

## 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

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**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  $\leq 40\%$  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.

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**Key Words:** celivarone ■ implanted cardioverter defibrillators ■ sudden death ■ ventricular arrhythmia

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.<sup>1,2</sup> These ventricular arrhythmias are responsible for two thirds of sudden cardiac deaths each year in the United States.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5,6</sup> These drugs help patients to avoid the discomfort of frequent device discharges and prevent battery depletion. In addition, frequent shocks are associ-

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ated with a higher mortality and frequent, expensive hospitalizations.<sup>6</sup>

### Clinical Perspective on p 2660

The most frequently used and most effective drug for this purpose is the benzofuran derivative amiodarone.<sup>7</sup> Its use, however, is limited by a wide range of organ-toxic side effects, difficult pharmacology, and a host of drug-drug interactions.<sup>7,8</sup> 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.<sup>5,9</sup>

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  $\alpha_1$ - and  $\beta_1$ -adrenergic responses and angiotensin II receptor stimulation.<sup>10</sup> 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.<sup>10,11</sup>

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.<sup>12,13</sup>

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.<sup>14</sup> 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  $\geq 21$  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  $\leq 40\%$ . 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).

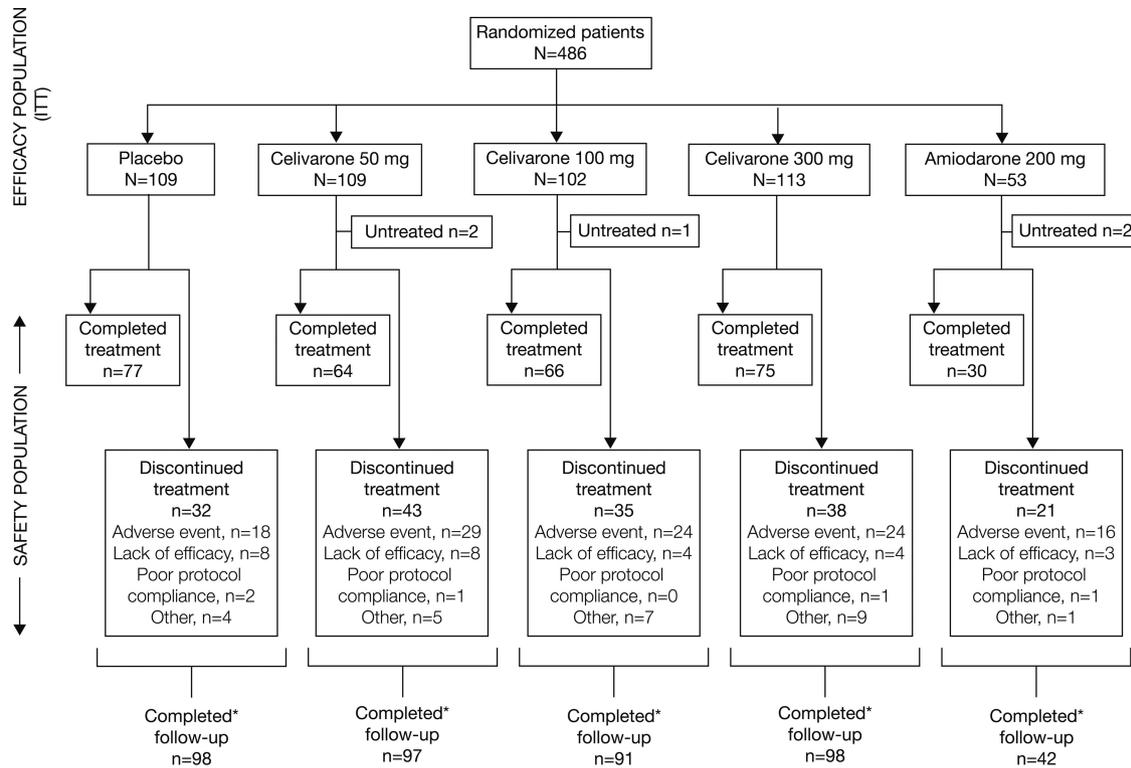
The only drugs prohibited during the study were Vaughan-Williams class I and III antiarrhythmic drugs as well as agents known to induce torsades de pointes.

