SYNOPSIS

Title of the study: Double blind placebo controlled dose ranging study of the efficacy and safety of celivarone 50, 100 or 300 mg OD with amiodarone as calibrator for the prevention of ICD interventions or death (DRI10936 – ALPHEE)

Investigator(s): [redacted]

Study centers: 151 active centers in 26 countries across Europe (Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden), Argentina, Australia, Canada, Chile, Israel, Japan, Mexico, Norway, Russian Federation, South Africa, Turkey, and the USA.

Publications (reference): Kowey PR, Crijns HJGM, Aliot EM, Capucci A, Kulakowski P, Radzik D, et al, on behalf of the ALPHEE study Investigators. 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. Circulation, published online November 14, 2011.

Study period:

Date first patient enrolled: 21 September 2009

Date last patient completed: 12 May 2011

Phase of development: 2b

Objectives:

Primary: To assess the efficacy of celivarone for the prevention of implantable cardioverter defibrillator (ICD) interventions or death.

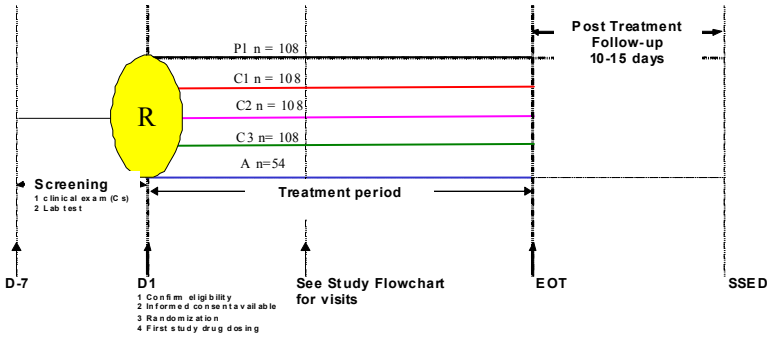
Secondary:

To assess the tolerability and safety of the different dose regimens of celivarone in the selected population.

To document SSR149744 plasma levels during the study.

Methodology: This was a dose-finding, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-arm study including a positive control calibrator arm. Eligible patients were randomized (2:2:2:2:1) via an interactive voice response system (IVRS) to placebo, celivarone 50 mg, celivarone 100 mg, celivarone 300 mg, or amiodarone group. The randomization was non-adaptative, centralized, and stratified by the timing of ICD implantation (less or more than 30 days) and by country.

A summary of the study design is provided in the figure below.



D: day
R: Randomization
C1= Celivarone 50 mg OD
C2= Celivarone 100 mg OD
C3= Celivarone 300 mg OD
A= Amiodarone 600 mg OD for 10 days then 200 mg OD
Pl= Placebo
EOT: End Of Treatment Visit
SSED: Scheduled Study End Date (190 days [up to +14days] after the randomization of the last patient)

Number of patients:

Planned: 486 patients (108 in the placebo group and in each of the 3 celivarone groups, and 54 in the amiodarone group)

Randomized and treated: 486 randomized and 481 treated patients (109 in the placebo group, 107 in the celivarone 50 mg group, 101 in the celivarone 100 mg group, 113 in the celivarone 300 mg group, and 51 in the amiodarone group)

Evaluated:

Efficacy: 486 patients (109 in the placebo and celivarone 50 mg groups, 102 in the celivarone 100 mg group, 113 in the celivarone 300 mg group, and 53 in the amiodarone group)

Safety: 481 patients (109 in the placebo group, 107 in the celivarone 50 mg group, 101 in the celivarone 100 mg group, 113 in the celivarone 300 mg group, and 51 in the amiodarone group)

Pharmacokinetics: 372 patients (107 in the celivarone 50 mg group, 101 in the celivarone 100 mg group, 113 in the celivarone 300 mg group, and 51 in the amiodarone group)

Diagnosis and criteria for inclusion: ICD patients with a left ventricular ejection fraction (LVEF) of 40% or less and one of the following criteria: at least one ICD therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) in the previous month, or ICD implantation in the previous month for documented VT/VF.

Study treatments

Investigational product	Celivarone (SSR149744C)	Amiodarone (as calibrator)	Placebo (as comparator)
Formulation	50-mg capsule 100-mg capsule	200-mg capsule	capsule
Route of administration	Oral, in fed conditions (breakfast, lunch, or dinner depending on the patient's habits)	Oral, in fed conditions (breakfast, lunch, or dinner depending on the patient's habits)	Oral, in fed conditions (breakfast, lunch, or dinner depending on the patient's habits)
Dose regimen	50, 100, or 300 mg once daily	600 mg once daily (loading dose) from Day 1 to Day 10, then 200 mg once daily	3 capsules once daily
Batch numbers	50 mg: [redacted] 100 mg: [redacted]	[redacted]	[redacted]

Duration of treatment: 6 months minimum

Duration of observation: 19 months for the 1st patient enrolled in the study: 1-week screening, treatment period going from the 1st day of treatment to the end-of-treatment (EOT) visit to be done 10-15 days prior to the scheduled study end date (SSED) defined as last patient randomization date + 190 days (up to +14 days).

