SYNOPSIS

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Title of the study:	Placebo controlled double blind dose ranging study of the efficacy and safety of SSR149744C 50, 100, 200, or 300 mg OD, with amiodarone as calibrator for the maintenance of sinus rhythm in patients with recent atrial fibrillation/flutter (MAIA).
Investigator:	[redacted]
Study centers:	105 active centers in 17 countries: Argentina, Australia, Canada, Chile, Denmark, France, Germany, Hungary, Italy, Japan, Netherlands, Poland, Russia, Spain, Sweden, Switzerland, USA.
Publications (reference):	None
Study period: Date first patient enrolled: 15 December 2004 Date last patient completed: 11 May 2006	**Phase of development:** Dose-ranging
Objectives:	***Primary*** To evaluate the efficacy of SSR149744C in the maintenance of sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation (AF)/atrial flutter (AFL) and select a dose. ***Secondary*** • To assess the efficacy of SSR149744C versus placebo on symptomatic AF/AFL recurrence and AF/AFL related symptoms; • to assess versus placebo the ventricular rate during the first AF/AFL episode in the different SSR149744C groups in case of AF/AFL recurrence; • to assess versus placebo the tolerability of the different dose regimens of SSR149744C; • to document SSR149744 plasma levels.
Methodology:	Multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-arm study with 4 SSR149744C dose regimens and amiodarone as a calibrator.
Number of patients Evaluated:	Planned: 660 Randomized: 673 Treated: 670 Efficacy: 673 (all randomized patients) Safety: 669 Pharmacokinetics: 665
Diagnosis and criteria for inclusion:	Male and female patients aged 21 years or more with documented sinus rhythm for at least 1 hour at the time of randomization with at least 1 AF/AFL episode documented by electrocardiogram (ECG) in the last 3 months.
Investigational product: Dose: Administration: Batch numbers:	SSR149744C: capsules of 50 or 100 mg Daily dose of 50 mg, 100 mg, 200 mg, or 300 mg Oral route in fed conditions 50 mg: [redacted]; 100 mg: [redacted]

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Duration of treatment: 3 months	**Duration of observation:** Approximately 4 months including screening and posttreatment follow up

Reference therapy:	Placebo capsules
Dose:	NA
Administration:	Oral route in fed conditions
Batch numbers:	[redacted]
Reference therapy:	Amiodarone 200 mg capsules
Dose:	Daily dose of 200 mg (with loading dose of 600 mg daily from Day 1 to Day 10)
Administration:	Oral route in fed conditions
Batch numbers:	[redacted]
Criteria for evaluation:	
Efficacy:	The primary endpoint was the time from randomization to the first recurrence of AF/AFL, documented by 12-lead ECG or trans-telephonic ECG monitoring (TTEM). The secondary endpoints were the following: • time from randomization to symptomatic first AF/AFL recurrence, and time from randomization to asymptomatic first AF/AFL recurrence; • mean ventricular heart rate (HR) during AF/AFL at first AF/AFL recurrence recorded by TTEM.
Safety:	Monitoring of adverse events (AEs), clinical laboratory evaluations (liver function, renal function, electrolytes, metabolism, white and red blood cells and platelets, digoxin/digitoxin and thyroid function tests), vital signs, and ECG.
Pharmacokinetics:	Plasma concentrations of SSR149744, amiodarone, and its metabolite desethylamiodarone 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 on Day 10 ± 2 days, within 8 to 16 hours postdose on Month 1 ± 5 days, within 1 hour predose on Month 2 ± 5 days, within 2 to 6 hours postdose in Month 3 ± 5 days, and any time at Month 3.5 ± 5 days. ***Assay*** SSR149744 plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method with a limit of quantification (LOQ) of 5 ng/mL. Plasma concentrations of amiodarone and its metabolite desethylamiodarone were determined using a validated high performance liquid chromatography method with ultraviolet detection, with a LOQ of 5 ng/mL.

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Statistical methods:

Efficacy analysis

Time from randomization to first AF/AFL recurrence was estimated using Kaplan-Meier curves. Two-sided Log-rank asymptotic test was used to compare each SSR149744C dose curve to the placebo curve, and statistical significance was assessed using Hochberg multiple comparison procedure. In this study report, incidence is presented at 90 days.

Hazard ratios with 95% confidence intervals (CIs) (each dose of SSR149744C versus placebo) were estimated using the Cox model, first with treatment group as the only factor and then adjusted using presence/absence of structural heart disease, time since last documented AF/AFL episode before randomization in classes (0,] 0 – 7] and >7 days) and AF or AFL history status as covariate prognostic factors.

Symptomatic/asymptomatic first AF/AFL recurrence was investigated in a survival competing risks analysis using a model of cause-specific hazards. The 2 types of events in competition were the time of symptomatic first AF/AFL recurrence and the time of asymptomatic first AF/AFL recurrence. Each SSR149744C dose group was compared to the placebo group for symptomatic first AF/AFL recurrence event using a 2-sided log-rank asymptotic test.

Ventricular HR recorded by TTEM at the time of the first AF/AFL recurrence was analyzed as a quantitative variable and compared between SSR149744C and placebo groups using an analysis of variance on treatment groups as covariate.

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.

All efficacy endpoints were analyzed on the all randomized population. The safety analysis was performed on all randomized patients who had at least 1 intake of study drug (exposed patients).

