



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

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behalf of the ALPHEE study investigators.*

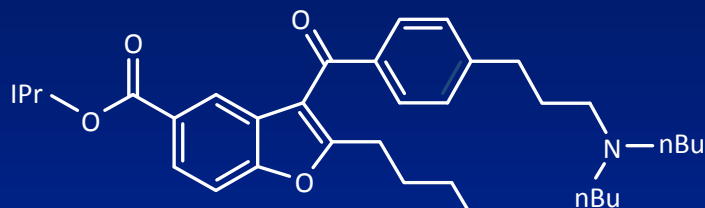
Disclosures

- Simultaneous online publication in Circulation—manuscript contains NIH registration information.
- All author disclosures are available in the simultaneously published, on line Circulation manuscript and in the meeting program.
- Sanofi-Aventis provided support for the research project but the steering committee was responsible for the design and the execution of the trial and for all of the results and interpretation.
- Dr. Kowey disclaims that he has been a consultant and speaker for Sanofi-Aventis as well as for several other pharmaceutical companies that develop and manufacture antiarrhythmic drugs for ventricular indications.

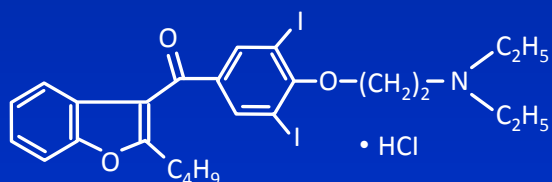
Background

- Sudden cardiac death is the most common cause of death in the US¹
- Ventricular arrhythmias (VA) are responsible for two thirds of sudden cardiac deaths in the US
- Implantable Cardioverter Defibrillators (ICDs) improve survival in patients at risk of VA's by delivery of shocks
- However frequent shocks reduce QoL, are associated with higher mortality, frequent expensive hospitalizations, deplete the ICD battery life and negatively impact healthcare resource utilization
- Current anti-arrhythmic drugs used to prevent ICD interventions are associated with difficult pharmacology, cardiac and extra cardiac toxicity a host of drug—drug interactions and are not approved in this indication

Celivarone Profile



Celivarone
Noniondinated benzofuran derivative



Amiodarone

Celivarone

Mechanism of action (in vitro and preclinical data)

Vaughan Williams Class I to IV
Ventricular activity
Anti-adrenergic activity

Dosing

Once daily

Drug-drug interactions

Low, based on in vitro CYP profile

Half Life

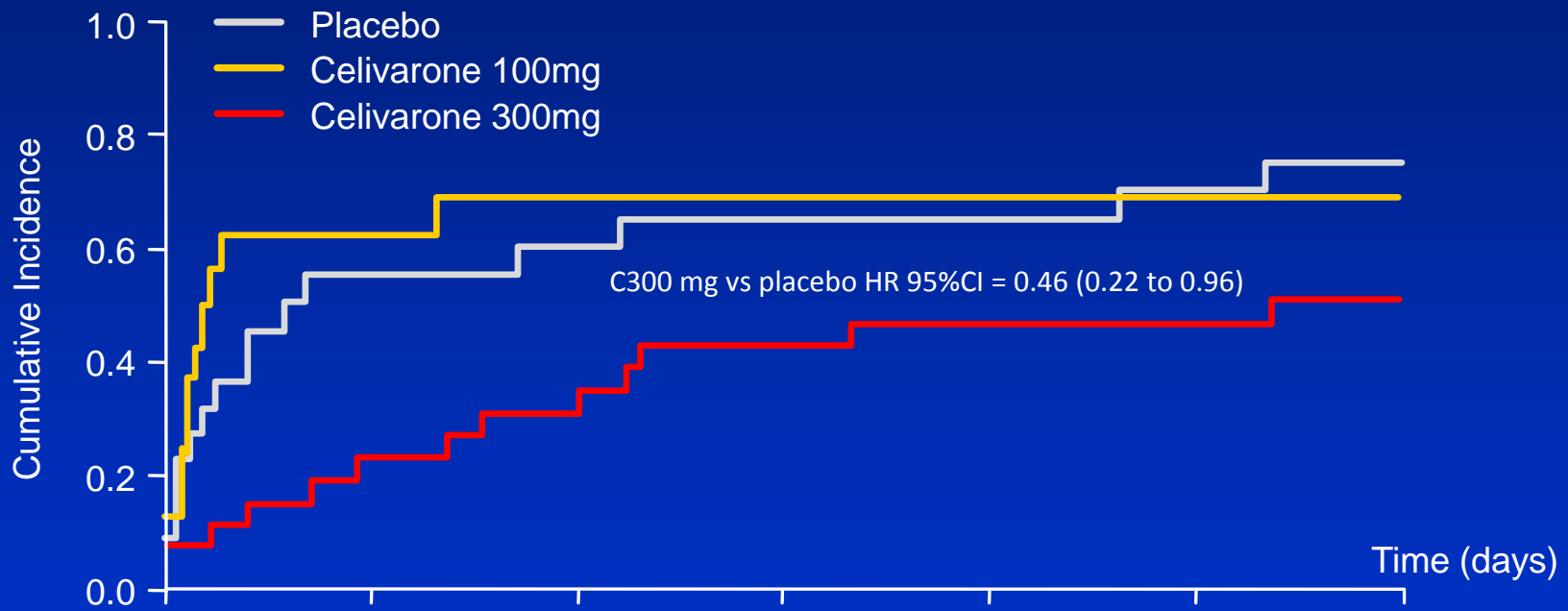
40-100 hours*

Extra cardiac side effects

Low potential
(no iodine, short half life)