### 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 2:2:2:1 for



\*Patients followed up until the scheduled study end date. Patients who died before this date were not considered as completed.

Figure 1. Disposition of patients. ITT indicates intention to treat.

placebo, celivarone 50 mg, celivarone 100 mg, celivarone 300 mg, and amiodarone.

**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

**Table 1. Baseline Characteristics of Patients**

	Placebo (n=109)	Celivarone 50 mg (n=109)	Celivarone 100 mg (n=102)	Celivarone 300 mg (n=113)	Amiodarone 200 mg (n=53)	All (n=486)
Age, mean (SD), y	64.7 (12.0)	65.8 (10.6)	62.8 (10.3)	63.0 (11.5)	66.8 (8.4)	64.4 (10.9)
Sex, n (%)						
Male	98 (89.9)	96 (88.1)	91 (89.2)	97 (85.8)	49 (92.5)	431 (88.7)
Female	11 (10.1)	13 (11.9)	11 (10.8)	16 (14.2)	4 (7.5)	55 (11.3)
Race, n (%)						
White	101 (92.7)	101 (92.7)	93 (91.2)	106 (93.8)	50 (94.3)	451 (92.8)
Black	4 (3.7)	3 (2.8)	5 (4.9)	2 (1.8)	1 (1.9)	15 (3.1)
Asian	4 (3.7)	5 (4.6)	3 (2.9)	3 (2.7)	1 (1.9)	16 (3.3)
Other	0	0	1 (1.0)	2 (1.8)	1 (1.9)	4 (0.8)
LVEF, mean (SD), %	29.2 (7.5)	28.3 (8.0)	29.8 (6.7)	29.1 (8.0)	29.2 (7.6)	29.1 (7.6)
LVEF, n (%)						
<35%	73 (67.0)	76 (69.7)	64 (62.7)	70 (61.9)	35 (66.0)	318 (65.4)
≥35%	36 (33.0)	33 (30.3)	38 (37.3)	43 (38.1)	18 (34.0)	168 (34.6)
Any congestive heart failure	96 (88.9)	96 (88.1)	84 (82.4)	99 (87.6)	42 (79.2)	417 (86.0)
NYHA class I*	16 (16.7)	14 (14.6)	13 (15.5)	15 (15.2)	7 (16.7)	65 (15.6)
NYHA class II*	55 (57.3)	57 (59.4)	52 (61.9)	63 (63.6)	25 (59.5)	252 (60.4)
NYHA class III*	25 (26.0)	25 (26.0)	19 (22.6)	21 (21.2)	10 (23.8)	100 (24.0)
Cardiovascular history,† n (%)						
Coronary artery disease	86 (78.9)	78 (71.6)	75 (73.5)	72 (63.7)	36 (67.9)	347 (71.4)
Hypertension	70 (64.2)	69 (63.3)	65 (63.7)	58 (51.3)	27 (50.9)	289 (59.5)
Ischemic dilated cardiomyopathy	61 (56.0)	54 (49.5)	51 (50.0)	52 (46.0)	28 (52.8)	246 (50.6)
Syncope	28 (25.7)	33 (30.3)	37 (36.3)	36 (31.9)	22 (41.5)	156 (32.1)
Atrial fibrillation	30 (27.5)	39 (35.8)	23 (22.5)	34 (30.1)	13 (24.5)	139 (28.6)
Nonischemic dilated cardiomyopathy	20 (18.3)	30 (27.5)	28 (27.5)	33 (29.2)	13 (24.5)	124 (25.5)
Nonrheumatic valvular heart disease	21 (19.3)	32 (29.4)	18 (17.6)	27 (23.9)	15 (28.3)	113 (23.3)
Indication for ICD implantation						
Primary prevention	34 (31.2)	44 (40.4)	34 (33.3)	43 (38.1)	18 (34.0)	173 (35.6)
Secondary prevention	75 (68.8)	65 (59.6)	68 (66.7)	70 (61.9)	35 (66.0)	313 (64.4)
Time since first ICD implantation, mean (SD), mo	27.3 (38.2)	32.2 (38.9)	28.7 (38.1)	27.8 (35.3)	27.7 (37.5)	28.8 (37.5)
Time since last appropriate ICD intervention,‡ mean (SD), d	12.4 (9.8)	13.6 (9.6)	13.4 (10.5)	14.4 (13.8)	10.2 (8.4)	13.1 (10.7)
Prior cardiovascular medications,§ n (%)						
β-blockers	101 (92.7)	96 (88.1)	92 (90.2)	101 (89.4)	43 (81.1)	433 (89.1)
ACE inhibitors or ARBs	90 (82.6)	93 (85.3)	88 (86.3)	100 (88.5)	43 (81.1)	414 (85.2)
Lipid-modifying agents	82 (75.2)	76 (69.7)	81 (79.4)	81 (71.7)	36 (67.9)	356 (73.3)
Diuretics	75 (68.8)	74 (67.9)	69 (67.6)	82 (72.6)	36 (67.9)	336 (69.1)
Calcium channel blockers	14 (12.8)	12 (11.0)	12 (11.8)	12 (10.6)	3 (5.7)	53 (10.9)

