SYNOPSIS

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Title of the study:	Double blind placebo controlled dose ranging study of the efficacy and safety of SSR149744C 300 or 600 mg for the conversion of atrial fibrillation/flutter (DRI5760)
Investigator:	[redacted]
Study centers:	43 active centers in 9 countries: Canada, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Portugal, and USA
Publications (reference):	None
Study period: Date first patient enrolled: 11 October 2005 Date last patient completed: 21 April 2006	**Phase of development:** Dose-ranging
Objectives:	***Primary*** • To assess versus placebo the efficacy of SSR149744C for the conversion of atrial fibrillation/flutter (AF/AFL) to sinus rhythm (SR) at the time of the planned electrical cardioversion. ***Secondary*** • To assess versus placebo the efficacy of SSR149744C for the control of ventricular rate in patients remaining in AF/AFL at the time of the planned electrical cardioversion; • to assess versus placebo the tolerability of the different dose regimens of SSR149744C; • to document SSR149744 plasma levels during the study.
Methodology:	This was a dose-ranging, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel arm study.
Number of patients Evaluated:	Planned: 141 Randomized: 150 Treated: 150 Efficacy: 150 Per protocol: 144 Safety: 149 Pharmacokinetics: 149
Diagnosis and criteria for inclusion:	Atrial fibrillation/atrial flutter for >72 hours and indication for cardioversion of the current AF/AFL episode as judged by the Investigator.
Investigational product: Dose: Administration: Batch numbers:	SSR149744C, 100 mg capsules Once daily dose of 300 or 600 mg for 2 days. Oral, in fed conditions [redacted]
Duration of treatment: 2 days	**Duration of observation:** About 5 weeks including screening, treatment and follow-up periods
Reference therapy: Dose: Administration: Batch number:	Placebo NA Oral, in fed conditions [redacted]

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Criteria for evaluation:

Efficacy:	***Primary variable*** Rate of spontaneous conversion to SR documented by electrocardiogram (ECG) at the time of the planned electrical cardioversion (Day [D] 3) ie, 48 hours after the first investigational product administration. ***Secondary variable*** Mean ventricular rate during AF/AFL measured on the 12-lead ECG performed just before the electrical cardioversion on Day 3, for patients still in AF/AFL 48 hours after the first investigational product administration. ***Other efficacy variable*** Rate of conversion to SR (spontaneous or electrical) at hospital discharge (planned on Day 3, ie, 48 hours following the last investigational product intake).
Safety:	Incidence of adverse events (AEs), changes in standard hematology and blood chemistry, vital signs, and ECGs.
Pharmacokinetics:	SSR149744 plasma concentrations on Day 1 (C_{max}) and Day 2 (C_{trough}).
Pharmacokinetic sampling times and bioanalytical methods:	***Sampling*** Blood samples for pharmacokinetic (PK) assay were taken at around peak plasma levels 4 hours postdosing on Day 1 and at trough plasma levels just before the dosing on Day 2. ***Assay*** SSR149744 plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a limit of quantification (LOQ) of 5 ng/mL.
Statistical methods:	***Efficacy analysis*** <u>Analysis of primary efficacy variable</u> Primary analysis: The rate of the spontaneous conversions to SR on Day 3, just before the time of the planned electrical cardioversion in each SSR149744C group was compared versus the placebo group, using a Fisher's exact test. The two--sided 95% exact confidence intervals (CIs) of the rates of spontaneous conversions in each treatment group were provided. This analysis was performed on the all randomized population and the per protocol (PP) population, excluding patients with major protocol deviations affecting the assessment of the primary endpoint. Secondary analysis: For patients who had a spontaneous conversion to SR, the time to the conversion defined as the time (in hours) elapsed between the randomization and the first 12-lead ECG confirming the conversion was calculated and the median given on the all randomized population.

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Statistical methods: ***(Continued)***

Analysis of secondary efficacy variable

The mean ventricular rate during AF/AFL measured on the 12-lead ECG performed on Day 3, just before the planned electrical cardioversion for patients still in AF/AFL 48 hours after the first investigational product intake, was summarized as a quantitative variable.

Comparisons between the treatment groups were assessed by an analysis of covariance (ANCOVA) with the baseline ventricular rate as covariate. The model included the 3 groups in order to take into account the study design, and the pairwise comparisons of each SSR149744C group versus the placebo group were based on the common residual issued from this model.