Rationale for ALPHEE

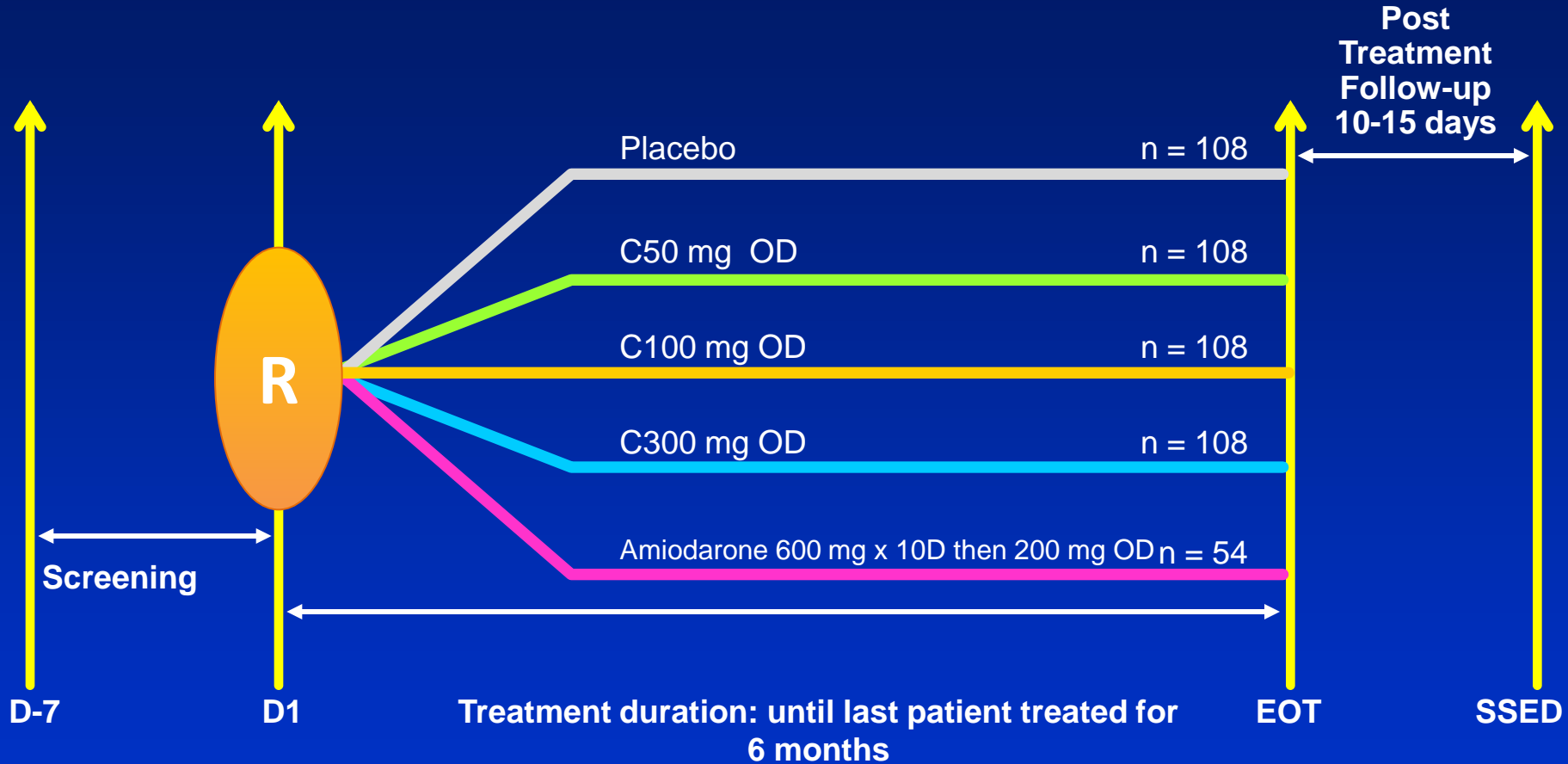
- ICARIOS post-hoc analysis in patients with last appropriate ICD therapy ≤ 30 days



Nb exposed on risk:

	0	30	60	90	120	150	180
Placebo	22	9	8	7	7	6	5
Celivarone 100mg	15	5	5	5	5	5	5
Celivarone 300mg	26	20	18	14	13	13	10

Study Design



D: day
 R: Randomization
 EOT: End Of Treatment Visit
 SSED: Scheduled Study End Date (190 days [up to +14 days] after the randomization of the last patient)

Inclusion Criteria

- ICD patients with a LVEF of $\leq 40\%$ AND one of the following criteria:
 - At least one ICD therapy for VT or VF in the previous month
 - OR ICD implantation in the previous month for documented VT/VF
- Signed informed consent for the study

Efficacy Variables

- **Primary efficacy variable:**
 - VT/VF triggered ICD interventions or sudden death.
 - VT/VF leading to any ICD interventions (ATP or ICD shock) adjudicated by a Central Adjudication Committee (up to 10 episodes/patient)
- **Secondary efficacy variable:**
 - ICD shocks or death

Sample Size Calculation

- 60% event rate at 6 months expected on placebo (based on ICARIOS and computer simulations)
- 44% RRR in at least one celivarone group vs Placebo
- Global alpha risk = 5% (3 comparisons)
- ≥ 108 pts per group for 85% power

ALPHEE - Final Enrollment per Country

151 centers in **26** countries

	Argentina	5
	Australia	22
	Belgium	12
	Canada	32
	Chile	1
	Czech Republic	29
	Denmark	15
	Finland	3
	France	22
	Germany	10
	Hungary	19
	Israel	17
	Italy	10
	Japan	10
	Mexico	2
	Netherlands	36
	Norway	2
	Poland	29
	Portugal	6
	Russia	24
	Slovakia	6
	South Africa	4
	Spain	18
	Sweden	8
	Turkey	11
	USA	133

Baseline Characteristics

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)	All (N=486)
Age(years)						
Mean (SD)	64.7 (12.0)	65.8 (10.6)	62.8 (10.3)	63.0 (11.5)	66.8 (8.4)	64.4 (10.9)
Median	67.0	66.0	62.0	64.0	66.0	65.5
≥75	24 (22.0%)	22 (20.2%)	14 (13.7%)	17 (15.0%)	7 (13.2%)	84 (17.3%)
Sex [n (%)]						
Male	98 (89.9%)	96 (88.1%)	91 (89.2%)	97 (85.8%)	49 (92.5%)	431 (88.7%)
Race [n (%)]						
Caucasian	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/Oriental	4 (3.7%)	5 (4.6%)	3 (2.9%)	3 (2.7%)	1 (1.9%)	16 (3.3%)
Other	0	0	1 (1%)	2 (1.8%)	1 (1.9%)	4 (0.8%)
BMI(kg/m²) [n (%)]						
<30	68 (62.4%)	72 (66.1%)	66 (64.7%)	69 (61.6%)	35 (67.3%)	310 (64.0%)
≥30	41 (37.6%)	37 (33.9%)	36 (35.3%)	43 (38.4%)	17 (32.7%)	174 (36.0%)