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.

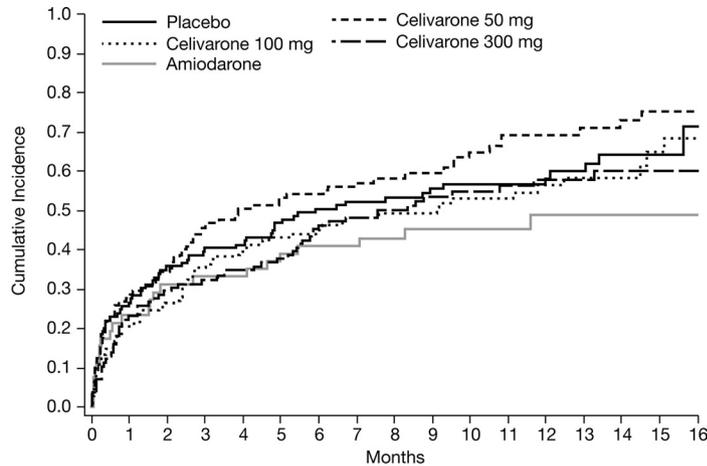
‡Only for patients with appropriate ICD intervention between ICD implantation and randomization.

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

||Data unavailable for 1 patient.

estimate of Lin and Wei for the covariance matrix. Cumulative mean functions and 95% CIs for each treatment group were calculated with the use of Nelson-Aalen estimates and Greenwood's variance estimation for each time point. Statistical significance for the primary end point was assessed with Hochberg's multiple comparison procedure.

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.



**Figure 2.** Kaplan-Meier cumulative incidence curves from randomization to first ventricular tachycardia/ventricular fibrillation-triggered implantable cardioverter-defibrillator intervention or sudden death (intention-to-treat population).

Number at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Placebo	109	66	54	40	27	9											
Celivarone 50 mg	109	58	48	31	19	10											
Celivarone 100 mg	102	66	56	40	24	10											
Celivarone 300 mg	113	75	57	41	27	8											
Amiodarone	53	34	30	22	15	8											

## 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  $\leq 30$  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;  $P=0.13$ ).

