. (CI), Fink A. (CI), Kaluzny M. (CI), Ercapic D. (CI), Schmitt J. (CI), Universitätsklinikum Frankfurt, Medizinische Klinik III; Butter C. (PI), Möller V. (CI), Ev.-Freikirchliches Krankenhaus und Herzzentrum Brandenburg in Bernau; Spitzer S. (PI), Károlyi L. (CI), Winkler J. (CI), FAZ Dresden-Neustadt GbR, Zentrum für Klinische Prüfungen; Schumacher B. (Former PI), Barth S. (Current PI), Barth S. (CI), Langbein A. (CI), Herz- und Gefäß-Klinik GmbH, Bad Neustadt; Willems S. (PI), Aydin A. (CI), Servatius H. (CI), Wilke I. (CI), Universitäres Herzzentrum Hamburg GmbH, Klinik für Kardiologie mit Schwerpunkt Elektrophysiologie.

**Hungary:** Faluközy J. (PI), Masszi J. (CI), Lupkovics G. (CI), Alami Szívkorhaz, Balatonfüred; Lupkovics G. (PI), Németh B. (CI), Sztaniszláv A. (CI), Zala Megyei Kórház, Zalaegerszeg; Tomcsányi J. (PI), Nényei Z. (CI), Toldy-Schedel E. (CI), Budai Irgalmasrendi Kórház, Kardiológia, Budapest; Simor T. (PI), Melczer L. (CI), Ruzsics B. (CI), Pécsi Tudományegyetem, Pécs. **Israel:** Viskin S. (PI), Rogowski O. (CI), Rosso R. (CI), Steinvil A. (CI), Zeitser D. (CI), Tel Aviv Sourasky Medical Center; Freedberg N. (PI), Antonelli D. (CI), Feldman A. (CI), Peres D. (CI), Haemek Medical Center, Afula; Katz A. (PI), Fishman E. (CI), Khalameizer V. (CI), Barzilai Medical Center, Ashkelon; Samniah N. (PI), Hamoud M. (CI) Bnei Zion Medical Center, Haifa; Glikson M. (CI), Sheba Medical Center, Tel Hashomer.

**Italy:** Padeletti L. (CI), Michelucci A. (CI), Perrotta L. (CI), Pieragnoli P. (CI), Porciani C. (CI), Ricciardi G. (CI), Azienda Universitario Ospedaliero Policlinico Di Careggi, Firenze; Botto G. (PI), Mariconti B. (CI), Russo G. (CI), Azienda Ospedaliera sant’Anna, Como; Favale S. (PI), Catucci S. (CI), Luzzi G. (CI), Nacci F. (CI), Palmisano P. (CI), Quadrini F. (CI), Azienda Ospedaliero Universitaria Policlinico di Bari; Calò L. (PI) De Ruvo E. (CI), Fagagnini A. (CI), Sciarra L. (CI), Zuccaro L.M. (CI), Policlinico Casilino, Roma; Mascioli G. (PI), Bakhtadze N. (CI), Belvito C. (CI), Borrelli A. (CI), Lucca E. (CI), Istituto Humanitas Gavazzeni, Bergamo.