Baseline Characteristics

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodaron e 200mg (N=53)	All (N=486)
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)
Median	30.0	30.0	30.0	30.0	30.0	30.0
LVEF [n (%)]						
< 35 %	73 (67.0%)	76 (69.7%)	64 (62.7%)	70 (61.9%)	35 (66.0%)	318 (65.4%)
CHF [n (%)]						
Yes	96 (88.9%)	96 (88.1%)	84 (82.4%)	99 (87.6%)	42 (79.2%)	417 (86.0%)
NYHA class * [n (%)]						
I	16 (16.7%)	14 (14.6%)	13 (15.5%)	15 (15.2%)	7 (16.7%)	65 (15.6%)
II	55 (57.3%)	57 (59.4%)	52 (61.9%)	63 (63.6%)	25 (59.5%)	252 (60.4%)
III	25 (26.0%)	25 (26.0%)	19 (22.6%)	21 (21.2%)	10 (23.8%)	100 (24.0%)
Baseline Creatinine clearance (mL/min) [n (%)]						
<30	1 (0.9%)	1 (0.9%)	2 (2.0%)	3 (2.7%)	2 (3.8%)	9 (1.9%)
[30-50[21 (19.3%)	15 (14.2%)	12 (12.1%)	11 (10.0%)	8 (15.4%)	67 (14.1%)
[50-80[31 (28.4%)	38 (35.8%)	34 (34.3%)	39 (35.5%)	17 (32.7%)	159 (33.4%)
≥80	56 (51.4%)	52 (49.1%)	51 (51.5%)	57 (51.8%)	25 (48.1%)	241 (50.6%)

Cardiac Medical History

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)	All (N=486)
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%)
Dilated ischemic CM	61 (56.0%)	54 (49.5%)	51 (50.0%)	52 (46.0%)	28 (52.8%)	246 (50.6%)
Dilated non-ischemic. CM	20 (18.3%)	30 (27.5%)	28 (27.5%)	33 (29.2%)	13 (24.5%)	124 (25.5%)
Valvular non-rheumatic	21 (19.3%)	32 (29.4%)	18 (17.6%)	27 (23.9%)	15 (28.3%)	113 (23.3%)
Hypertrophic cardiomyopathy	1 (0.9%)	3 (2.8%)	1 (1.0%)	2 (1.8%)	1 (1.9%)	8 (1.6%)
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%)
Atrial flutter	3 (2.8%)	12 (11.0%)	3 (2.9%)	9 (8.0%)	1 (1.9%)	28 (5.8%)
Ischemic stroke	8 (7.3%)	3 (2.8%)	8 (7.8%)	5 (4.4%)	5 (9.4%)	29 (6.0%)

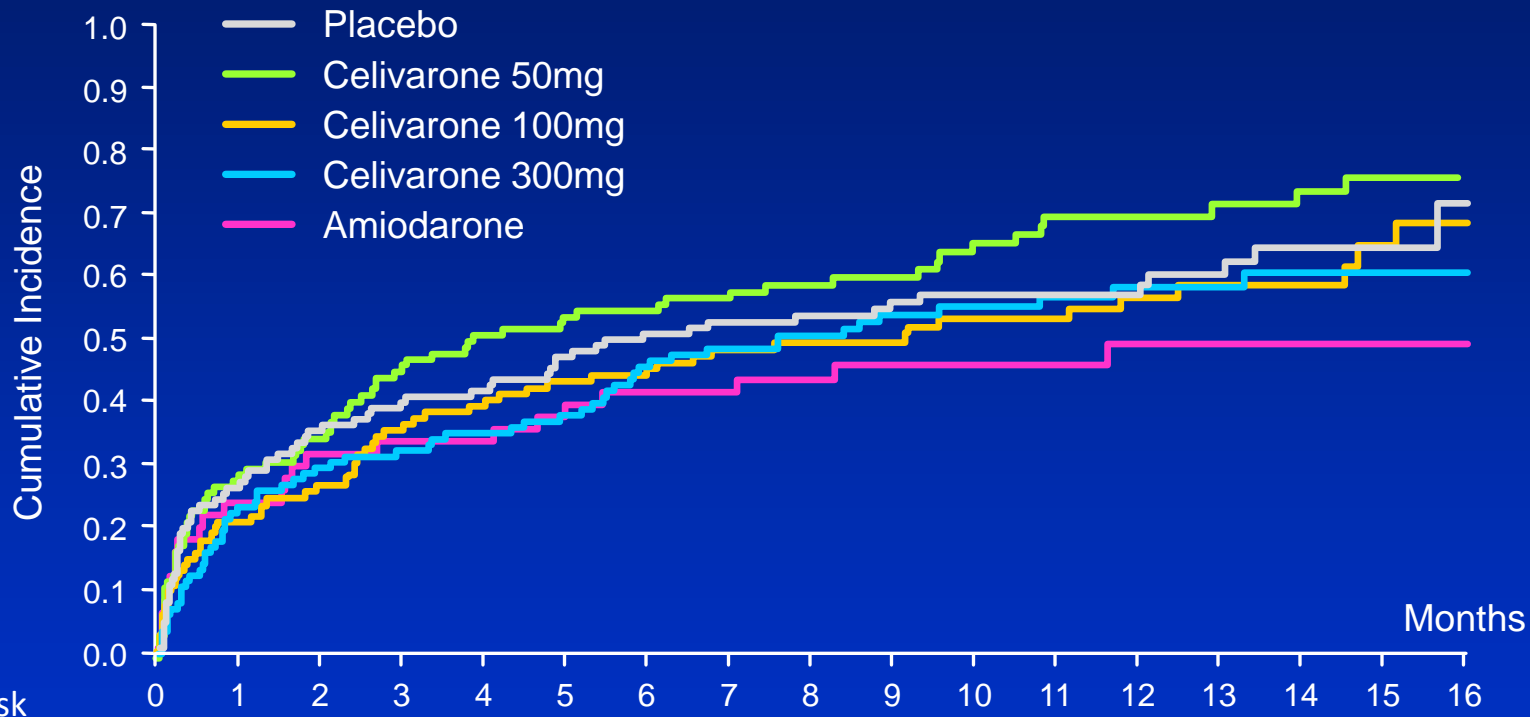
Primary Endpoint

1st VT/VF Triggering ICD Intervention Or Sudden Cardiac Death

Analysis Value	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)
Patients with 1° endpoint	67	73	60	62	24
VT/VF	66	73	60	61	20
SCD	1	0	0	1	4
HR (95% CI) 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)
p-value (vs Placebo)	-	0.2872	0.5908	0.3934	0.1283
<i>Hochberg significance threshold* (significance)</i>	-	0.017 (NS)	0.050 (NS)	0.025 (NS)	-