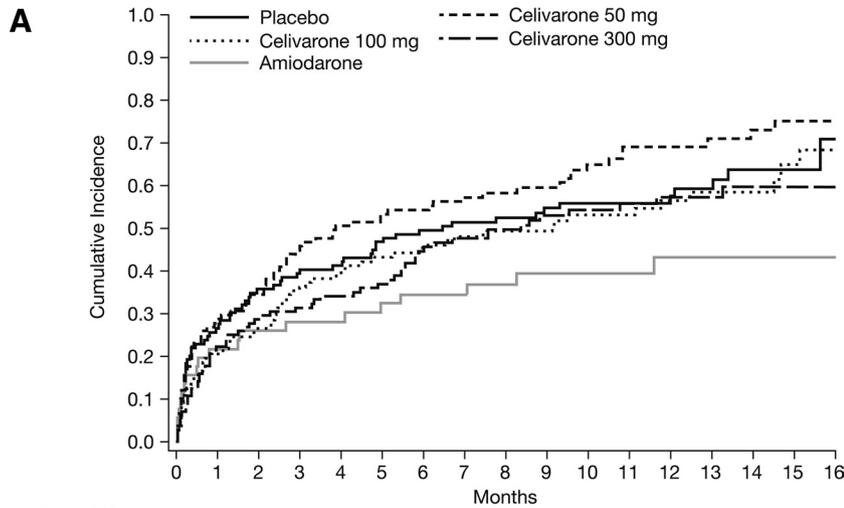
Analysis of the first component of the primary end point (VT/VF-triggered ICD intervention alone) showed no statistically significant differences between the celivarone groups and the placebo group (Figure 3A) and did not show any evidence of a dose effect. There was, however, a significant decrease 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 ( $P=0.0207$ ).

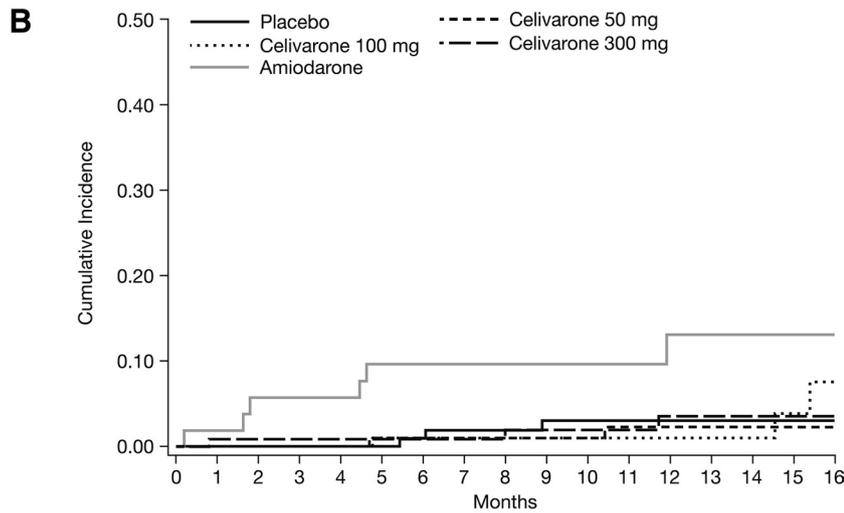
The proportion of patients with multiple ICD interventions (up to 10) is shown in Figure 4A. The HRs versus placebo were 1.045, 0.839, and 0.681 for the celivarone 50-, 100-, and 300-mg groups, respectively. Mean cumulative number of occurrences (up to 10 arrhythmic episodes or sudden death per patient) 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



Number at Risk						
Placebo	109	66	54	40	27	9
Celivarone 50 mg	109	58	48	31	19	10
Celivarone 100 mg	102	66	56	40	24	10
Celivarone 300 mg	113	75	57	41	27	8
Amiodarone	53	34	30	22	15	8



Number at Risk						
Placebo	109	107	105	83	60	26
Celivarone 50 mg	109	107	106	80	56	30
Celivarone 100 mg	102	101	100	83	54	32
Celivarone 300 mg	113	111	106	87	60	24
Amiodarone	53	49	46	38	25	16

**Figure 3.** Kaplan-Meier cumulative incidence curves from randomization to the first episode of each component of the primary end point (intention-to-treat population). **A**, Ventricular tachycardia/ventricular fibrillation-triggered implantable cardioverter-defibrillator intervention. **B**, Sudden death.