**Japan:** Kurita T. (PI), Akaiwa Y. (CI), Hirota T. (CI), Motoki K. (CI), Yasuoka R. (CI), Kinki University Hospital, Osaka; Kamakura S. (PI), Aiba T. (CI), Aihara N. (CI), Noda T. (CI), Okamura H. (CI), Satomi K. (CI), Shimizu W. (CI), Suyama K. (CI), Yamada Y. (CI), National Cerebral and Cardiovascular Center, Osaka; Hagiwara N. (PI), Ejima K. (CI), Manaka T. (CI), Sato T. (CI), Serizawa N. (CI), Shiga T. (CI), Shoda M. (CI), Suzuki A. (CI), Suzuki T. (CI), Yagishita D. (CI), Tokyo Women’s Medical University Hospital; Sugi K. (PI), Ito N. (CI), Kujime S. (CI), Nakamura K. (CI), Noro M. (CI), Numata A. (CI), Sakata T. (CI), Toho University, Ohashi Medical Center, Tokyo; Aizawa Y. (Former PI), Furushima H. (Current PI), Aizawa Y. (CI), Furushima H. (CI), Hosaka Y. (CI), Izumi D. (CI), Niigata University Medical and Dental Hospital; Fujii K. (PI), Date M. (CI), Higuchi Y. (CI), Imai M. (CI), Inoue K. (CI), Ito N. (CI), Iwakura K. (CI), Kimura R. (CI), Kurotobi T. (CI), Masuda M. (CI), Morisawa D. (CI), Nagai H. (CI), Nakatani S. (CI), Okamura A. (CI), Okazaki Y. (CI), Omiya
S. (CI), Ozawa M. (CI), Shibuya M. (CI), Sotomi Y. (CI), Takagi T. (CI), Toyoshima Y. (CI), Sakurabashi Watanabe Hospital, Osaka. Mexico: Colin L. (PI), Morales J. (CI), Instituto Nacional De Cardiologia, Mexico City. The Netherlands: Kimman G. (PI), Ruiter J. (CI), Medisch Centrum Alkmaar; Alings A. (PI), Simmers T. (CI), Amphia Ziekenhuis Molengracht, Breda; Crijns H. (PI), Limantoro I. (CI), Moens A. (CI), Pisters R. (CI), Weijis B. (CI), Blaauw Y. (CI), Kietselaer B. (CI), Academisch Ziekenhuis Maastricht; Ramdat Misier A. (PI), Elvan A. (CI), Ghani A. (CI), Rik H. (CI), Isaal Klinieken, Zwolle; Khan M. (PI), Henrikus A. (CI), Sepehrkhoy S. (CI), Vos N. (CI), Herrman J. (CI), De Ruiter G. (CI), Onze Lieve Vrouwe Gasthuis, Amsterdam; Jordaens L. (PI), De Groot N. (CI), Haitsma D. (CI), Szili-Torok T. (CI), Van Belle Y. (CI), Erasmus Medisch Centrum, Afdeling Klinische Electrofyiologie, Rotterdam. Norway: Gjertsen E. (PI), Tøssebro M. (CI), Falang J.E. (CI), Vestre Viken Hf, Sykehuset Buskerud, Drammen. Poland: Kulakowski P. (PI), Czepiel A. (CI), Makowska E. (CI), Swiatkowski M. (CI), Pracownia Elektrofizjologii Klinicznej - Klinika Kardiologii, Warszawa; Kornacewicz-Jach Z. (PI), Kazmierczak J. (CI), Wielusinski M. (CI), Akademia Medyczna, Zachodniopomorskie; Drozd J. (PI), Jakubowski P. (CI), Kaczmarek K. (CI), Oszczygiel A. (CI), Piestreniewicz K. (CI), Rosiak M. (CI), Uniwersytecki Szpital Kliniczny No. 3, Łódź; Lubinski A. (PI), Binkowski B. (CI), Bissinger A. (CI), Kubinski P. (CI), Uniwersytet Medyczny W Łodzi, Łódź; Kubica J. (PI), Fabiszak T. (CI), Szpital Uniwersytecki im. Dr A. Jurasza W Bydgoszczy, Klinika Kardiologii i Chorób Wewnętrznych, Kujawsko-pomorskie; Stolarz P. (PI), Grabowski M. (CI), Steckiewicz