Secondary efficacy analysis was performed on the all randomized population.

Analysis of other efficacy variable

The proportion of patients with a conversion at hospital discharge (spontaneous + electrical) was described as a qualitative variable, on the all randomized population.

Safety analysis

Safety data were summarized by treatment group using descriptive statistics. Potentially clinically significant abnormalities (PCSAs) in laboratory parameters, vital signs and ECG parameters were flagged and analyzed.

Safety analyses were performed on all randomized patients who took at least 1 dose of investigational product.

Summary:

This study was conducted in 9 countries. It was planned to enroll 141 patients in the study according to the protocol. However, a total of 158 patients were screened of whom 150 patients were randomized in the study (52 patients each in the placebo and 600 mg groups and 46 patients in the 300 mg group). One patient had received SSR149744C 600 mg for 2 days and was considered not randomized because the study site ran out of supply of the study treatment that had to be allocated to the patient per interactive voice response system (IVRS), and it was decided to continue the treatment administration. This patient was excluded in efficacy and safety analyses (randomized and PP populations).

Most of the randomized patients were male Caucasians with a mean age [standard deviation (SD)] of 66.9 (±9.76) years.

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Efficacy results:

Primary variable

Primary analysis:

In the all randomized population, spontaneous conversions to SR on Day 3 were observed in 4 (7.7%) patients in the 600 mg group and 2 (3.8%) patients in the placebo group. No conversion was observed in the 300 mg group.

No significant difference was observed between each of the 300 mg and 600 mg groups versus the placebo group. The same results as for the all randomized population were obtained in the PP population.

Secondary analysis:

For patients with spontaneous conversion to SR on Day 3, median time to conversions was 26.7 hours (range: 1.4 to 36.1 hours) in the 600 mg group. For the 2 patients who converted in the placebo group, time to conversion was 8.2 and 29 hours.

Secondary variable

In the all randomized population, a slight decrease of the mean ventricular heart rate (HR) from baseline to Day 3 was observed in each treatment group [mean (±SD) = 91.4 (21.45) at baseline versus 87.5 (21.85) beats per minute (bpm) on Day 3 in the 300 mg group, 91.8 (24.04) at baseline versus 86.7 (20.68) bpm on Day 3 in the 600 mg group, and 89.5 (21.96) at baseline versus 85.3 (21.52) bpm on Day 3 in the placebo group]. No significant difference was found between each of the 300 mg and 600 mg groups versus the placebo group.

Other efficacy variable

The rates of conversion to SR at hospital discharge were 66.7% in the 300 mg group and 80% in the 600 mg group (versus 77.6% in the placebo group).

Safety results:

No death was reported in the study. The incidence of serious adverse events (SAEs) was very low in the SSR149744C groups and not different from that observed in the placebo group.

The overall incidence of treatment-emergent adverse events (TEAEs) in the 300 mg and 600 mg doses of SSR149744C was similar to that observed in the placebo group: 32.6%, 39.2%, and 36.5% of patients, respectively.

The most frequently reported TEAEs were cardiac disorders (8.7%, 11.8%, and 11.5% of in the 300 mg, 600 mg, and placebo group, respectively). The incidence of all cardiac disorders observed in the 300 mg and 600 mg groups were comparable to that in the placebo group. Incidence of other TEAEs such as vascular disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and nervous system disorders were very low (ranging from 1 to 6 patients).

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Safety results: *(Continued)*	In total, 4 SAEs were reported by 4 patients in the study: 1 patient in the 300 mg group had cerebrovascular accident, 1 patient in the 600 mg group had ischaemic stroke, 1 patient in the placebo group had pulmonary edema, and 1 patient in the placebo group had cardiac failure. One patient was withdrawn from the study drug due to TEAE (same patient with cerebrovascular accident that was reported as an SAE). All SAEs and TEAE leading to withdrawal were reported as recovered by the end of the study. There was no evidence of clinically relevant changes in laboratory, vital signs, or ECG parameters including QTc.
Pharmacokinetic results	SSR149744 C_{trough} and C_{max} values observed in the present study were consistent with those values previously reported in healthy subjects. No evidence of gender effect, age effect, and cytochrome P450 3A4 (CYP3A4) inhibitor effect was observed.
Conclusions:	[redacted]
Date of report:	29 March 2007