SYNOPSIS

Title of the study: An eight-week, multinational, multicenter, double-blind, active- and placebo controlled clinical trial evaluating the efficacy and tolerability of three fixed doses of SSR125543 (20 mg daily, 50 mg daily, and 100 mg daily) in outpatients with major depressive disorder (DFI5687)

Investigator(s): [redacted]

Study center(s): 68 centers and 11 countries (Belgium, Canada, Chile, Estonia, Finland, France, Germany, Russia, Slovakia, South Africa, Sweden)

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 24/Feb/2010

Date last patient completed: 14/Mar/2011

Phase of development: Phase 2

Objectives:

Primary

The primary objective was to evaluate the efficacy of three fixed doses of SSR125543 (20 mg daily, 50 mg daily, and 100 mg daily) compared to placebo in outpatients with major depressive disorder (MDD), as assessed by the change from baseline (Day -1) to Day 56 in the 17- item Hamilton Depression Rating Scale (HAM-D) total score.

Secondary

To evaluate the tolerability and safety of SSR125543 in outpatients with major depressive disorder.
To evaluate plasma concentrations of SSR125543.

Methodology: Phase 2, multiple country, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, comparing 3 fixed doses of SSR125543 and placebo, using escitalopram 10mg as daily active control, during an 8-week treatment period.

- Screening Period (1 week): during this period, the patients did not receive investigational product (IP)
- Treatment Phase (8 weeks): the patients were randomized to receive the double blind IP
- Post-treatment Phase (2 weeks): a 2-week follow-up period, within 14 ± 3 days of the last dose of IP, was included for all patients. During this phase, the patients did not receive IP

Number of patients:	Planned: Approximately 580 patients (116 patients per treatment group)		
Placebo arm			
Number of patients:	Planned: 116	Randomized: 117	Treated: 116
Evaluated:	Efficacy: 114	Safety: 116	Pharmacokinetics: 0
SSR125543 arm			
Number of patients:	Planned: 348	Randomized: 364	Treated: 361
Evaluated:	Efficacy: 355	Safety: 361	Pharmacokinetics: 355
Escitalopram arm			
Number of patients:	Planned: 116	Randomized: 117	Treated: 115
Evaluated:	Efficacy: 114	Safety: 115	Pharmacokinetics: 114

Diagnosis and criteria for inclusion: Patients aged greater than 18 years (>18) or less than 64 years (<64) diagnosed with major depressive disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI) criteria.

Investigational product: SSR125543

Dose: 20 mg, 50 mg, and 100 mg

Administration: oral, daily in the morning with food

Batch number(s): [redacted]

Duration of treatment: 8 weeks

Duration of observation: 11 weeks

Reference therapy: Placebo

Dose: 0 mg

Administration: oral, daily in the morning with food

Batch number(s): [redacted]

Reference therapy: escitalopram

Dose: 10mg

Administration: oral, daily in the morning with food

Batch number(s): [redacted]

Criteria for evaluation:

The current report is an abbreviated report, and as such, mainly presents baseline, primary efficacy results, safety and pharmacokinetic (PK) concentration data. Detailed safety data are available in the appendices.

Pharmacokinetics: SSR125543 concentrations (in blood and plasma) pre-dose and post-dose. Blood and plasma concentrations of SSR125543 were assayed using a validated liquid chromatography method coupled with tandem mass spectrometry (LC-MS/MS) with a lower limit of quantification of 10 ng/mL

Statistical methods:

Efficacy

Primary analysis

The primary efficacy endpoint was the change from baseline (Visit 2; Day – 1) to Visit 7 (Day 56) in the 17-item HAM-D total score. All efficacy analyses were performed using the modified intent–to-treat (mITT) population defined as all randomized patients taking at least one dose of double-blind study medication and providing any post-baseline HAM-D data, irrespective of compliance with the study protocol and procedures. Patients were analyzed in the treatment group to which they were randomized.

The change from baseline in the HAM-D total score was analyzed using a mixed-effect model with repeated measures (MMRM), including fixed effects for treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of centered-baseline score and centered-baseline score-by-visit interaction, under the missing at random framework and with an unstructured correlation matrix to model the within-patient errors. Parameters were estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom were estimated using Kenward and Roger's approximation.

The primary comparisons were between each SSR125543 dose group and placebo using a Bonferroni-Hommel method as the multiple comparison procedure to control the global type I error rate at 5%. The comparison between the active control (escitalopram) and placebo was performed to document sensitivity of the study (at the 5% significance level). Baseline adjusted least-square means (LS-means) estimates at Day 56 by treatment group, as well as the differences of these estimates versus placebo, with their corresponding standard errors, degrees of freedom, Student t-test statistics and associated 95% confidence intervals were estimated from the model. Student t-tests were used to determine the statistical significance.