R. (CI), i Katedra i Klinika Kardiologii, Warszawski Uniwersytet Medyczny; Miekus P. (PI), Dulak E. (CI), Konarzewski M. (CI), Szpital Miejski Oddzial Kardiologiczny, Pomorskie. Portugal: Cunha P. (PI), Feliciano J. (CI), Olveira M. (CI), Almeida Santos S. (CI), Hospital De Santa Marta, Lisboa; Providencia L. (PI), António N. (CI), Mendes P. (CI), Monteiro P. (CI), Saraiva F. (CI), Teixeira R. (CI), Elvas L. (CI), Hospitais Da Universiadeade De Coimbra; Primo J. (PI), Adão L. (CI), Gonçalves H. (CI), Oliveira M. (CI), Centro Hospitalar Vila Nova De Gaia. Russian Federation: Shubik Y. (PI), Rivin A. (CI), Veleslavova O. (CI), North-West Center For Diagnostic and Treatment of Arrhythmia, St Petersburg; Popov S. (PI), Antonchenko I. (CI), Batalov R. (CI), Krivolapov S. (CI), Research Institute of Cardiology, Tomsk; Berns S. (PI), Barbarash O. (CI), Gorbunova E. (CI), Kazachek Y. (CI), Khomenko E. (CI), Research Institute of Complex Problems of Cardiovascular Disease, Kemerovo; Mikhailov S. (PI), Kireev K. (CI), Ostern O. (CI), Pyrov S. (CI), Bulatov D. (CI), Tsepennikova N. (CI), Sverdlovsk Regional Clinical Hospital #1, Ekaterinburg; Gizatulina T. (PI), Zinin M. (CI), Kazantseva A. (CI), Tyumen Regional Clinical Hospital, Samara; Duplyakov D. (PI), Mitronin A. (CI), Zemlyanova M. (CI), Samara Regional Cardiology Dispensary; Novikova T. (PI), Zavaritskaya O. (CI), Perchatkin D. (CI), Sautova E. (CI), Pokrovskaya City Hospital, St Petersburg. Slovakia: Hatala R. (PI), Hatalova K. (CI), Urban L. (CI), Cardioconsult
S.R.O, Bratislava; Stancak B. (PI), Misikova S. (CI), Olexa P. (CI), Vychodoslovensky Ustav Srdccievnych Chorob, Kosice. **South Africa:** Ebrahim I. (PI), Badenhorst J. (CI), Blomerus P. (CI), Unitas Hospital, Centurion. **Spain:** Mont L. (PI), Tolosana J.M. (CI), Hospital Clínic i Provincial, Barcelona; Sabaté X. (PI), Anguera I. (CI), Hospital Universitari de Bellvitge, Barcelona; Merino J. (PI), Cozar R. (CI), Peinado R. (CI), Pérez Silva A. (CI), Moreno Reviriego S. (CI), Hospital La Paz, Madrid; Fernández Lozano I. (PI), Castro V. (CI), Toquero J. (CI), Ros N. (CI), Clinica Puerta de Hierro, Madrid; Garcia Seara F.J. (PI), Complejo Hospitalario Universitario de Santiago, La Coruña; Olague J. (PI), Sancho-Tello M.J. (CI), Osca J. (CI), Cano O. (CI), Nuevo Hospital La Fe - Politécnico, Valencia; Diaz-Infante E. (PI), Cruz Fernández J.M. (CI), Hospital Universitatio Virgen Macarena, Sevilla. **Sweden:** Blomström-Lundqvist C. (PI), Blomström P. (CI), Lännerholm S. (CI), Malmborg H. (CI), Mörtzell D. (CI), Ostrowska B. (CI), Sciaraffi E. (CI), Teder P. (CI), Akademiska Sjukhuset, Kardiologkliniken, Uppsala; Kjellman B. (PI), Olson J. (CI), Södersjukhuset, Verksamhetsområde Kardiologi, Stockholm; Keseck M. (PI), Rönn F. (CI), Norrlands Universitetssjukhus, Umeå; Wecke L. (PI), Karolinska