*p-value must be below this threshold in order to be significant

Primary Endpoint 1st VT/VF Triggering ICD Intervention or Sudden Cardiac Death



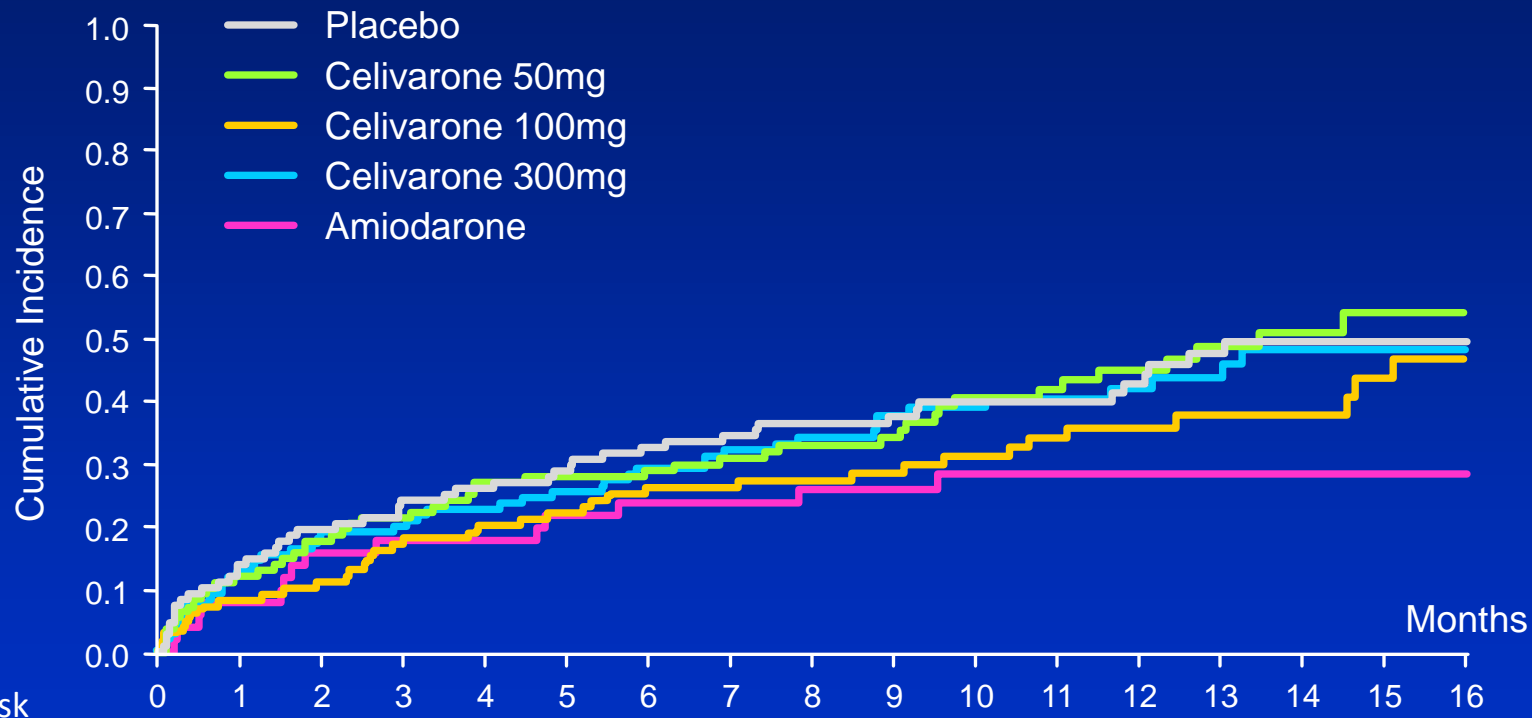
Placebo	109	66	54	40	27	9
Celivarone 50mg	109	58	48	31	19	10
Celivarone 100mg	102	66	56	40	24	10
Celivarone 300mg	113	75	57	41	27	8
Amiodarone	53	34	30	22	15	8

Secondary Endpoint: First Shock Or Death From Any Cause

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
- Shock	46	45	36	42	8
- Death from any cause	2	4	2	5	6
Hazard ratio (95% CI) vs Placebo (Cox stratified)		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)
p-value (stratified log- rank)	-	0.9094	0.2968	0.8377	0.0503
Hochberg significance threshold* (significance)	-	0.050 (NS)	0.017 (NS)	0.025 (NS)	-