Criteria for evaluation:

Efficacy:

Primary endpoint: The primary efficacy variable was defined as VT/VF triggered ICD interventions or sudden death (whichever occurred first). The presence of VT or VF leading to any ICD interventions (shocks or antitachycardia pacing [ATPs]) was documented by ICD interrogation. The Central Adjudication Committee adjudicated the 10 first episodes of VT/VF leading to an ICD intervention for a patient. Only adjudicated data occurred between the randomization and the SSED were analyzed. Sudden death data came from the central review of fatal events performed by a subset of Steering Committee members.

The main analytical approach was the time in days elapsed between the randomization and the first occurrence of primary endpoint. The second analytical approach was the time in days elapsed between the randomization and each of first 10 occurrences of primary endpoint.

Secondary endpoint: The secondary efficacy variable was defined as time to first ICD shock or death from any cause.

Tertiary and other endpoint: The tertiary efficacy variable was defined as time to first cardiovascular hospitalization (Investigator's judgement with preprinted form) or death from any cause.

Other efficacy variables were inappropriate shocks and supraventricular arrhythmia.

Safety: Safety variables were defined as adverse events (AEs) reported by the patient or noted by the Investigator, clinical laboratory data (hematology and clinical chemistry), vital signs (blood pressure), and electrocardiogram (ECG) parameters.

The main safety criterion was the incidence of treatment-emergent adverse events (TEAEs) classified as deaths, serious adverse events (SAEs), AEs leading to treatment discontinuation, and all AEs (including AEs of special interest [AESI] defined as alanine aminotransferase [ALT] ≥3 upper limit of normal [ULN] or ≥2 times the baseline value if baseline ALT ≥ ULN).

Pharmacokinetics: Celivarone, amiodarone, and desethylamiodarone plasma concentrations (concentration observed just before treatment administration during repeated dosing [C_{trough}] and maximum concentration observed [C_{max}]) were assessed.

Plasma concentrations obtained from patients in the celivarone or amiodarone groups were classified as C_{trough} if time interval between last dose before sampling and sampling was less than 2 hours or between 16 and 24 hours, and as C_{max} if time interval between last dose before sampling and sampling was between 2 and 8 hours.

Pharmacokinetic sampling times and bioanalytical methods:

Investigators were recommended to collect blood samples for pharmacokinetic (PK) assay within 1 hour predose on Day 5 ± 2 days, within 2 to 6 hours postdose in Month 1 ± 5 days, within 8 to 16 hours postdose in Month 2 ± 5 days, within 1 hour predose in Month 3 ± 14 days, within 2 to 6 hours postdose in Month 6 ± 14 days, and any time in Month 12 ± 14 days.

Celivarone plasma concentrations were determined using a validated liquid chromatography with tandem mass spectrometry method with a limit of quantification (LOQ) of 5 ng/mL. Amiodarone and its metabolite desethylamiodarone plasma concentrations were determined using a validated high performance liquid chromatography method with UV detection, with a LOQ of 5 ng/mL.

Statistical methods:

Analysis populations:

Efficacy populations:

The main efficacy population was the intent-to-treat (ITT) population defined as all randomized patients analyzed according to the treatment group allocated by IVRS randomization.

The secondary population for efficacy analysis was the per-protocol population defined as a subset of the ITT population containing patients without a major efficacy-related protocol deviation.

Safety population: The safety population included all randomized patients who did actually receive at least 1 dose or partial of a dose of investigational product (IP) analyzed according to the treatment actually received. If a patient had taken more than one treatment, the treatment actually received was the treatment taken for the longest period during the study.

Pharmacokinetic population: The PK population corresponded to the safety population.

Efficacy analyses:

The primary analysis of the primary endpoint was the time from randomization to first VT/VF triggering ICD intervention or sudden death. The comparison of each celivarone dose group versus the placebo group was performed using a stratified two-sided Log-rank asymptotic test according to stratum of randomization (timing of ICD implantation $\leq$30 days / >30 days).

Hazard ratio with 95% confidence interval (each celivarone dose versus placebo) was estimated using the Cox model.

The secondary efficacy analysis of the primary endpoint was the comparison between placebo and each celivarone dose performed on recurrent episodes. The maximum number of episodes was limited to 10 per patient. Hazard ratios between treatment groups were estimated by Andersen-Gill mean intensity model and the robust sandwich estimate of Lin and Wei for the covariance matrix.

