SYNOPSIS

Name of company:	**TABULAR FORMAT**	**(For National Authority Use only)**
Name of finished product:	**REFERRING TO PART OF THE DOSSIER:**	
Name of active substance(s):	**Volume:**	
	Page:	

Title of the study: Double blind placebo controlled dose ranging study of the efficacy and safety of SSR149744C 100 or 300 mg for the prevention of ventricular arrhythmia-triggered ICD interventions (DRI5349)

Investigator: [redacted]

Study centers: 44 centers in 8 countries in Europe and N. America

Publications (reference): None

Study period:

Date first patient enrolled: 27 June 2005

Date last patient completed: 23 February 2007

Phase of development: Dose-ranging

Objectives:

Primary: to assess the efficacy of celivarone for the prevention of ventricular-arrhythmia triggered implantable cardioverter defibrillator (ICD) interventions

Secondary:

- to assess versus placebo the tolerability of the different dose regimens of celivarone in the selected population
- to document plasma celivarone levels during the study

Methodology: Double blind, multicenter, randomized, parallel arm, placebo-controlled study with 2 doses of celivarone

Number of patients:	Planned: 150	Randomized: 153	Treated: 151
Evaluated:	Efficacy: 153	Safety: 151	Pharmacokinetics: 151

Diagnosis and criteria for inclusion: Male or female patients with an ICD implanted during the previous year for documented spontaneous life-threatening ventricular arrhythmia OR implanted with an ICD and with at least 1 appropriate ICD therapy (shock or antitachycardia pacing [ATP]) for ventricular tachycardia (VT) or ventricular fibrillation (VF) in the previous year. Left ventricular ejection fraction (LVEF) measured by 2D-echocardiography must have been documented to be less than 40% in the last 6 months and the ICD had to have the following characteristics: data logging function with cumulative counting of device intervention (shocks and ATP); electrogram (EGM) storage capabilities; ventricular demand pacing.

Investigational product: celivarone 100 mg capsules

Dose: 100 mg or 300 mg celivarone

Administration: Oral

Dose regimen: Once daily administration with food

Batch numbers: [redacted]

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume:	
	Page:	

Duration of treatment: 6 months

Duration of observation: About 7 months (including the screening period, the 6-month treatment period, and the posttreatment visit)

Reference therapy: Placebo

Dose: NA

Administration: Oral

Batch number: [redacted]

Criteria for evaluation:

Efficacy:

Primary variable:

the occurrence of all VT or VF arrhythmia episodes documented by ICD interrogation, including stored EGMs, leading to any ICD intervention (ATP or ICD shock), until 180 days after randomization

Secondary variable:

the occurrence of all arrhythmia episodes leading to at least 1 documented ICD shock (irrespective of its appropriateness), until 180 days after randomization

Other variables:

the occurrence of all VT arrhythmia episodes documented by ICD interrogation, including stored EGMs, and terminated by ATP therapy, until 180 days after randomization

the occurrence of all VT or VF arrhythmia episodes documented by ICD interrogation, including stored EGMs, leading to at least 1 ICD shock, until 180 days after randomization

Symptoms evaluated at each visit (dizziness, dyspnea, palpitations, presyncope, syncope)

Safety: Monitoring of adverse events, clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) parameters

Pharmacokinetics: Plasma concentrations of celivarone were assessed

Pharmacokinetic sampling times and bioanalytical methods:

Sampling

Investigators were recommended to take 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 4 ± 5 days, within 2 to 6 hours postdose in Month 6 ± 5 days, any time in Month 6.5 ± 5 days.

Assay

Plasma celivarone concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method with a limit of quantification of 5 ng/mL (DOH0544).

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume:	
	Page:	

Statistical methods:

Populations:

All efficacy analyses were performed on the all randomized population. The primary analysis and descriptive analyses on the primary efficacy variable were also performed on the per protocol population.The safety analysis was performed on all randomized patients who had at least 1 intake of study drug (exposed patients).