*p-value must be below this threshold in order to be significant

Secondary Endpoint: First Shock Or Death From Any Cause



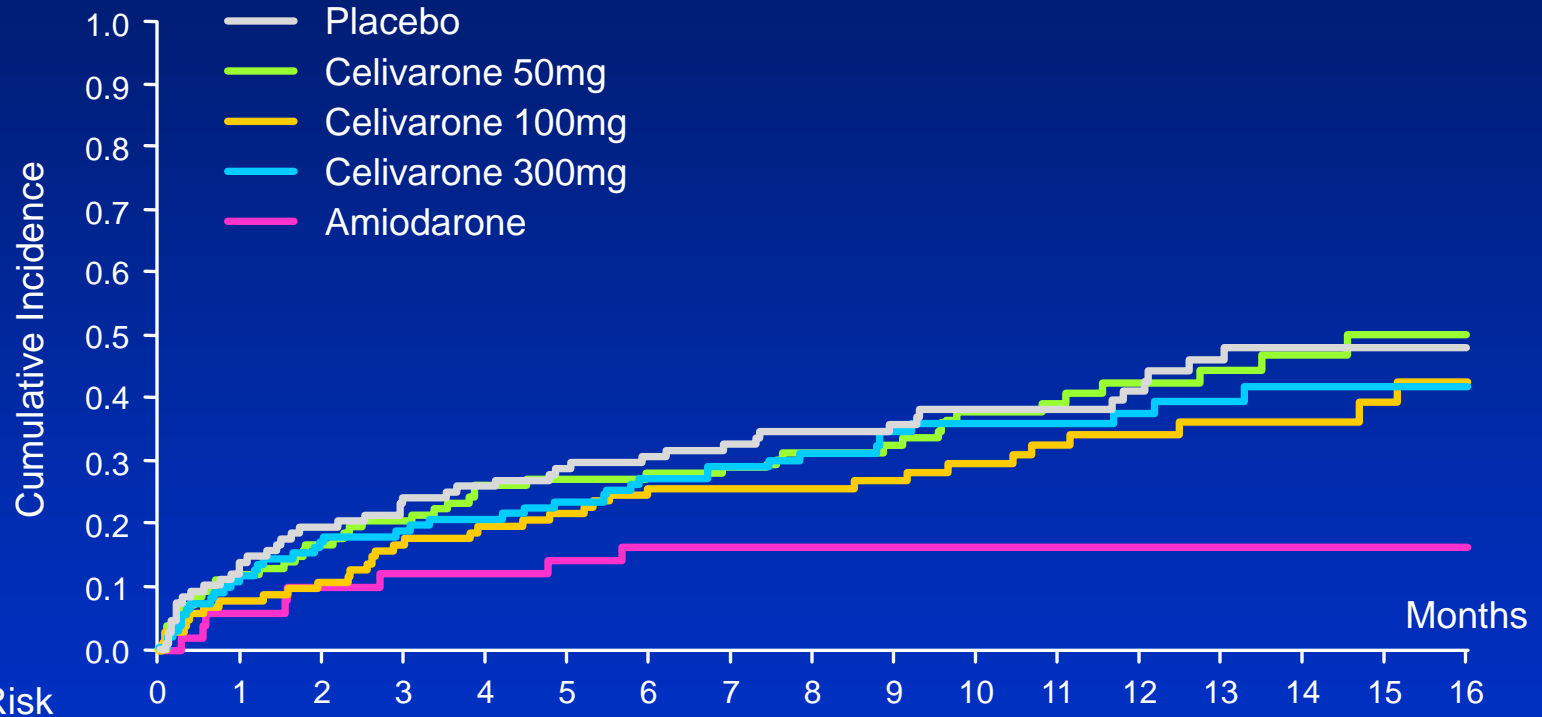
Placebo	109	82	73	57	39	15
Celivarone 50mg	109	85	77	55	34	14
Celivarone 100mg	102	84	75	56	35	19
Celivarone 300mg	113	90	77	55	36	12
Amiodarone	53	42	39	31	23	14

Secondary Endpoint Component: ICD Shock

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	46	45	36	42	8
Hazard ratio (95% CI) vs Placebo (Cox stratified)	-	0.988 (0.655 to 1.49)	0.789 (0.51 to 1.222)	0.896 (0.589 to 1.364)	0.333 (0.157 to 0.706)
p-value vs Placebo (stratified long-rank)	-	0.9535	0.2874	0.6076	0.0026
Hochberg significance threshold* (significance)	-	0.050 (NS)	0.017 (NS)	0.025 (NS)	-

*p-value must be below this threshold in order to be significant

Secondary Endpoint Component: ICD Shock



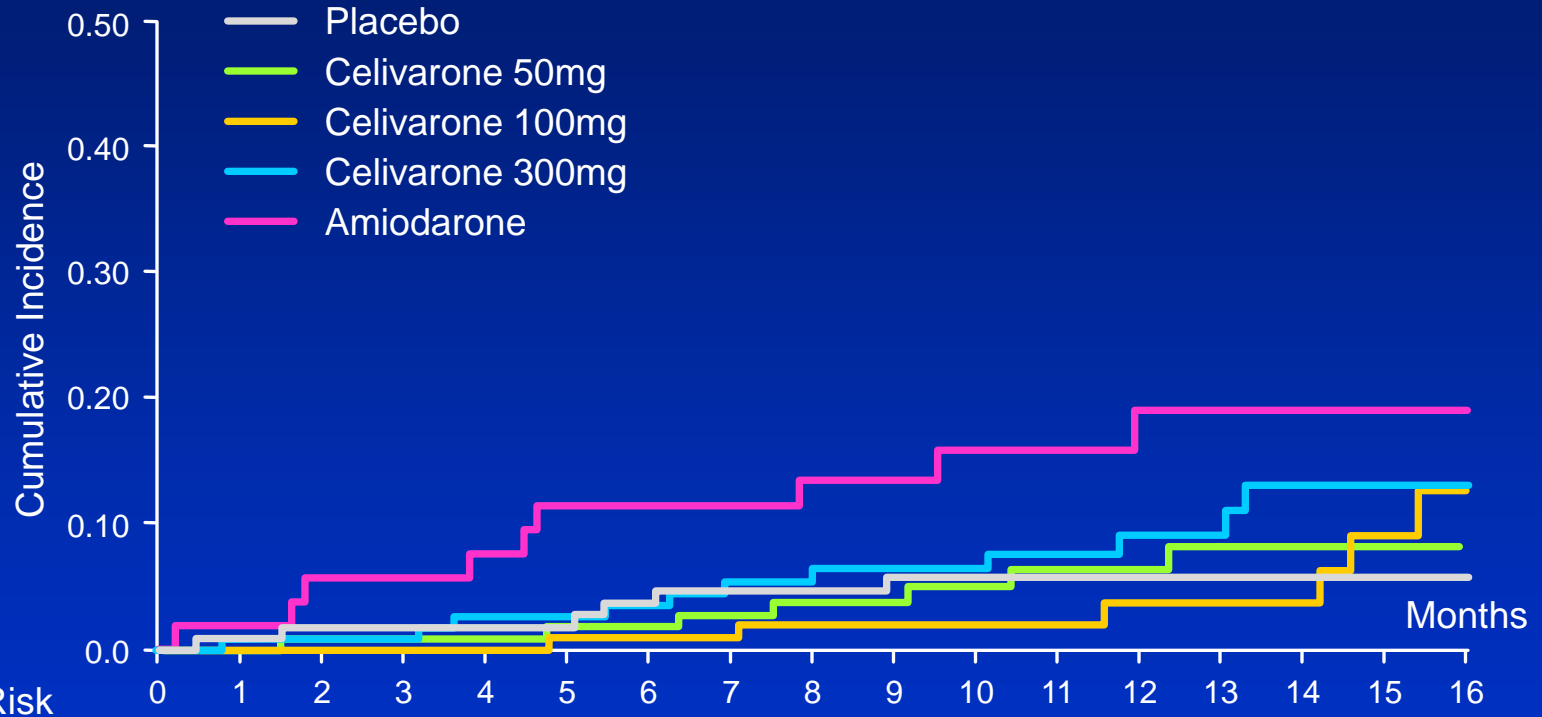
Placebo	109	82	73	57	39	15
Celivarone 50mg	109	84	76	54	34	14
Celivarone 100mg	102	84	75	56	35	19
Celivarone 300mg	113	89	77	55	36	12
Amiodarone	53	42	38	31	23	14