Statistical significance on the primary endpoint was assessed using Hochberg multiple comparison procedure.

The other key secondary endpoint analysis was the time from randomization to first ICD shock or death from any cause. Survival analysis was performed in the same way than the primary endpoint analysis. To address the multiplicity in endpoints, a closed testing procedure was used.

Statistical significance on the secondary endpoint was assessed using Hochberg multiple comparison procedure.

Safety analyses:

The analysis of AEs was performed on TEAEs, defined as AEs that developed or worsened or became serious during the period going from the first IP administration up to 10 days post-treatment. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA, version 14), and TEAEs were summarized by treatment group.

In addition to the routine safety analysis, overviews of specific AE groupings were presented. These events were summarized by primary system-organ class (SOC) and preferred term (PT) for TEAEs and were defined as:

- Heart failure events using the narrow selection of the Standardized MedDRA Query (SMQ) “Cardiac failure”.
- Liver disorders events using the broad and narrow selection of SMQ “Liver related investigations, signs and symptoms” or events in SOC “Hepatobiliary disorders”.
- Interstitial lung disease (ILD) using the narrow SMQ “ILD”.
- Severe skin disorders using the narrow SMQ “Severe skin disorders”.
- Peripheral neuropathy including optic neuropathy using the narrow SMQ “Peripheral neuropathy”.

Descriptive statistics for all laboratory variables, vital signs, and ECG parameters (raw data and changes from baseline) were summarized for each visit or study assessment (baseline, each postbaseline time point, last on-treatment value) by treatment group. For liver function, renal function, and electrolyte parameters, thyroid stimulating hormone (TSH), blood pressure and ECG parameters, mean changes from baseline with the corresponding standard error were to be plotted over time (at same time points) in each treatment group. Individual values for laboratory evaluations, vital signs, and ECG data were flagged for potentially clinically significant abnormalities (PCSAs, version 3.0 - 14-Sep-2009) and the incidence of PCSAs at any time during the TEAE period was summarized by biological function and/or treatment group.

Pharmacokinetic analyses:

The occurrence of steady state was assessed graphically first, by plotting C_{trough} throughout the study visits (Day 5, Month 1, Month 2, Month 3, Month 6, and Month 12) over all evaluable patients and also for each dose level.

Descriptive statistics (number of observations, arithmetic and geometric means, standard deviation [SD], coefficient of variation, minimum and maximum) were calculated for celivarone single or average C_{trough} and for celivarone single or average C_{max} for each celivarone dose level. For $C_{max,av}$ and $C_{trough,av}$, dose proportionality was assessed using a power model.

Summary:

Patient disposition: A total of 515 patients were screened, of whom 486 were randomized to one of the 5 treatment groups and 481 received at least 1 dose of IP. Most of the patients (66.7%) were randomized in the stratum ICD implantation >30 days before randomization. Out of 486 randomized patients, 169 (34.8%) did not complete the treatment period; this proportion was similar across groups. In all groups, the main reason for treatment discontinuation was AE. No patients were lost to follow-up.

Analysis populations – Randomized population

	Placebo	Celivarone 50mg	Celivarone 100mg	Celivarone 300mg	Amiodarone 200mg	All
Randomized population	109 (100%)	109 (100%)	102 (100%)	113 (100%)	53 (100%)	486 (100%)
Randomized in stratum : ICD implantation <= 30 days	38 (34.9%)	35 (32.1%)	32 (31.4%)	41 (36.3%)	16 (30.2%)	162 (33.3%)
Randomized in stratum : ICD implantation > 30 days	71 (65.1%)	74 (67.9%)	70 (68.6%)	72 (63.7%)	37 (69.8%)	324 (66.7%)
Efficacy populations						
Intent-to-Treat (ITT)	109 (100%)	109 (100%)	102 (100%)	113 (100%)	53 (100%)	486 (100%)
Per Protocol	97 (89.0%)	99 (90.8%)	89 (87.3%)	101 (89.4%)	50 (94.3%)	436 (89.7%)
Safety population	109	107	101	113	51	481

Note: The safety population patients are tabulated according to treatment actually received (as treated).
For the other populations, patients are tabulated according to their randomized treatment.