Efficacy analysis:

Primary variable

Main analysis

Recurrent events were compared between each celivarone dose group and the placebo group. Hazard ratios between treatment groups were estimated by the Andersen-Gill mean intensity model and the robust sandwich estimate of Lin and Wei (1989) for the covariance matrix. This analysis included all patients, but censored those with an extremely high number of events. Where *n* denotes the 95th percentile of the distribution of number of events by patient, patients with number of events greater than *n* were censored at the date of occurrence of their n^{th} event; *n* was defined before database lock.

Cumulative mean functions in each treatment group were calculated using Nelson-Aalen estimates, for each protocol time-point.

Statistical significance was assessed using Hochberg multiple comparison procedure.

Supportive analyses

The primary efficacy variable underwent 3 supportive analyses using the same model as for the main analysis:

- introducing the following covariates: indication for ICD therapy, duration between the randomization date and the date of last appropriate ICD therapy, LVEF
- taking into account “on treatment” events only
- integrating non-classified episodes if the number of ATPs or shocks was filled in

Secondary variables*:* each celivarone dose group was compared with the placebo group using the same methodology as in the primary analysis on the primary efficacy variable.

Safety analysis:

The number of patients with treatment emergent adverse events (TEAEs) was summarized in each treatment group. For laboratory parameters, vital signs and ECG parameters, descriptive statistics on raw values, changes from baseline, and number of potentially clinically significant abnormalities (PCSAs) were provided.

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume:	
	Page:	

Summary:

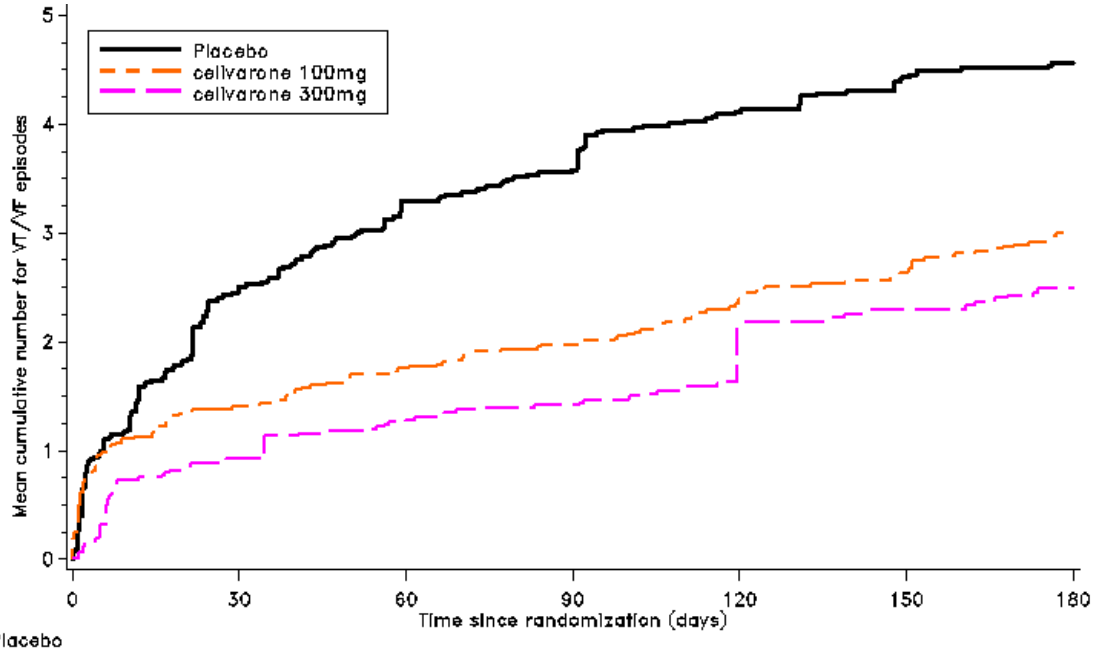
Efficacy results: In patients with an ICD, fewer VT and VF arrhythmia episodes were observed in the celivarone 100 and 300 mg groups than in the placebo group over 180 days, with hazard ratios of 0.651 and 0.541, respectively. The difference between each dose of celivarone and placebo on VT or VF episodes in the primary analysis did not reach statistical significance (p-value of 0.172 for the celivarone 300 mg group, to be compared with 0.025 for Hochberg multiple comparisons adjustment). The table below shows Nelson-Aalen survival estimates and the Andersen-Gill mean intensity model test for celivarone 100 and 300 mg compared with placebo. Patients with more than 27 events were censored at the date of their 27th event.