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

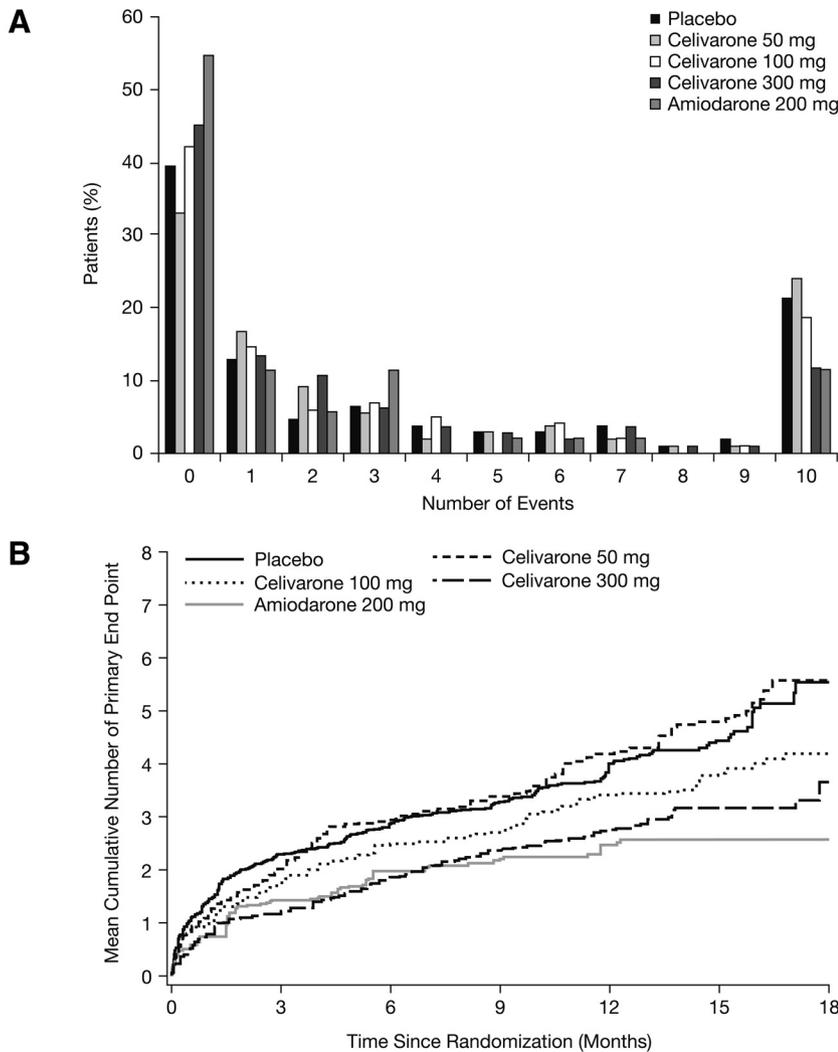
amiodarone group, the HR versus placebo was 3.327 (95% CI, 1.182–9.367;  $P=0.0158$ ); this was contributed to by a difference in the number of sudden deaths.

**Pharmacokinetic Data**

With follow-up to 12 months of repeated administration, mean steady state values of celivarone  $C_{max}$  were 103, 215, and 763 ng/mL at 50, 100, and 300 mg, respectively. At steady state, mean  $C_{trough}$  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



**Figure 4.** Recurrent episodes of the primary end point (ventricular tachycardia/ventricular fibrillation-triggered implantable cardioverter-defibrillator intervention or sudden death) (intention-to-treat population). **A.** Percentage of patients by number of events (limited to a maximum of 10 per patient) experienced during the study. **B.** Mean cumulative number of the first 10 events per patient.