Supportive analysis

To assess the sensitivity of the primary analysis, supportive analysis of covariance (ANCOVA) was conducted based on the "Last observation carried forward (LOCF)" strategy. This analysis used treatment group as fixed effect and centered baseline HAM-D total score as covariate.

This model provided the baseline adjusted LS-mean estimates at end of treatment by treatment group, as well as the difference of the estimate versus placebo, with their corresponding standard error, Student t-test statistics and associated 95% confidence interval.

All analyses of secondary efficacy parameters were for exploratory purposes only.

Safety

All safety analyses were performed using the safety population defined as all randomized patients exposed to IP, regardless of the amount of treatment administered, analyzed according to the treatment actually received. The incidences of treatment-emergent adverse events (TEAEs), deaths, serious adverse events (SAEs), adverse events leading to treatment discontinuation, and study specific adverse events were summarized by treatment group using counts and percents.

Analysis of laboratory, vital signs and electrocardiogram (ECG) data focused on descriptive statistics and summaries of potentially clinically significant abnormality (PCSA) values.

In order to protect the safety of patients exposed to SSR125543 in DFI5687, safety data collected in this trial were reviewed and evaluated in a blinded manner by a data monitoring committee (DMC).

Pharmacokinetic

Plasma and whole blood SSR125543 concentrations were summarized by descriptive statistics.

Summary: This report presents the final results of the primary and secondary efficacy endpoints, safety data and PK concentration data.

A total of 592 patients with diagnosed MDD according to the DSM-IV-TR were randomized and treated: 116 patients in the placebo arm, 361 patients in the SSR125543 arms (SSR125543 20 mg arm: 119 patients; SSR125543 50 mg arm: 122 patients; SSR125543 100 mg arm: 120 patients), and 115 patients in the 10 mg escitalopram arm.

Efficacy results:

Primary efficacy endpoint

The primary analysis did not show statistically significant differences on the HAM-D total score at Visit 7 between any dose of SSR125543 and placebo (LS-mean difference of 1.09, -1.04 and -0.97 for respectively SSR125543 20 mg, 50 mg and 100 mg versus placebo). However, it showed a difference between escitalopram 10 mg and placebo (LS-mean difference of -2.08, p-value=0.0364). This difference confirmed assay sensitivity for the study.

Secondary efficacy endpoints

The analyses of the secondary endpoints, change from baseline to last visit in Montgomery-Asberg Depression Rating Scale (MADRS) total score and treatment responders based on the HAM-D total score, did not show differences between SSR125543 treatment groups and the placebo group. Consistent with the primary analysis, a larger difference was observed for treatment responders (p-value= 0.0331) and MADRS total score (p-value=0.0901) between escitalopram and placebo groups.

Safety results:

Regarding tolerability, approximately 70% of patients experienced treatment emergent adverse events (66.4% in SSR125543 20 mg group, 63.9% in SSR125543 50 mg group, 67.5% in SSR125543 100 mg group, 72.2% in escitalopram 10 mg group and 65.5% in placebo group). The most frequently reported TEAEs (more than 5% in any SSR125543 group and higher than placebo) were headache, nausea, dry mouth, dizziness, somnolence, constipation, fatigue and neutropenia One death (suicide) occurred in the study (SSR125543 100 mg group); this event was considered to be post-TEAE, as the last known date of IP intake was more than 3 weeks before the event. The percentages of treatment emergent SAE were similar between the three SSR125543 treatment groups (0.8% in each SSR125543 group) and the placebo group (1.7%), but slightly higher in the escitalopram 10 mg group (4.3%). The percentage of patients who discontinued due to TEAE was slightly higher in the SSR125543 100 mg group (12.5%) than in the other treatment groups (9.0% in SSR125543 50 mg, 8.4% in SSR125543 20 mg, 8.7% in escitalopram 10 mg and 5.2% in placebo) mainly due to neutropenia. Analyses of PCSA for laboratory, vital signs and ECG showed similar results between the five treatment groups. The percentage of patients with suicidal ideation or behavior during treatment was similar between the five treatment groups.

Pharmacokinetic results:

Doses of SSR125543 at 20, 50, and 100 mg once daily led to mean (standard deviation) plasma concentrations of 192.59 (177.19), 400.70 (291.86) and 841.04 (583.44) ng/mL, respectively, prior to dosing and 617.64 (368.79), 1313.91 (959.46) and 2854.28 (1543.72) ng/mL at 3 to 7 hours post dose on Day 56.

Conclusions: [redacted]

Date of report: 05-Sep-2011