	Placebo (N=53)	celivarone 100mg (N=52)	celivarone 300mg (N=48)
Day 5			
Number of events, n	52	49	11
Nelson-Aalen estimates	1.0	0.9	0.2
Day 14			
Number of events, n	86	58	36
Nelson-Aalen estimates	1.6	1.1	0.8
Day 30			
Number of events, n	131	72	44
Nelson-Aalen estimates	2.5	1.4	0.9
Day 60			
Number of events, n	170	90	60
Nelson-Aalen estimates	3.3	1.8	1.3
Day 90			
Number of events, n	184	101	67
Nelson-Aalen estimates	3.6	2.0	1.4
Day 120			
Number of events, n	210	120	102
Nelson-Aalen estimates	4.1	2.3	2.2
Day 150			
Number of events, n	225	134	107
Nelson-Aalen estimates	4.4	2.6	2.3
Day 180			
Number of events, n	231	152	116
Nelson-Aalen estimates	4.6	3.0	2.5
Hazard ratio (95% CI) (a)	-	0.651 (0.306 to 1.387)	0.541 (0.224 to 1.305)
p-value	-	0.266	0.172
Significance threshold (b)		0.050	0.025

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.
This analysis censored patients at the date of occurrence of their *n*th event, where *n* denotes the 95th percentile of the distribution of number of events by patient.

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume:	
	Page:	

The mean cumulative number of VT or VF events by patient during study (with censoring at 27 events per patient) is displayed in the figure below.



Placebo							
Nb at risk	53	50	50	49	47	47	44
Nb event	0	131	170	184	210	225	231
celivarone 100mg							
Nb at risk	52	51	51	51	50	49	47
Nb event	0	72	90	101	120	134	152
celivarone 300mg							
Nb at risk	48	47	47	46	45	44	41
Nb event	0	44	60	67	102	107	116

Supportive analyses that repeated the primary analysis but took into account covariables or “on treatment” events only, or which integrated non-classified events, produced consistent results.

From the analysis of all arrhythmia episodes leading to at least 1 ICD shock and irrespective of its appropriateness, fewer events were observed in the celivarone 300 mg group than in the placebo group, but the difference was not statistically significant.

Safety results: Overall, the percentage of patients with at least 1 TEAE was similar in all treatment groups: 88.7% in the placebo group, 78.4% in the celivarone 100 mg group, and 83.0% in the celivarone 300 mg group. Serious TEAEs were reported in 18.9% of patients in the placebo group, in 27.5% of patients in the celivarone 100 mg, and in 25.5% of patients in the celivarone 300 mg group. One TEAE leading to death occurred in the placebo group (a case of worsening congestive heart failure leading to death 44 days after last intake of investigational product). The incidence of patients discontinuing treatment due to TEAE was comparable in all treatment groups (10.6% to 13.2% of patients).

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume:	
	Page:	

As expected in the patient population, the most frequently reported TEAEs were cardiac disorders. These were reported with a comparable incidence in all treatment groups.

The incidence of patients with PCSAs in laboratory parameters in the celivarone groups was similar to that in the placebo group. However, increased creatinine concentration ≥150 µmol/L was observed in more patients in the celivarone 100 mg (19.6%) and 300 mg (21.7%) groups than in the placebo group (13.2%).

There was no clinically relevant difference in the frequency of PCSAs observed in vital signs among treatment groups.

The percentage of patients with corrected QT-intervals ≥500 ms was similar between the placebo and celivarone groups, ranging from 22.6% to 27.7% for QT-interval corrected according to Bazett's formula (QTcB) and from 15.1% to 17.6% for QT-interval corrected according to Fridericia's formula (QTcF). A change from baseline >60 ms in QTcB and QTcF was recorded with similar incidence in all treatment groups. No case of torsades de pointes was observed.

Pharmacokinetic results: Celivarone PK characteristics observed in patients were consistent with those already reported in healthy subjects. No deviation from dose proportionality was observed between 100 mg and 300 mg.

Conclusions: [redacted]

Date of report: 28-Nov-2007