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Sponsor / Company: Sanofi	**Study Identifiers:** NCT00822744, 2008-001718-26
Drug substance(s): SSR411298	**Study code:** DFI10560

Title of the study:

An eight-week, multicenter, randomized, double-blind, placebo-controlled dose-finding study, with escitalopram (10 mg daily) as active control, to evaluate the efficacy, safety and tolerability of three fixed doses of SSR411298 (10, 50, or 200 mg daily) in elderly patients with Major Depressive Disorder (FIDELIO)

Study center(s):

62 centers in 7 countries (Chile, Mexico, Romania, Russian Federation, Slovakia, South Africa, and Ukraine)

Study period:

Date first patient enrolled: 18 December 2008

Date last patient completed: 16 February 2010

Phase of development: 2

Objectives:

Primary

- To evaluate the efficacy of 3 fixed doses of SSR411298 (10, 50 or 200mg daily) compared to placebo, in elderly patients with Major Depressive Disorder (MDD), based on the 17-item Hamilton Depression Rating Scale (HAM-D).

Secondary

- To evaluate the tolerability and safety of an 8-week treatment with SSR411298 versus placebo in elderly patients with MDD.

- To evaluate the effect of SSR411298 on disability, anxiety, cognitive function, sleep, pain and somatic symptoms related to depression, and bone markers.

- To assess SSR411298 plasma concentrations.

- To assess plasma endocannabinoid concentrations.

Methodology:

Phase 2, multiple country, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, comparing 3 fixed doses of SSR411298 and placebo, using escitalopram 10 mg as active control, during an 8-week treatment period.

Number of patients:	Planned:	SSR411298 arms: 300	Placebo arm: 100	Escitalopram arm: 100
	Randomized:	SSR411298 arms: 318	Placebo arm: 106	Escitalopram arm: 103
	Treated:	SSR411298 arms: 316	Placebo arm: 106	Escitalopram arm: 103
Evaluated:	Efficacy:	SSR411298 arms: 316	Placebo arm: 105	Escitalopram arm: 99
	Safety:	SSR411298 arms: 316	Placebo arm: 106	Escitalopram arm: 103
	Pharmacokinetics:	SSR411298 arms: 299	Placebo arm: 102	Escitalopram arm: 91

Diagnosis and criteria for inclusion:

Patients (male or female) 60 years or older, with diagnosed MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR), and confirmed by the Mini International Neuropsychiatric Interview (MINI). Patients with recurrent episode for at least 1 month prior to the first visit.

Study treatments

Investigational medicinal product(s): SSR411298 or placebo or Escitalopram

Formulation: capsule containing either SSR411298 10 or 50 or 200 mg, or placebo or Escitalopram 10 mg

Route(s) of administration: oral

Dose regimen: one capsule once daily in the morning with food

Duration of treatment: 8 weeks

Duration of observation: up to 10 weeks (up to 1-week screening, 8-week treatment and 1–week post-treatment follow-up)

Criteria for evaluation:

Efficacy:

Primary: 17-item Hamilton Depression Rating Scale (HAM-D) total score

Secondary: Montgomery and Asberg Depression Rating Scale (MADRS); Clinical Global Impression (CGI) scale; Hamilton-Depression mood, factor, and core item scores; 15-item Geriatric Depression Scale (GDS); Sheehan Disability Scale (SDS); Hamilton-Anxiety Rating Scale (HAM-A)

Safety:

Adverse events and other clinical and paraclinical parameters (e.g., physical examination, body weight, body temperature, heart rate, blood pressure, laboratory tests in fasting conditions, ECG); Discontinuation-Emergent Signs and Symptoms checklist (DESS); Cognitive Function tests (Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, 2-Digit Cancellation Test); Pittsburgh Sleep Quality Index (PSQI); Columbia-Suicide Severity Rating Scale (C-SSRS); bone markers; 15-item Patient Health Questionnaire (PHQ-15) and Pain Visual Analog Scale

Pharmacokinetics: SSR411298 plasma concentrations

Pharmacodynamics: Endocannabinoid plasma concentrations

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

SSR411298 plasma samples were collected at predose and from 3 to 5 hours after SSR411298 dose intake (and within 20 minutes of ECG measurement) on Days 21and 56. Plasma concentrations of SSR411298 were determined by a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 10 ng/mL.

Statistical methods:

The primary efficacy variable was the change from baseline (Day – 1) to Visit 8 (Day 56) in the 17-item HAM-D total score. All efficacy analyses were performed using the intent-to-treat (ITT) population defined as all randomized patients taking at least one dose of double-blind study medication and providing any post-baseline efficacy 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 SSR411298 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-squares 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.