Patient disposition - Randomized population

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)	All (N=486)
Randomized and not treated	0	2 (1.8%)	1 (1.0%)	0	2 (3.8%)	5 (1.0%)
Subject's request for not being treated	0	2 (1.8%)	0	0	1 (1.9%)	3 (0.6%)
Randomized and treated	109 (100%)	107 (98.2%)	101 (99.0%)	113 (100%)	51 (96.2%)	481 (99.0%)
Did not complete the study treatment period	32 (29.4%)	43 (39.4%)	35 (34.3%)	38 (33.6%)	21 (39.6%)	169 (34.8%)
Subject's request for treatment discontinuation	9 (8.3%)	19 (17.4%)	14 (13.7%)	13 (11.5%)	8 (15.1%)	63 (13.0%)
Reason for treatment discontinuation						
Adverse event	18 (16.5%)	29 (26.6%)	24 (23.5%)	24 (21.2%)	16 (30.2%)	111 (22.8%)
Lack of efficacy	8 (7.3%)	8 (7.3%)	4 (3.9%)	4 (3.5%)	3 (5.7%)	27 (5.6%)
Poor compliance to protocol	2 (1.8%)	1 (0.9%)	0	1 (0.9%)	1 (1.9%)	5 (1.0%)
Other	4 (3.7%)	5 (4.6%)	7 (6.9%)	9 (8.0%)	1 (1.9%)	26 (5.3%)
Status at last study contact						
Alive	103 (94.5%)	99 (90.8%)	96 (94.1%)	102 (90.3%)	44 (83.0%)	444 (91.4%)
Dead	6 (5.5%)	9 (8.3%)	6 (5.9%)	11 (9.7%)	9 (17.0%)	41 (8.4%)
Lost to follow-up	0	0	0	0	0	0
Missing	0	1 (0.9%)	0	0	0	1 (0.2%)

Note: Percentages are calculated using the number of patients randomized as denominator.
Note: A patient is considered as lost to follow up if vital status page is not filled in during the Scheduled Study End Date visit (SSED). Died patients and withdrew consent patients are not considered as lost to follow up. Two patients who died after SSED are counted Alive at time of last contact.
Missing = A not treated patient who withdrew consent just after randomization

Study disposition: The mean and median duration of follow-up was about 12 months, similar across groups, and almost 76% (368/486) of patients were followed for at least 9 months.

Study completion - Randomized population

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)	All (N=486)
Number of patients who completed the follow-up						
Completed the follow-up	98 (89.9%)	97 (89.0%)	91 (89.2%)	98 (86.7%)	42 (79.2%)	426 (87.7%)
Duration of follow-up (months)						
Number	109	108	102	113	53	485
Mean (SD)	11.95 (3.74)	11.87 (3.74)	12.23 (3.59)	11.86 (3.65)	11.09 (4.67)	11.88 (3.80)
Median	12.12	11.94	12.16	12.35	11.47	12.06
Q1 : Q3	9.10 : 14.52	8.74 : 15.00	9.99 : 15.18	9.63 : 14.36	8.54 : 15.01	9.03 : 14.95
Min : Max	0.4 : 18.2	1.4 : 19.2	0.3 : 18.6	0.8 : 18.5	0.2 : 17.8	0.2 : 19.2
Number of patients with cumulative duration of follow-up by category [n(%)]						
≥ 1 day	109 (100%)	108 (99.1%)	102 (100%)	113 (100%)	53 (100%)	485 (99.8%)
≥ 1 month	108 (99.1%)	108 (99.1%)	101 (99.0%)	112 (99.1%)	51 (96.2%)	480 (98.8%)
≥ 3 months	107 (98.2%)	107 (98.2%)	101 (99.0%)	112 (99.1%)	49 (92.5%)	476 (97.9%)
≥ 6 months	104 (95.4%)	106 (97.2%)	100 (98.0%)	108 (95.6%)	46 (86.8%)	464 (95.5%)
≥ 9 months	82 (75.2%)	79 (72.5%)	83 (81.4%)	87 (77.0%)	37 (69.8%)	368 (75.7%)
≥ 12 months	56 (51.4%)	52 (47.7%)	52 (51.0%)	60 (53.1%)	24 (45.3%)	244 (50.2%)
≥ 15 months	26 (23.9%)	27 (24.8%)	29 (28.4%)	23 (20.4%)	14 (26.4%)	119 (24.5%)
≥ 18 months	2 (1.8%)	4 (3.7%)	2 (2.0%)	5 (4.4%)	0	13 (2.7%)

Completed patients are patients who have been follow until the defined time window of Scheduled Study End Date (SSED).
Patients who died before SSED visit are not considered as completed
Duration of follow up is calculated for all randomized patients using SSED date. If this date is missing, the last contact date is used.