Summary:

Efficacy results:

Fewer recurrences of AF/AFL were observed in the SSR149744C treatment groups than in the placebo group with the lowest incidence at 90 days observed in the 50 mg group (52.1%) with risk reduction of 28%. However, there was no significant difference between placebo and any SSR149744C dose on the time to AF/AFL recurrence in patients with recent AF/AFL. No dose effect relationship on AF/AFL recurrence was observed.

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Primary analysis on time to first AF/AFL - comparison of each dose of SSR149744C versus placebo - Kaplan-Meier survival estimates and Logrank test - all randomized population (N = 673)

	Placebo (N=110)	**SSR149744C 50mg (N=113)**	**SSR149744C 100mg (N=109)**	**SSR149744C 200mg (N=118)**	**SSR149744C 300mg (N=115)**
Number of events, n	73	59	61	74	65
Median Survival Time (95% CI)	28.0 (12.0 to 45.0)	68.0 (28.0 to .)	51.0 (15.0 to .)	22.0 (13.0 to 62.0)	34.0 (13.0 to .)
5 days					
Number of events, n	35	27	30	27	29
Kaplan-Meier estimates (95% CI)	32.1 (23.3% to 40.9%)	24.1 (16.2% to 32.0%)	27.5 (19.1% to 35.9%)	23.0 (15.4% to 30.6%)	25.7 (17.6% to 33.7%)
10 days					
Number of events, n	43	37	43	45	44
Kaplan-Meier estimates (95% CI)	39.4 (30.3% to 48.6%)	33.1 (24.4% to 41.9%)	39.4 (30.3% to 48.6%)	38.4 (29.6% to 47.2%)	39.1 (30.1% to 48.1%)
30 days					
Number of events, n	57	48	52	64	56
Kaplan-Meier estimates (95% CI)	52.3 (42.9% to 61.7%)	43.1 (33.9% to 52.3%)	47.7 (38.3% to 57.1%)	54.6 (45.6% to 63.7%)	49.8 (40.6% to 59.1%)
60 days					
Number of events, n	69	55	57	68	60
Kaplan-Meier estimates (95% CI)	63.3 (54.3% to 72.3%)	49.4 (40.1% to 58.7%)	52.3 (42.9% to 61.7%)	58.1 (49.1% to 67.0%)	53.4 (44.2% to 62.7%)
90 days					
Number of events, n	73	58	61	74	64
Kaplan-Meier estimates (95% CI)	67.1 (58.3% to 76.0%)	52.1 (42.8% to 61.4%)	56.0 (46.6% to 65.3%)	63.3 (54.5% to 72.0%)	57.0 (47.8% to 66.2%)
Log-rank test p-value	-	0.055	0.170	0.572	0.247
Hochberg multiple comparisons adjusted p-value (a)	-	0.220	0.510	0.572	0.494
Hazard ratio (95% CI) (b)	-	0.72 (0.51 to 1.01)	0.79 (0.56 to 1.11)	0.91 (0.66 to 1.26)	0.82 (0.59 to 1.15)

Notes: Comparisons are performed between each dose of SSR149744C and Placebo. 95% CIs are computed using Greenwood's variance estimation.
a: p-value adjusted as compared to the threshold determined by the Hochberg multiple comparisons procedure;
b: Supportive analysis: Cox model without adjustment

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Efficacy results: *(continued)*	In the amiodarone group, the number of events (39) and the incidence (36.9%) at 90 days are in agreement with the literature. Treatment effect in the different SSR149744C groups compared with placebo was not statistically significant when adjusted for pre-specified baseline prognostic factors in the secondary analysis of the primary endpoint (close to unadjusted results). Fewer symptomatic AF/AFL events were observed in the SSR149744C treatment groups than in the placebo group with this difference being significant for the 50 mg ($p = 0.022$) and 100 mg doses ($p = 0.018$). These results must be interpreted with caution, however, as there was no adjustment for multiple comparisons. Mean ventricular HR at the first recurrence of AF/AFL recorded by TTEM was slightly lower in the SSR149744C groups than in the placebo group. The effect was more pronounced in the amiodarone group.	
Safety results:	Overall, a similar percentage of patients with TEAEs was observed in all treatment groups. The percentage of patients with serious TEAEs in the SSR149744C 300 mg group (6.2%) was similar to that in the placebo group (6.4%), and there was no increase with increased SSR149744C dose. One TEAE leading to death occurred in the SSR149744C 200 mg group (a case of lung neoplasm diagnosed 2 days after first intake of investigational product). The incidence of patients discontinuing treatment due to TEAE was highest in the amiodarone group (13.9%) while it was comparable in the SSR149744C groups and on placebo (<8%). No case of torsades de pointes was observed. The incidence of patients with PCSAs in laboratory parameters was low and similar across treatment groups except for thyroid function where a higher incidence of abnormal values was observed for free triiodothyronine (FT3) and thyroid stimulating hormone in the amiodarone group compared with the SSR149744C and placebo groups. There was no clinically relevant difference in PCSAs observed in vital signs across treatment groups.	

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Safety results (*continued*):	The number of patients with QTcB and QTcF ≥500 ms was low and similar in the placebo and SSR149744C treatment groups, ranging from 3.7% to 6.5% for QTcB and from 1.7% to 2.8% for QTcF. This number was highest in the amiodarone group with 12% and 13% of patients having QTcB and QTcF ≥500 ms, respectively.	
Pharmacokinetic results:	The SSR149744 PK profile observed in patients was consistent with that already reported in healthy subjects. No deviation from dose proportionality was observed between 50 mg and 300 mg.	
Conclusions:	[redacted]	
Date of report:	18 April 2007	