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

All safety analyses were performed using the safety population defined as all randomized patients exposed to investigational product (IP), regardless of the amount of treatment administered, analyzed according to the treatment actually received. The incidences of treatment-emergent adverse events, deaths, serious adverse events, adverse events leading to treatment discontinuation, and adverse events of special interest were summarized by treatment group using counts and percents. Analysis of labs, vital signs and 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 SSR411298 in DFI10560, safety data collected in this trial were reviewed and evaluated in an unblinded manner by a data monitoring committee.

SSR411298 concentrations were summarized by descriptive statistics**.**

Summary:

Population characteristics:

A total of 525 elderly patients with diagnosed MDD according to the DSM-IV-TR were randomized and treated: 106 patients in the placebo arm, 316 patients in the SSR411298 arms (SSR411298 10 mg arm: 105 patients; SSR411298 50 mg arm: 106 patients; SSR411298 200 mg arm: 105 patients), and 103 patients in the 10 mg escitalopram arm.

Efficacy results:

Based on the primary MMRM analysis, there was no statistically significant difference between any dose of SSR411298 and placebo for the mean change from baseline to Day 56 in the 17-item HAM-D total score. By this same MMRM analysis, patients treated with escitalopram showed a statistically significant decrease (p-value = 0.0243) from baseline in HAM-D total score compared to the placebo arm, thereby demonstrating assay sensitivity.

No dose-response effect of SSR411298 across secondary efficacy endpoints could be concluded.

Safety results:

A majority of treated patients experienced at least one treatment emergent adverse event (TEAE) (placebo arm: 50%; SSR411298 arms: 43.8% [10 mg], 52.8% [50 mg]; 53.3% [200 mg]; and 10 mg escitalopram arm: 58.3%). The rates of TEAE were similar across SSR411298 treatment groups and similar to placebo treated patients.

Headache (5.7% on SSR411298 10 mg, 11.3% on SSR411298 50 mg, and 9.5% on SSR411298 200 mg), suicidal ideation (5.7% both on SSR411298 50 mg and 200 mg), diarrhoea (5.7% on SSR411298 10 mg), dizziness (5.7% on SSR411298 50 mg), and nausea (6.7% on SSR411298 200 mg) were the most frequent TEAE observed in the SSR411298 arm.

Nausea (11.7%), headache (8.7%), dizziness and somnolence (5.8% for each) were the most frequent TEAE observed in the 10 mg escitalopram arm.

One patient (0.9%) in the placebo arm, 3 patients in the SSR411298 arms (SSR411298 50 mg: 2 patients [1.9%], and SSR411298 200 mg: 1 patient [1%]), and 3 patients (2.9%) in the escitalopram arm had at least 1 serious TEAE. One death occurred in the escitalopram arm. It was due to a serious adverse event (cerebral haemorrhage).

A higher rate of premature treatment discontinuation due to adverse events (AE) was observed in the escitalopram and SSR411298 50 mg treatment groups mostly due to psychiatric and nervous system disorder AE. A total of 22 patients experienced an AE leading to treatment discontinuation: 3 patients in the placebo arm, 10 patients in the SSR411298 arm (SSR411298 10 mg: 1 patient, SSR411298 50 mg: 7 patients, and SSR411298 200 mg: 2 patients), and 9 patients in escitalopram arm. The most common cause of discontinuation in the SSR411298 treatment groups were related to psychiatric and nervous system and disorders.

There were 2 AE reported for acute confusional state: one patient in the SSR411298 200 mg arm, and one in the SSR411298 50 mg arm. There was no AE reported for suicidality (complete suicide, suicide attempt, suicidal behavior or suicidal ideation with explicit plans or active preparation for suicide). Two (2) cases of ALT ≥3 ULN were observed in the SSR411298 200 mg arm without bilirubin elevation and the ALT values returned to normal after treatment cessation. Other laboratory, ECG, and vital signs parameters did not show clinically significant imbalance between the SSR411298 arms and placebo or escitalopram.

Pharmacokinetic results:

Doses of SSR411298 at 10, 50 and 200 mg once daily led to mean (SD) plasma concentrations of 45.8 (86.9), 254 (469) and 1060 (1430) ng/mL, respectively, prior to dosing; and 352 (267), 1560 (1250) and 3440 (2310) ng/mL at 3 to 5 hours post dose on Day 56.

Issue date: 18-Feb-2013