Good Clinical Practice non-compliance: An accidental unblinding of a limited number sponsor staff by the IVRS provider (ICON) occurred when 32 out of 486 patients were included in the study. On 26 August 2009, ICON mistakenly extended web-based access to 2 reports containing unblinding information to Investigational Product Managers (IPMs) who should not have such access. On 12 November 2009, the Canadian IPM accessed the reports, noted the error, and alerted ICON who immediately revoked access to IPMs the same day. The IPM in Canada attested that she did not share, print, or take note of any unblinded data. As per ICON audit trail, only one other IPM in Czech Republic had accessed one of the 2 accessible unblinded reports on 21 October 2009. This IPM attested that he did not even notice that the report contained unblinded data. ICON documented their investigation of the issue and its root cause in an incident report in May 2010 including corrective and preventative actions, in particular the update of user procedures and related user training. In conclusion, this incidence had no detrimental impact since protection of the blind was not jeopardized and appropriate measures were taken to avoid recurrence.

Demographics and baseline characteristics: The mean (SD) age was 64.4 (10.9) years, similar across groups, and the majority of patients (88.7%) were males. As required by the inclusion criteria, this population had severe underlying heart disease, the median LVEF being 30.0% and 65.4% of patients having an LVEF <35%. Overall, 86.0% of patients had congestive heart failure at baseline, of whom 60.4% had New York Heart Association (NYHA) class II and 24.0% NYHA class III. The main cardiac conditions were coronary artery disease and hypertension. About 25% of patients had non-ischemic dilated cardiomyopathy. As expected, given the underlying cardiac disease, almost 90% of patients were on betablockers, 85.2% on agents acting on the renin-angiotensin system, 73.3% on lipid modifying agents, and almost 70% on diuretics. The patients' baseline characteristics were comparable across groups.

Exposure: The median duration of treatment was about 9 months. The minimum exposure was observed in the amiodarone group with a median of 8.41 months and a mean ± SD of 7.81 ± 5.89 months. Similar durations were observed in the other groups and overall 28.7% of patients were treated for 12 months.

Exposure to investigational product - Randomized and treated population

	Placebo (N=109)	Celivarone 50mg (N=107)	Celivarone 100mg (N=101)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=51)	All (N=481)
Cumulative exposure to treatment (patient years)	83.0	76.8	76.7	85.0	33.2	354.8
Duration of study treatment (months)						
Number	109	107	101	113	51	481
Mean (SD)	9.14 (4.97)	8.62 (5.30)	9.12 (4.99)	9.02 (4.97)	7.81 (5.89)	8.85 (5.15)
Median	9.13	8.54	9.17	9.23	8.41	8.97
Q1 : Q3	6.24 : 12.48	4.01 : 13.01	6.01 : 12.85	5.85 : 12.88	1.48 : 12.29	4.73 : 12.85
Min : Max	0.1 : 17.9	0.1 : 18.4	0.0 : 18.1	0.1 : 17.7	0.0 : 17.1	0.0 : 18.4
Number of patients with cumulative duration of study treatment by category [n(%)]						
≥ 1 month	102 (93.6%)	98 (91.6%)	94 (93.1%)	106 (93.8%)	39 (76.5%)	439 (91.3%)
≥ 3 months	93 (85.3%)	85 (79.4%)	88 (87.1%)	92 (81.4%)	34 (66.7%)	392 (81.5%)
≥ 6 months	82 (75.2%)	72 (67.3%)	75 (74.3%)	84 (74.3%)	31 (60.8%)	344 (71.5%)
≥ 9 months	55 (50.5%)	52 (48.6%)	52 (51.5%)	58 (51.3%)	23 (45.1%)	240 (49.9%)
≥ 12 months	32 (29.4%)	32 (29.9%)	29 (28.7%)	32 (28.3%)	13 (25.5%)	138 (28.7%)
≥ 15 months	16 (14.7%)	14 (13.1%)	16 (15.8%)	14 (12.4%)	8 (15.7%)	68 (14.1%)
≥ 18 months	0	1 (0.9%)	1 (1.0%)	0	0	2 (0.4%)

Note: Patients are considered in the treatment group they actually received the most longer during the study.

Efficacy results:

The cumulative number of patients with a primary endpoint was 67 in the placebo group and 73, 60, and 62 in the celivarone 50, 100, and 300 mg groups, respectively. For the primary analysis of the primary endpoint combining VT/VF triggered ICD interventions or sudden death, the hazard ratio (HR) versus placebo was 1.199, 0.909, and 0.86 in the celivarone 50, 100, and 300 mg groups, respectively; none of these were statistically significant and there was no evidence of a dose effect.