Secondary Endpoint Component: Death

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	6	8	6	11	9
Hazard Ratio (95% CI)	-	1.18 (0.396 to 3.513)	1.051 (0.338 to 3.261)	1.775 (0.655 to 4.805)	3.327 (1.182 to 9.367)
p-value vs placebo	-	0.7654	0.9320	0.2527	0.0158
Hochberg significance threshold* (significance)	-	0.025 (NS)	0.050 (NS)	0.017 (NS)	-

*p-value must be below this threshold in order to be significant

Secondary Endpoint Component: Death



Placebo	109	107	105	83	60	26
Celivarone 50mg	109	107	106	80	56	30
Celivarone 100mg	102	101	100	83	54	32
Celivarone 300mg	113	11	106	87	60	24
Amiodarone	53	49	46	38	25	16

Classification Of Fatal Cases As Per Adjudication

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)
Total of deaths	6 (5.5%)	9 (8.3%)	8 (7.8%)	11 (9.7%)	9 (17.0%)
Cardiovascular reason	6 (5.5%)	6 (5.5%)	7 (6.9%)	9 (8.0%)	7 (13.2%)
Sudden arrhythmic death	3 (2.8%)	2 (1.8%)	3 (2.9%)	3 (2.7%)	6 (11.3%)
Acute myocardial infarction	0	0	0	1 (0.9%)	0
Congestive heart failure or cardiogenic shock	2 (1.8%)	3 (2.8%)	3 (2.9%)	3 (2.7%)	1 (1.9%)
Stroke	0	0	0	2 (1.8%)	0
Other cardiovascular cause	1 (0.9%)	1 (0.9%)	1 (1.0%)	0	0
VT storm leading to ablation, tamponade, surgery, sepsis	1 (0.9%)	0	0	0	0
Non cardiovascular reason	0	3 (2.8%)	0	2 (1.8%)	1 (1.9%)
Undetermined	0	0	1 (1.0%)	0	1 (1.9%)

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 .
Safety Population (having received at least one dose)

Conclusions

- Celivarone was not effective for the prevention of ICD interventions or sudden cardiac deaths
- The use of amiodarone in the calibrator arm validated the study design
- Tolerability of celivarone was satisfactory
- An unmet medical need remains for the prevention of shocks in patients with an ICD. A search for alternative antiarrhythmic drugs and procedures for this indication should continue

Committees

Steering Committee

- PR Kowey (US)
- H Crijns, (NL)
- EM Aliot (FR)
- A Capucci, (IT)
- SJ Connolly, (CN)
- SH Hohnloser (GE)
- P Kulakowski (PL)
- D Radzik (FR)
- D Roy (CND)
- BN Singh (US)

Data Monitoring Committee

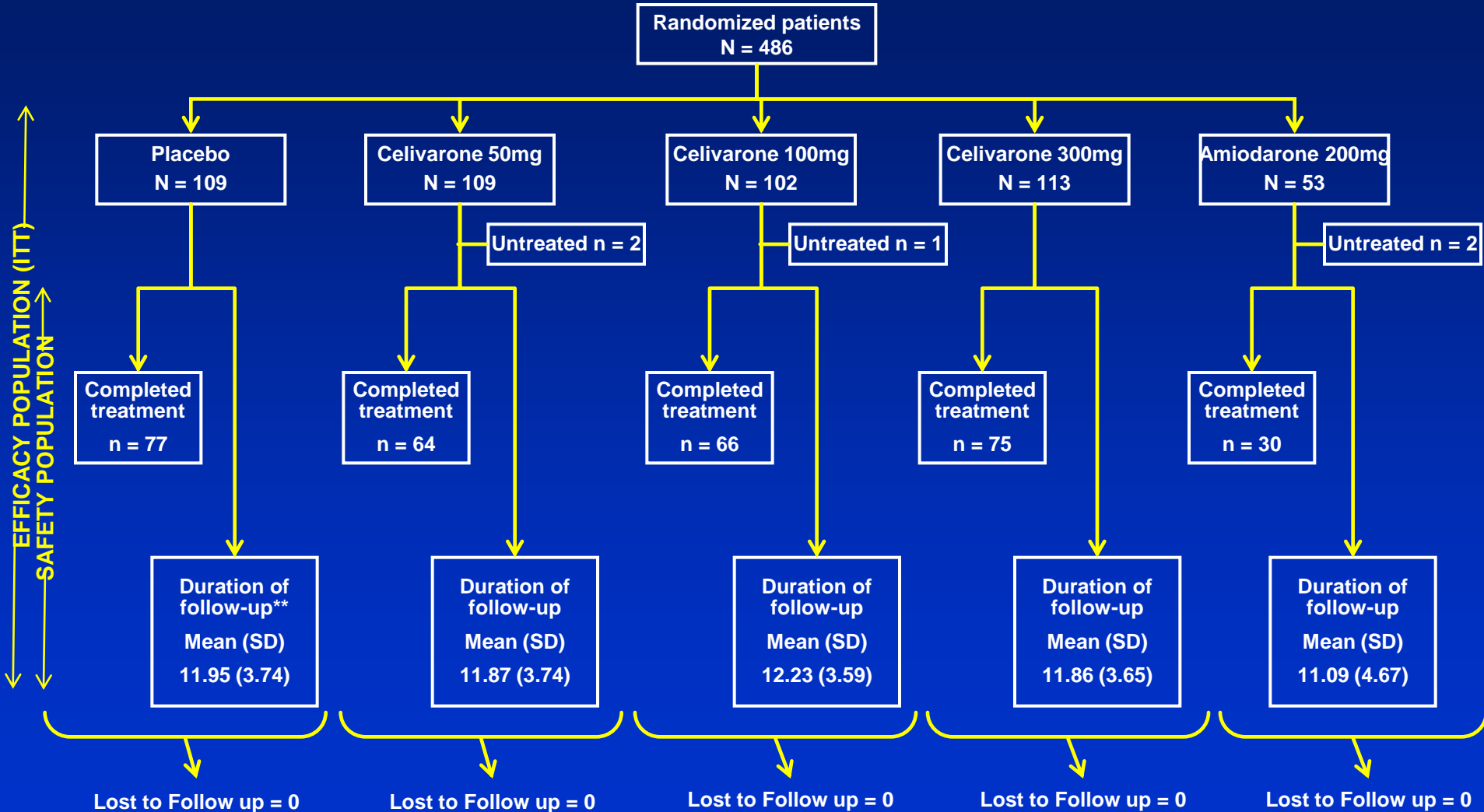
- J Seltzer (US)
- BP Knight (US)
- AH Kadish (US)
- A. Smith (US)