Placebo							
Number at Risk	109	93	86	66	40	18	2
Number of Events	0	233	285	317	353	366	378
Celivarone 50 mg							
Number at Risk	109	94	86	64	42	21	3
Number of Events	0	204	289	319	364	384	394
Celivarone 100 mg							
Number at Risk	102	91	86	67	39	22	1
Number of Events	0	166	233	251	289	300	305
Celivarone 300 mg							
Number at Risk	113	105	96	74	45	17	1
Number of Events	0	128	195	241	263	276	278
Amiodarone 200 mg							
Number at Risk	53	43	39	31	21	11	0
Number of Events	0	69	92	100	106	108	108

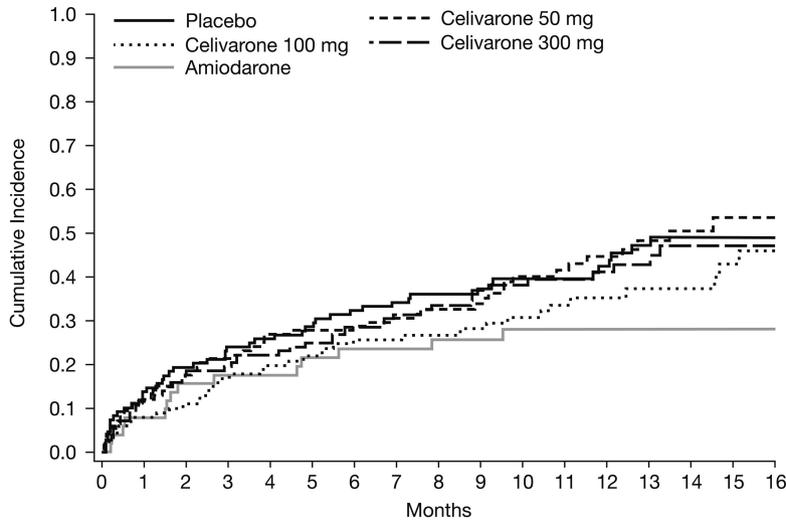
patients experienced treatment-emergent adverse events in each of the treatment groups, and approximately half of these were serious treatment-emergent adverse events (Table 2). There was no evidence of a dose effect in the celivarone groups for treatment-emergent adverse events, serious treatment-emergent 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  $\geq 500$  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



**Figure 5.** Kaplan-Meier cumulative incidence curves from randomization to first implantable cardioverter-defibrillator shock or death from any cause (intention-to-treat population).

Number at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Placebo	109	82	73	57	39	15											
Celivarone 50 mg	109	85	77	55	34	14											
Celivarone 100 mg	102	84	75	56	35	19											
Celivarone 300 mg	113	90	77	55	36	12											
Amiodarone	53	42	39	31	23	14											

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.

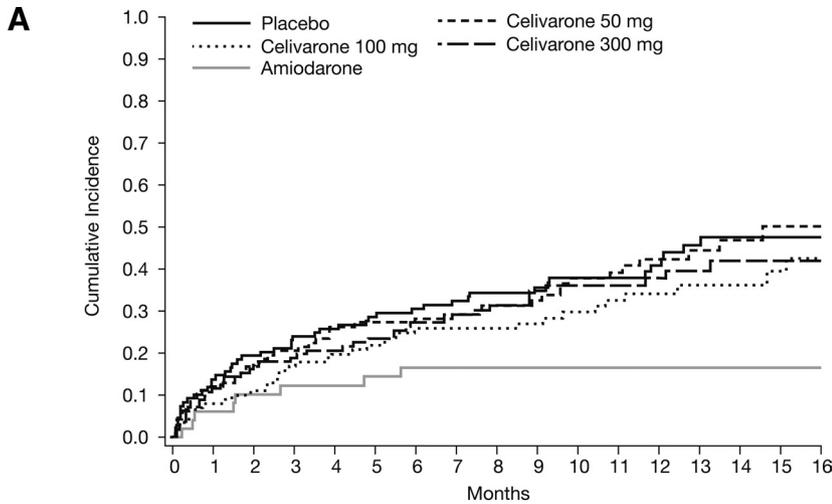
Antiarrhythmic drugs have been poorly and inadequately studied for ventricular indications. Surrogates are unreliable, and it is unethical to expose placebo-assigned patients to the risk of a malignant arrhythmia. Consequently, double-blind, placebo-controlled, dose-ranging studies have been conducted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

tation of the ICD can be complex, and, as a result, studies in this population are uncommon.