Time to first arrhythmic episode VT/VF triggering ICD intervention or sudden death - ITT population

Analysis Value	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)
Number of patients with endpoint	67	73	60	62	24
Median survival (95% CI) (days)[a]	177.0 (114.00 to 363.00)	116.0 (75.00 to 248.00)	274.0 (125.00 to 435.00)	227.0 (164.00 to NC)	NC (139.00 to NC)
month 1					
Number of patients with endpoint	29	31	21	26	12
Cumulative incidence of events (95% CI)[a]	0.266 (0.183 to 0.349)	0.287 (0.202 to 0.372)	0.206 (0.127 to 0.284)	0.231 (0.153 to 0.309)	0.233 (0.118 to 0.349)
month 3					
Number of patients with endpoint	44	49	37	36	17
Cumulative incidence of events (95% CI)[a]	0.404 (0.312 to 0.496)	0.457 (0.363 to 0.552)	0.363 (0.269 to 0.456)	0.321 (0.234 to 0.407)	0.332 (0.203 to 0.461)
month 6					
Number of patients with endpoint	55	58	46	51	21
Cumulative incidence of events (95% CI)[a]	0.505 (0.411 to 0.598)	0.543 (0.448 to 0.638)	0.451 (0.354 to 0.548)	0.462 (0.369 to 0.556)	0.410 (0.275 to 0.545)
month 12					
Number of patients with endpoint	62	70	55	61	24
Cumulative incidence of events (95% CI)[a]	0.583 (0.487 to 0.680)	0.691 (0.596 to 0.786)	0.565 (0.462 to 0.668)	0.578 (0.480 to 0.676)	0.489 (0.344 to 0.633)
month 15					
Number of patients with endpoint	65	73	58	62	24
Cumulative incidence of events (95% CI)[a]	0.643 (0.539 to 0.747)	0.752 (0.653 to 0.851)	0.649 (0.528 to 0.771)	0.602 (0.499 to 0.705)	0.489 (0.344 to 0.633)
stratified log-rank p-value[b]					
vs Placebo	-	0.2872	0.5908	0.3934	0.1283
significance threshold[c]	-	0.017	0.050	0.025	-
	-	NS	NS	NS	
stratified hazard ratio (95% CI)[d]					
vs Placebo	-	1.199 (0.858 to 1.676)	0.909 (0.64 to 1.289)	0.86 (0.608 to 1.216)	0.697 (0.437 to 1.113)
Endpoint's composition					
VT/VF triggered by ICD intervention	66	73	60	61	20
Sudden Death Adjudicated	1	0	0	1	4

a: Kaplan-Meier estimates .
b : Log-rank stratified according to randomization stratum - time of ICD implantation (<= 30 days / > 30 days)
c : According to Hochberg multiple comparisons procedure, p-value must be below this threshold in order to be significant. If a test is significant, the procedure stops and the comparison associated to p-value lower or equal to the tested p-value are declared statistically significant.
d : Determined from Cox regression model stratified according to randomization stratum - time of ICD implantation (<=30 days / > 30 days)
Sudden death according adjudicator's judgment.
No multiplicity process has been performed for comparison Amiodarone vs Placebo (sensitivity analysis)

For the secondary analysis of the primary endpoint taking into account not only the first ICD intervention but the 10 first episodes of VT/VF, the HR versus placebo was 1.045, 0.839, and 0.681 in the celivarone 50, 100, and 300 mg groups, respectively. Although this could indicate a dose effect and a trend towards efficacy, given the unadjusted p-value of 0.049 in the celivarone 300 mg group, this result was not statistically significant when analyzed with the Hochberg correction for multiplicity of comparisons.

Time of first 10 arrhythmic episode VT/VF triggered ICD intervention or sudden death - Nelson-Aalen estimates - ITT population

	Placebo	Celivarone 50mg	Celivarone 100mg	Celivarone 300mg	Amiodarone 200mg
Month 1					
Number of events, n	146	119	96	85	37
Nelson-Aalen estimates	1.4 (1.2 to 1.6)	1.1 (0.9 to 1.3)	1.0 (0.8 to 1.2)	0.8 (0.6 to 0.9)	0.7 (0.5 to 1.0)
Month 3					
Number of events, n	233	204	166	127	69
Nelson-Aalen estimates	2.3 (2.0 to 2.6)	2.0 (1.7 to 2.3)	1.7 (1.5 to 2.0)	1.2 (1.0 to 1.4)	1.4 (1.1 to 1.8)
Month 6					
Number of events, n	279	287	231	193	92
Nelson-Aalen estimates	2.8 (2.5 to 3.1)	2.9 (2.6 to 3.3)	2.5 (2.1 to 2.8)	1.8 (1.6 to 2.1)	2.0 (1.6 to 2.4)
Month 12					
Number of events, n	342	363	289	262	106
Nelson-Aalen estimates	3.7 (3.3 to 4.1)	4.2 (3.7 to 4.6)	3.4 (3.0 to 3.8)	2.7 (2.4 to 3.1)	2.5 (2.0 to 2.9)
Month 18					
Number of events, n	378	394	305	277	108
Nelson-Aalen estimates	5.5 (4.7 to 6.4)	5.6 (4.9 to 6.3)	4.2 (3.6 to 4.8)	3.3 (2.8 to 3.8)	2.6 (2.1 to 3.1)
Hazard ratio (95% CI) (a)	-	1.045 (0.73 to 1.50)	0.839 (0.57 to 1.24)	0.681 (0.46 to 1.00)	0.599 (0.34 to 1.05)
p-value	-	0.812	0.377	0.049	0.071
Significance threshold (b)		0.050	0.025	0.017	
		NS	NS	NS	