Universitetssjukhuset Solna, Hjärtkliniken, Stockholm. **Turkey:** Ozin B. (PI), Atar I. (CI), Cakmak A. (CI), Turk E. (CI), Karabulut A. (SC), Kececi E. (SC), Baskent Universitesi Tip Fakultesi, Kardiyojoloji A.D., Ankara; Adalet K. (PI), Atun I. (CI), Bilge A. (CI), Yalin K. (CI), Istanbul Universitesi Istanbul Tip Fakultesi, Kardiyojoloji A.D.; Turkoglu C. (PI), Aliyev F. (CI), Karakozak D. (CI), Turhan N. (CI), Istanbul Universitesi Kardiyojoloji Enstitusu, Kardiyojoloji A.D. **USA:** Burton M.E. (PI), Chazal R. (CI), Bounds D. (SC), The Heart Group at Lee Memorial Heath Systems, Ft. Myers, Florida; Cannon L. (PI), Overton N. (CI), Levanovich P. (CI), Cardiac and Vascular Research Center of Northern Michigan, Petoskey; Clark D. (PI), Macdonell A. (CI), Augusta Cardiology Clinic, Georgia; Cossu S. (PI), Connelly T. (CI), Malone M. (SC), Charlotte Heart and Vascular Institute, Port Charlotte, Florida; Dinerman J. (PI), Allison S. (CI), Tabereaux P. (CI), Drenning D. (CI), Gessler C. (CI), Haught W.H. (CI), Vasquez A. (CI), Strickland W. (CI), Cheng S.-C. (CI), The Heart Center Research, LLC, Huntsville, Alabama; Engel G. (PI), Winkle R. (CI), Mead R. (CI), Smith N. (CI), Patrawala R. (CI), Cardiovascular Medicine and Cardiac Arrhythmias, East Palo Alto, California; Good E. (PI), Pelosi F. (CI), Chugh A. (CI), Bogun F. (CI), Jongnarangsing K. (CI), Crawford T. (CI), The University of Michigan, Ann Arbor, Michigan; Guguchev P. (PI), Filart R. (CI), Duran A. (CI), Alvarez L. (CI), Orlando Heart Center, Florida; Gupta D. (PI), Gupta R. (CI), Kamykowski P. (CI), Tennessee Center For Clinical Trials, Tullahoma; Herre J. (PI), Bernstein R. (CI), Sentara Cardiovascular Research Institute, Norfolk, Virginia; Hobson J. (PI), Walsh R. (CI), The Heart and Vascular Institute of Florida, Clearwater; Kaplan A. (PI), Ambrosia A. (SC), Kramer N. (CI), Wiles B. (SC), Skloven Z.D. (CI), CardioVascular Associates of Mesa, Arizona; Kappler J. (PI), Shinn T. (CI), Han J. (CI), Greenstein R. (CI), Winston S. (SC), Trinity Health, Ypsilanti, Michigan;
Kwasman M. (PI), Muelheims G. (CI), Goldberg H.R. (CI), Spokane Cardiology, Washington; Lakkireddy D. (PI), Berenbom L. (CI), Dendi R. (CI), Emert M. (CI), Pimental R. (CI), University of Kansas Hospital, Mid America Cardiology Associates, Kansas City; Lee J. (PI), Brodine W. (CI), Christensen K. (CI), Sun D. (CI), Tung R. (CI), Kansas City Heart Foundation, Missouri; Leman R. (PI), Cuoco F. (CI), Gold M. (CI), Sturdivant J.L. (CI), Clarke E. (SC), Adams A. (SC), Schulz M. (SC), Medical University of South Carolina, Gazes Research Institute, Charleston; Chilson D. (Current PI), Lessmeier T. (Former PI), Eteri B. (CI), Heart Clinics Northwest, Spokane, Washington; Love J. (PI), Langburd L. (CI), Corsello A. (CI), Miller H.M. (CI), Field M. (CI), Cardiovascular