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H Crijns – Chairman (NL), J Blaauw (NL), K Vernooy (NL),
V Van Empel (NL), R Smid Ter Bekke (NL), L Guedon (FR),
C Kouakam (FR), N Sadoul (FR), H Blangy (FR), L Freysz (FR),
P Mabo (FR), C Leclercq (FR).

BACKUP SLIDES

Study Flow



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

** Duration in months

Treatment Duration

	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)

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
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

Baseline Medications

Therapeutic Class	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)	All (N=486)
Beta blocking agents	101 (92.7%)	96 (88.1%)	92 (90.2%)	101 (89.4%)	43 (81.1%)	433 (89.1%)
Agents acting on the renin-angiotensin system	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%)
Vasoprotectives	30 (27.5%)	23 (21.1%)	22 (21.6%)	25 (22.1%)	13 (24.5%)	113 (23.3%)
Calcium channel blockers	14 (12.8%)	12 (11.0%)	12 (11.8%)	12 (10.6%)	3 (5.7%)	53 (10.9%)

Patients' disposition

	Placebo (N=109)	Celivarone 50mg (N=109)	Celivarone 100mg (N=102)	Celivarone 300mg (N=113)	Amiodarone 200mg (N=53)	All (N=486)
Randomized and treated	109 (100%)	107 (98.2%)	101 (99.0%)	113 (100%)	51 (96.2%)	481 (99.0%)
Treatment discontinuation for:						
Adverse event	32 (29.4%)	43 (39.4%)	35 (34.3%)	38 (33.6%)	21 (39.6%)	169 (34.8%)
Lack of efficacy	18 (16.5%)	29 (26.6%)	24 (23.5%)	24 (21.2%)	16 (30.2%)	111 (22.8%)
Other*	8 (7.3%)	8 (7.3%)	4 (3.9%)	4 (3.5%)	3 (5.7%)	27 (5.6%)
Deaths	6 (5.5%)	6 (5.5%)	7 (6.9)	10 (8.8%)	2 (3.8%)	31 (6.4%)
Lost to follow-up	6 (5.5%)	9 (8.3%)	6 (5.9%)	11 (9.7%)	9 (17.0%)	41 (8.4%)
	0	0	0	0	0	0

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).

Deaths and consent withdrawals are not considered lost to follow up

Two patients who died after SSED are counted Alive at time of last contact.