Notes: Comparisons are performed between each dose of celivarone and Placebo.
a: Andersen-Gill mean intensity model and the robust sandwich estimate of Lin and Wei for the covariance matrix.
b : According to Hochberg multiple comparisons procedure p-value must be below this threshold in order to be significant. If a test is significant, the procedure stops and the comparison associated to p-value lower or equal to the tested p-value are declared statistically significant.
Notes: Only 10 first occurrences of primary endpoint are taken into account in the analysis.

For the secondary endpoint combining ICD shocks or death from all cause, the cumulative number of patients with an event was 48 in the placebo group and 49, 38, and 47 in the celivarone 50, 100, and 300 mg groups, respectively. The HR versus placebo was 1.023, 0.797, and 0.959 in the celivarone 50, 100, and 300 mg groups, respectively; none of these were statistically significant and there was no evidence of a dose effect.

Time of first shock or death from any cause - ITT population

Analysis Value	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)
Number of patients with endpoint	48	49	38	47	14
Median survival (95% CI) (days)a	NC (350.00 to NC)	405.0 (324.00 to NC)	495.0 (437.00 to NC)	521.0 (350.00 to NC)	NC (NC to NC)
month 1					
Number of patients with endpoint	15	13	8	14	4
Cumulative incidence of events (95% CI)a	0.138 (0.073 to 0.202)	0.120 (0.059 to 0.182)	0.079 (0.026 to 0.131)	0.124 (0.063 to 0.185)	0.078 (0.005 to 0.152)
month 3					
Number of patients with endpoint	26	23	18	22	9
Cumulative incidence of events (95% CI)a	0.240 (0.159 to 0.320)	0.213 (0.136 to 0.290)	0.178 (0.103 to 0.253)	0.195 (0.122 to 0.268)	0.176 (0.072 to 0.281)
month 6					
Number of patients with endpoint	35	31	26	32	12
Cumulative incidence of events (95% CI)a	0.323 (0.235 to 0.411)	0.287 (0.202 to 0.372)	0.257 (0.172 to 0.342)	0.286 (0.202 to 0.370)	0.235 (0.119 to 0.352)
month 12					
Number of patients with endpoint	44	44	33	43	14
Cumulative incidence of events (95% CI)a	0.424 (0.327 to 0.521)	0.446 (0.344 to 0.548)	0.352 (0.252 to 0.451)	0.411 (0.313 to 0.508)	0.281 (0.156 to 0.407)
month 15					
Number of patients with endpoint	48	48	36	46	14
Cumulative incidence of events (95% CI)a	0.490 (0.384 to 0.596)	0.537 (0.417 to 0.657)	0.430 (0.308 to 0.552)	0.472 (0.363 to 0.582)	0.281 (0.156 to 0.407)
stratified log-rank p-valueb					
vs Placebo	-	0.9094	0.2968	0.8377	0.0503
significance thresholdc	-	0.050	0.017	0.025	-
	-	NS	NS	NS	
stratified hazard ratio (95% CI)d					
vs Placebo	-	1.023 (0.687 to 1.524)	0.797 (0.521 to 1.221)	0.959 (0.64 to 1.436)	0.556 (0.306 to 1.009)
Endpoint's composition					
Shock	46	45	36	42	8
Death from any cause	2	4	2	5	6

a: Kaplan-Meier estimates .
b : Log-rank stratified according to randomization stratum - time of ICD implantation (<= 30 days / > 30 days)
c : According to Hochberg multiple comparisons procedure, p-value must be below this threshold in order to be significant. If a test is significant, the procedure stops and the comparison associated to p-value lower or equal to the tested p-value are declared statistically significant.
d : Determined from Cox regression model stratified according to randomization stratum - time of ICD implantation (<=30 days / > 30 days)

The sensitivity of the study could be considered sufficient and the study design valid because a significant reduction in the number of VT/VF episodes triggering an ICD intervention including ICD shocks or ATPs was observed in the amiodarone group in comparison to placebo. A significant decrease (HR=0.595, p=0.0399) in the incidence of VT/VF episodes was observed in the amiodarone group versus placebo consistent with the expected ventricular antiarrhythmic effects of this calibrator, as well as a trend (p=0.1283) towards a decrease (HR=0.697) in the incidence of the primary endpoint combining VT/VF episodes and sudden death. Similarly, in the amiodarone group compared with placebo, a significant decrease (HR=0.333, p=0.0026) in the incidence of ICD shocks was observed consistent with the known properties of this agent as well as a trend on the secondary endpoint combining shocks or death from any cause (HR=0.556, p=0.0503). Of note, although amiodarone appeared effective for the prevention of arrhythmia, the Kaplan-Meier analysis showed a significantly higher number of deaths in the amiodarone group in comparison to placebo, mainly from sudden cardiac death; however, this result should be interpreted with caution given the relatively low number of events.

