SYNOPSIS

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

Title of the study:	Effect of a single oral 120 µg dose of SSR150106XB compared to placebo on the assessment of post-dental surgical pain after extraction of an impacted or partially impacted third molar in 90 male and female patients – Randomized, double-blind, placebo-controlled, parallel-group study (PDY5808)
Investigator:	[redacted]
Study center:	
Publications (reference):	None
Study period: Date first patient enrolled: 03 February 2006 Date last patient completed: 30 August 2006	**Phase of development:** Phase IIa
Objectives: Primary: Secondary:	• To assess the effect of a single oral 120 µg dose of SSR150106XB on the intensity of post-dental surgery pain as compared to placebo. • To assess the failure rate, the pain relief, the onset of action, and the duration of action as compared to placebo, • Safety and tolerability of a single oral 120 µg dose of SSR150106XB, • Pharmacokinetic assessment of SSR150106 and its metabolite SSR150655.
Methodology:	Monocenter, randomized, double-blind, placebo-controlled, parallel-group study
Number of patients Evaluated:	Planned: 90 Randomized: 91 Treated: 91 Efficacy: 91 Safety: 91 Pharmacokinetics: 43
Diagnosis and criteria for inclusion:	Male or female patients aged 18-45 years, genotyped non-CYP2D6 (isoenzyme 2D6 of cytochrome P450 enzyme) poor metabolizers (PM), with elective surgical extraction of at least one lower impacted or partially impacted third molar and with pain intensity of at least 40 mm on the visual analogue scale (VAS).
Investigational product: Dose: Administration: Batch number:	SSR150106XB 5 mL solution in 10 mL vial 120 µg once Oral in 240 mL of noncarbonated water [redacted]
Duration of treatment:	1 day **Duration of observation:** 3 to 8 weeks
Reference therapy: Dose: Administration: Batch number:	Placebo solution 0 µg Oral in 240 mL of noncarbonated water [redacted]

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Criteria for evaluation:

Efficacy:	***Primary:*** Total pain intensity (AUC) over an 8-hour period ($SPID_{0-8}$) was assessed. ***Secondary:*** The following secondary criteria were assessed: • Total pain relief as a summed, time-weighted pain relief to 8 hours ($TOTPAR_{0-8}$); • Maximum pain experienced using visual analogue scale (VAS) (mm); • Time to first maximum pain (hours-h) [patients not using rescue medication were censored]; • Time to meaningful pain relief recorded using a stopwatch (h); • Time to perceptible pain relief recorded using a stopwatch (h); • Time to first request of rescue medication (h) [patients not using rescue medication over the 8-hour period were censored]; • Global pain assessment; • Pain intensity calculated using VAS with and without the last observation-carried-forward (LOCF); • Pain relief calculated using verbal rating score (VRS) scale with and without LOCF; • Pain intensity change from baseline using VAS with LOCF; • Failure rate.
Safety:	Clinical, biological tolerability including adverse events (AEs), standard hematology and blood chemistry, vital signs and electrocardiogram (ECG) parameters.
Pharmacokinetics:	Plasma concentrations of SSR150106 and its metabolite, SSR150655, were used to estimate the following pharmacokinetic (PK) parameters using noncompartmental analysis: maximum plasma concentration observed (C_{max}), first time to reach C_{max} (t_{max}), area under the plasma concentration versus the time curve calculated using the trapezoidal method from time zero to t_{last} (AUC_{last}) and area under plasma concentration versus time curve from time 0 to real time 24 h ($AUC_{0-24.}$).
Pharmacokinetic sampling times and bioanalytical methods:	Blood samples for assessment of SSR150106 and SSR150655 PK were taken, for each subject, just prior to dosing and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after SSR150106XB administration. The plasma concentrations of SSR150106 and SSR150655 were determined by a validated liquid chromatography-mass spectrometry method (DOH0296) with a limit of quantification (LOQ) of 0.005 ng/mL for both compounds.

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Statistical methods: Efficacy:	***Primary:*** $SPID_{0-8}$, the total pain intensity (AUC) over an 8-hour period was analyzed with a linear fixed effects model. Estimate and 95% confidence interval (CI) of the treatment difference between SSR150106XB 120 µg and placebo were derived from the model. For patients taking rescue medication, the LOCF approach was used in the $SPID_{0-8}$ calculation. ***Secondary:*** The secondary pharmacodynamic (PD) parameters were summarized by descriptive statistics or graphs. Failure rate was calculated as the number (%) of patients who took rescue medication within 8 hours.
Safety:	Safety and tolerability of SSR150106XB were evaluated from the review of individual values and descriptive statistics. Treatment-emergent adverse events (TEAEs) were listed and summarized by treatment. Abnormalities in hematology and biochemistry parameters, vital signs in supine and orthostatic change, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria. In addition, descriptive statistics were provided for vital signs and ECG raw and changes from baseline.
Pharmacokinetics:	The PK parameters C_{max}, AUC_{0-24} and AUC_{last} were summarized using the arithmetic and geometric means, standard deviation (SD), coefficient of variation (CV%), minimum and maximum values. In addition, t_{max} was summarized using range and median.
Summary:	
Efficacy results:	Only 4 patients out of 44 on SSR150106XB did not take any rescue medication versus 1 out of 46 on placebo. The mean time to taking rescue medication within 8 hours was 1.7 hours on SSR150106XB versus 2.2 hours on placebo. There was no difference in time to perceptible pain relief between SSR150106XB (26/44 patients) and placebo (23/46 patients) (0.4 hour versus 0.4 hour, respectively) and in time to meaningful pain relief between SSR150106XB (11/44 patients) and placebo (10/46 patients) (1.5 hours versus 1.0 hour, respectively). Failure rate was 90.9% on SSR150106XB versus 97.8% on placebo. SSR150106XB 120 µg had no significant analgesic effect compared to placebo.
Safety results:	The number of patients with at least 1 TEAE was similar in both treatment groups [32/46 (69.6%) in the placebo group versus 34/45 (75.6%) in the SSR150106XB group]. There were no deaths or SAEs reported during the study. There were no relevant changes in laboratory test results, vital signs or ECG parameters. Overall SSR150106XB was well tolerated by patients genotyped non-CYP2D6 PM.

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Pharmacokinetic results

Mean (CV%) PK parameters of SSR150106 and SSR150655 after a single oral dose of 120 µg SSR150106XB in patients undergoing dental surgery non-CYP2D6 PM are presented in the table below.

PK Parameters	**SSR150106**	**SSR150655**
C_{max} (ng/mL)	0.0569 (81%)	0.0775 (33%)
t_{max} (h)	2.00 (0.50, 5.00)	7.98 (3.00, 24.05)
AUC_{0-24} (h.ng/mL)	0.452 (116%)	1.35 (32%)

Tabulated values are Mean (CV%) except for t_{max} where values are Median (Min, Max)

All patients treated with a single oral dose of SSR150106XB 120 µg were exposed to the drug and its metabolite (SSR150655).

Conclusions: [redacted]

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