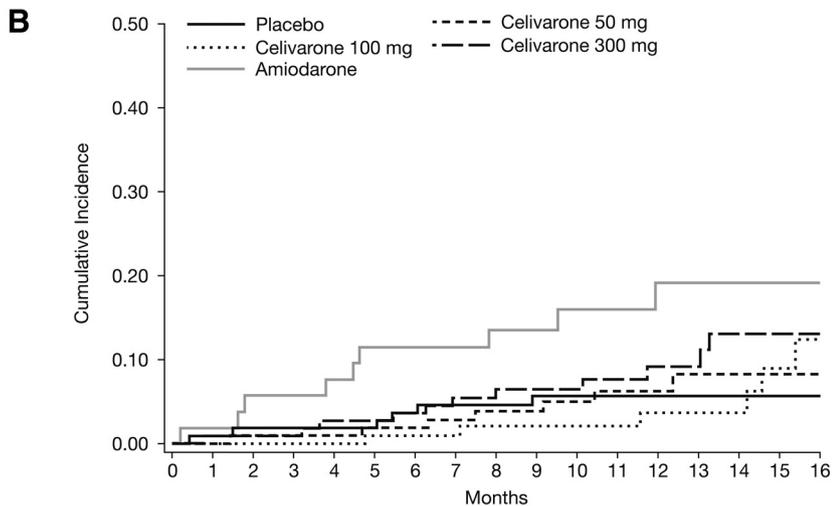
The efficacy of antiarrhythmic drugs in preventing shocks in patients with ICDs has been investigated in a few published studies. Sotalol reduced the risk of death from any cause or the delivery of a first shock for any reason, death from any cause, or the delivery of a first appropriate shock in a 12-month, double-blind, placebo-controlled multicenter study.<sup>9</sup> 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.<sup>5</sup> In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients study (OPTIC; n=412), amiodarone plus a  $\beta$ -blocker significantly reduced the risk of ICD shock compared with a  $\beta$ -blocker alone or sotalol alone.<sup>7</sup> 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.<sup>15</sup> 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-



Number at Risk						
Placebo	109	82	73	57	39	15
Celivarone 50 mg	109	84	76	54	34	14
Celivarone 100 mg	102	84	75	56	35	19
Celivarone 300 mg	113	89	77	55	36	12
Amiodarone	53	42	38	31	23	14



Number at Risk						
Placebo	109	107	105	83	60	26
Celivarone 50 mg	109	107	106	80	56	30
Celivarone 100 mg	102	101	100	83	54	32
Celivarone 300 mg	113	111	106	87	60	24
Amiodarone	53	49	46	38	25	16

**Figure 6.** Kaplan-Meier cumulative incidence curves from randomization to the first episode of each component of the secondary end point (intention-to-treat population). **A**, Implantable cardioverter-defibrillator shock. **B**, Death from any cause.

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).<sup>14</sup>

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.<sup>14</sup> 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).<sup>16</sup> Finally, patients received treatment over a longer period to permit a better assessment of safety as well as durability of clinical efficacy.

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

	Placebo (n=109)	Celivarone 50 mg (n=107)	Celivarone 100 mg (n=101)	Celivarone 300 mg (n=113)	Amiodarone 200 mg (n=51)
Any TEAE	92 (84.4)	92 (86.0)	87 (86.1)	98 (86.7)	44 (86.3)
Any serious TEAE	53 (48.6)	45 (42.1)	53 (52.5)	49 (43.4)	23 (45.1)
Any TEAE leading to death*	4 (3.7)	2 (1.9)	5 (5.0)	6 (5.3)	3 (5.9)
Discontinued because of TEAE	18 (16.5)	29 (27.1)	24 (23.8)	24 (21.2)	16 (31.4)
TEAEs occurring in $\geq 5\%$ 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.

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

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.<sup>14</sup> 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.

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### 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.