Consultants of Maine, Scarborough; Nadar V. (PI), Lewin S. (CI), Man D. (CI), Safwat A.G. (CI), Heritage Cardiology Associates, Camp Hill, Pennsylvania; Onofer J. (Former PI), Woollett I. (Current PI, Former CI), Hagan E. (SC), Dryer J. (SC), McMeekin J. (SC), Cardiovascular Associates, Ltd, Chesapeake, Virginia; Pires L. (PI), Hassan S. (CI), St John Hospital and Medical Center, Detroit, Michigan; Sandler D. (PI), Cameron C. (CI), Cogert G. (CI), Oklahoma Heart Institute, Tulsa; Sangrigoli R. (PI), Smith D.L. (CI), Guarino J.C. (CI), Boland D.G. (CI), Sangrigoli R.A. (CI), McGarvey J. Jr (CI), Gejer E. (SC), Grzywacz F. (CI), Harding J.D. (CI), Central Bucks Specialists, Doylestown, Pennsylvania; Chinitz L. (Former PI), Bernaski E. (Current PI), Aizer A. (CI), Holmes D. (CI), Morlote M. (CI), Bernstein N. (CI), New York Cardiovascular Associates, Gotham Cardiovascular Research, PC, New York; Su W. (PI), Heuser R. (CI), Rhee E. (CI), Tung-Takher N. (CI), Heart Rhythm Specialists of Arizona, Phoenix; Thal S. (PI), Goldman S. (CI), Thai H. (CI), Juneman E. (CI), Movahed M. (CI), Southern Arizona VA Healthcare System, Tuscson; Yesenosky G. (PI), Trabachino S. (SC), Garibian G. (CI), Cardiology Consultants of Philadelphia, Crozer Chester Medical Center, Philadelphia, Pennsylvania; Chough S. (PI), Nora M. (CI), O’Toole M. (CI), Kawasaki R. (CI), Saleem M. (CI), Gami A. (CI), Cash C. (CI), Midwest Heart Foundation, Downers Grove, Illinois; Kron J. (PI), Stecker E. (CI), Stajduhar K. (CI), Oregon Health and Sciences University, Portland; Caruso A. (PI), Ngo M. (CI), Cardiovascular Associates of Virginia, Midlothian; Olsovsky M. (PI), Blonder R. (CI), Mikaelian B. (CI), Kuwana M. (SC), Greenberg D. (CI), Pikes Peak Cardiology, Colorado Springs, Colorado; Bedwell N. (PI), Alford C. (CI), Brown C. (CI), Hardy W. (CI), LeDoux J. (CI), The Heart Group PC, Mobile, Alabama; Cardona F. (PI), Wassmer P. (CI), McGee T. (SC), Akers L. (SC), The Heart and Vascular Institute of Florida, St Petersburg; Beshai J. (PI), Burke M. (CI), Shah D. (CI), Weisberg I. (CI), Baez-Escudero J. (CI), Sherry D. (SC), Moyer D. (SC), O’Keefe L. (SC), University of Chicago, Illinois; Blanck Z. (PI), Aurora Cardiovascular Services, Milwaukee, Wisconsin; Teixeira J. (PI), Deraad R. (SC), Walder J. (CI), Black Hills Clinical Research, Rapid City, South Dakota; Pierce D. (PI), Backus N. (CI), Baird J. (CI), Boyer J. (CI), Brown D. (CI), Elliott J. (CI), Fairlamb J. (CI), Gallaway S. (CI), Hulett J. (CI), Kennett J. (CI), Klein D. (CI), Lucas J. (CI),
Lutz K. (CI), Ravipudi S. (CI), Spaedy T. (CI), Tran T. (CI), Woods W. (CI), Missouri
Cardiovascular Specialists, Columbia; Jackson B. (PI), Kim G. (CI), Ari Clinical Trials, Inc.,
Redondo Beach, California.
PI = principal investigator; CI= clinical investigator; SC = study coordinator.