*other includes poor protocol compliance

ALPHEE Countries/Sites/Patients

Number of active countries

26 countries in Americas, Europe and Asia

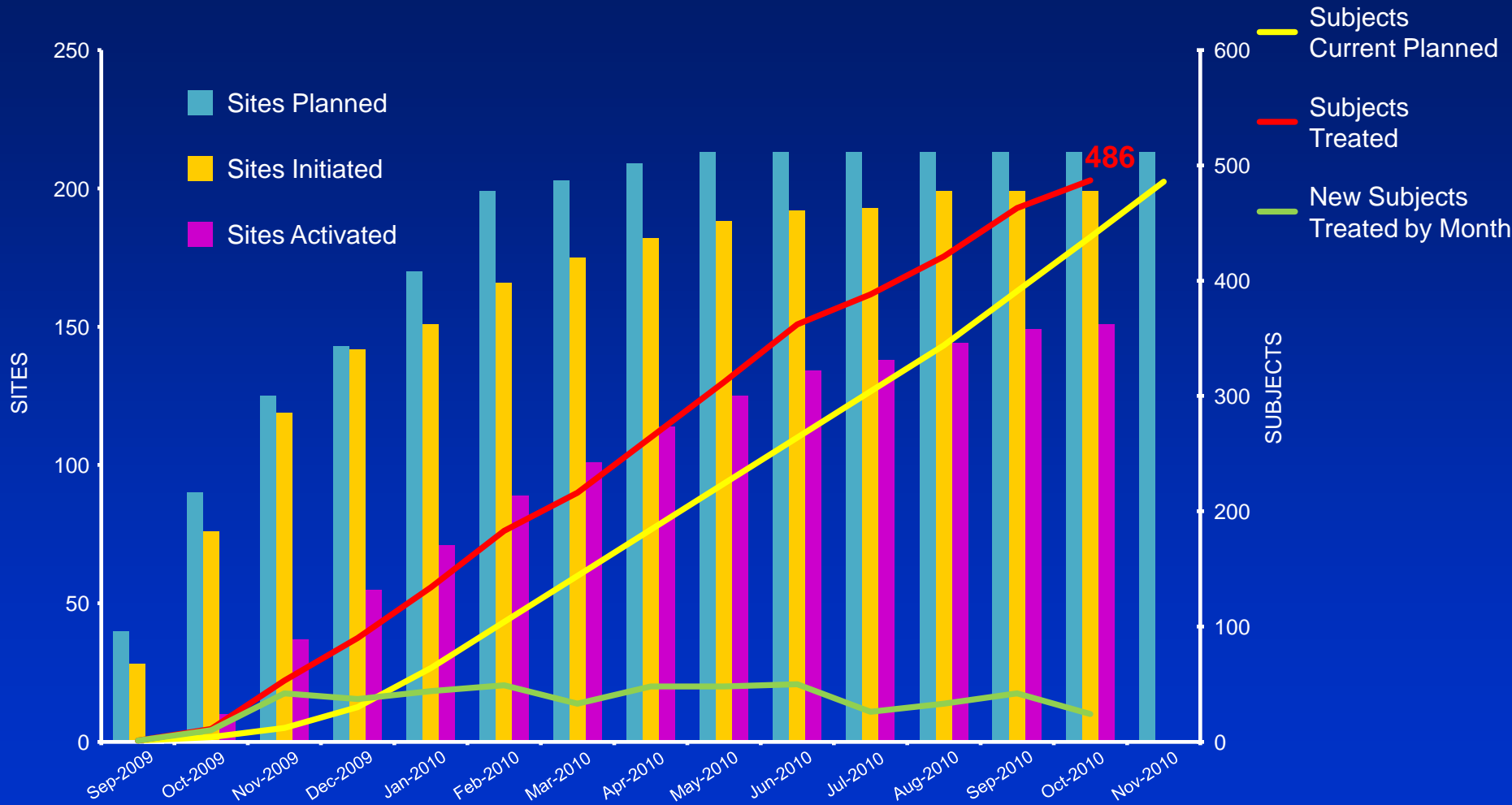
Number of active sites

151 active sites including at least one pt

Number of patients

- 1st pt randomized: 21-Sep-2009
- 486 randomized patients
- Last pt randomized: 11-Oct-2010

ALPHEE - Enrollment



Sensitivity analysis of the primary endpoint

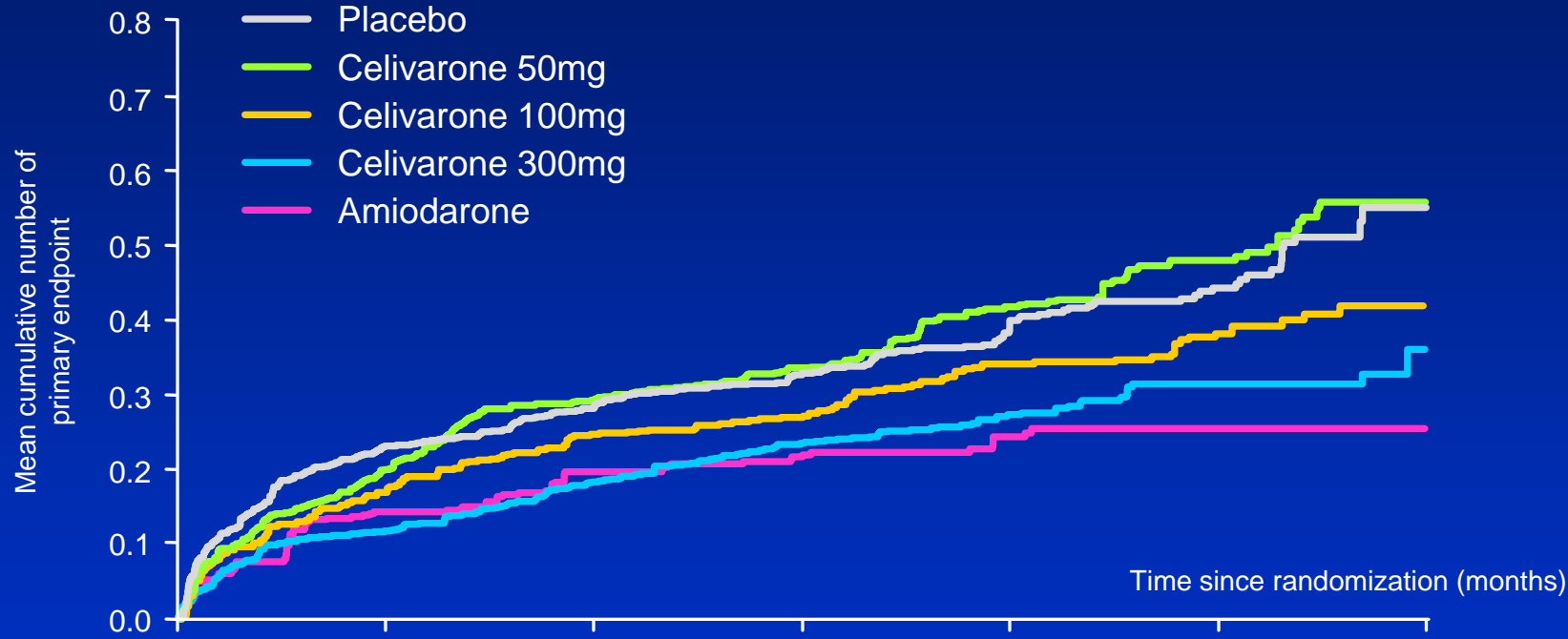
Cumulative mean function curves of first 10 occurrences

	Placebo	Celivarone 50mg	Celivarone 100mg	Celivarone 300mg	Amiodarone 200mg
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
Hochberg significance threshold* (significance)		0.050 (NS)	0.025 (NS)	0.017 (NS)	

*p-value must be below this threshold in order to be significant

Sensitivity analysis of the primary endpoint

Cumulative mean function curves of first 10 occurrences



Number at Risk

	0	3	6	9	12	15	18
Placebo	109	93	86	66	40	18	2
Celivarone 50mg	109	94	86	64	42	21	3
Celivarone 100mg	102	91	86	67	39	22	1
Celivarone 300mg	113	105	96	74	45	17	1
Amiodarone	53	43	39	31	21	11	0