Efficacy data for all analyses are provided in the CSR Appendix.

Safety results:

The overall incidence of patients who had TEAEs was similar across groups (86.0%, 86.1%, and 86.7% in the celivarone 50, 100, and 300 mg groups, respectively, 86.3% in the amiodarone group, versus 84.4% in the placebo group) and about half of these TEAEs were serious (see table below). This proportion was consistent with the high risk population included in the study. There was no evidence of a dose effect for the occurrence of TEAEs, SAEs, and AEs leading to premature IP discontinuation in the celivarone groups. The incidences of these events were similar in the amiodarone group as compared to the celivarone and placebo groups except for the incidence of AEs leading to IP discontinuation which appeared to be higher in comparison to placebo.

As expected, given the underlying disease of the population, cardiac disorders were the most frequently reported TEAEs including mainly ventricular arrhythmias/cardiac arrest, heart failure, and supra-ventricular arrhythmias. These events occurred in the celivarone groups without trend for a dose effect. One case of torsades de pointes was reported in a 52-year-old male patient randomized to celivarone 300 mg who was concomitantly treated with citalopram; the event was reported in the context of an electrical storm with repeated ICD shocks.

There was no trend in the celivarone groups with regard to laboratory abnormalities in particular for liver, renal, and thyroid functions, or concerning ECG abnormalities. The analysis of the QTc Bazett and Fridericia did not show an apparent dose effect on the proportion of patients with increased values. In the amiodarone group, there were numerically more thyroid gland disorders in comparison to placebo and an increase in creatinine plasma levels and in mean TSH were observed. The proportion of patients with a QTcF-interval $\geq$500 ms or with an increase from baseline over 60 ms was higher in the amiodarone group than in the placebo group.

Overview of treatment emergent adverse events - Safety population

n(%)	Placebo (N=109)	Celivarone 50mg (N=107)	Celivarone 100mg (N=101)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=51)
Patients with any TEAE	92 (84.4%)	92 (86.0%)	87 (86.1%)	98 (86.7%)	44 (86.3%)
Patients with any treatment emergent SAE	53 (48.6%)	45 (42.1%)	53 (52.5%)	49 (43.4%)	23 (45.1%)
Patients with any TEAE leading to death	4 (3.7%)	2 (1.9%)	5 (5.0%)	6 (5.3%)	3 (5.9%)
Patients with any TEAE leading to permanent treatment discontinuation	18 (16.5%)	29 (27.1%)	24 (23.8%)	24 (21.2%)	16 (31.4%)

TEAE: Treatment emergent adverse event SAE: Serious adverse event .
n (%) = number and percentage of patients with at least one TEAE .

All TEAEs are presented by primary SOC, High Level Group Term (HLGT), High Level Term (HLT) and PT in the CSR Appendix. Narratives for patients with TEAEs leading to death, serious TEAEs, TEAEs leading to treatment discontinuation (withdrawal), or AESIs are presented as supportive information. All laboratory data, vital signs, ECG parameters are provided in the CSR Appendix.

Pharmacokinetic results:

Following up to 12-month repeated administrations of celivarone, mean steady-state values of C_{max} were 103 ng/mL, 215 ng/mL, and 763 ng/mL at 50, 100, and 300 mg, respectively. At steady-state, mean C_{trough} values were 48.1 ng/mL, 99.6 ng/mL, and 290 ng/mL at 50, 100, and 300 mg, respectively.

Celivarone PK characteristics observed in the present study were consistent with those already reported in patients.

Given the high variability in C_{trough} at 50, 100, and 300 mg, it was difficult to give an accurate estimation of time to achieve steady-state. This could be explained by a high dispersion of the data (most of the patients having 2 or 3 PK samplings out of 6) and a low number of patients available by visit.

Amiodarone and its metabolite desethylamiodarone PK characteristics observed in the present study were consistent with those already reported in patients.

The figure of celivarone C_{trough} concentrations at 50, 100, and 300 mg is presented as supportive information.
All PK data are provided in the CSR Appendix.

Conclusions: [redacted]

Date of report: 18-Nov-2011