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Sponsor: Sanofi Drug substance(s): SR48968/Saredutant	Study Identifiers: NCT Number: NCT00531622 EudraCT Number: 2007-003159-36 Study code: EFC10290
Title of the study: An eight-week, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of saredutant 100 mg once daily in combination with escitalopram 10 mg once daily in patients with major depressive disorder	
Study center(s): Approximately 62 centers worldwide from the US, France, Finland, Argentina, Sweden, and Mexico	
Study period: Date first patient enrolled: 10/09/2007 Date last patient completed: 14/01/2009	
Phase of development: Phase 3	

Objectives:

The primary study objectives were to evaluate:

- the efficacy of saredutant 100 mg once daily in combination with escitalopram 10 mg once daily compared to saredutant placebo in combination with escitalopram 10 mg once daily in patients with major depressive disorder, as assessed by the change from baseline (Day –1) to Day 56 in the 17-item Hamilton Depression Rating Scale (HAM-D) total score;
- the effect of saredutant 100 mg once daily in combination with escitalopram 10 mg once daily compared to saredutant placebo in combination with escitalopram 10 mg once daily on sexual function in patients with major depressive disorder, as assessed by the change from baseline (Day -1) to Day 56 in the Changes in Sexual Functioning Questionnaire (CSFQ) total score.

The secondary objective of this study was to evaluate the tolerability and safety of saredutant 100 mg once daily in combination with escitalopram 10 mg once daily in patients with major depressive disorder.

Methodology:

Eight-week, multinational, multicenter, randomized, double-blind, parallel group study design, in which saredutant 100 mg and placebo were administered in combination with escitalopram 10 mg. The study consisted of three phases:

1) screening phase was a 1-week, placebo, single-blind period;

2) randomization phase was an 8-week, double-blind treatment period;

3) post-treatment phase was a 1-week, drug-free, follow-up period.

At entry into the randomization phase, patients were to be randomized in a 1:1:1 ratio to one of the following 3 groups: saredutant 100 mg + escitalopram 10 mg, saredutant placebo + escitalopram 10 mg, and saredutant placebo + escitalopram placebo. Randomization was carried out at the center level and stratified according to gender and the level of sexual function (Males: CSFQ total score ≤ 47 for low, normal otherwise; Females: CSFQ total score ≤ 37 for low, normal otherwise).

Number of patients :	Planned: Approximately 615 patients (205 patients per group) Randomized: 643 Treated: 638
Evaluated:	
	Efficacy: 627 Safety: 638

Diagnosis and criteria for inclusion:

- Diagnosis of major depressive disorder, recurrent, 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;
- Male or female outpatients;
- 18 to 65 years of age (Modified per Protocol Amendment 1).

Study treatments

Investigational medicinal product(s):

Saredutant (size 0 Swedish Orange capsules)

Formulation: 100 mg

Route(s) of administration: oral

Dose regimen: Once daily

Noninvestigational medicinal product(s):

Escitalopram tablets (size 0 over-encapsulated Swedish Orange capsules)

Formulation: 10 mg

Route(s) of administration: oral

Dose regimen: Once daily

Placebo (size 0 Swedish Orange capsules, identical in appearance to saredutant and over-encapsulated escitalopram)

Formulation: 100 mg

Route(s) of administration: oral

Dose regimen: Once daily

Duration of treatment: The total study duration for one patient participating in all three phases, including the post-treatment phase, was 10 weeks.

Duration of observation: The duration of observation is 9 weeks: 8 weeks during the randomized treatment phase and 1 week during the post-treatment phase.

Criteria for evaluation:

Efficacy: Efficacy was evaluated using the co-primary endpoints, the change from baseline (Visit 2, Day -1) to Visit 7 (Day 56) in the HAM-D and CSFQ total scores, as well as secondary endpoints: Change from baseline in the CGI-S Severity of Illness score at Visit 7 (Day 56); change from baseline in the HAM-D depressed mood item score (#1) at Visit 7 (Day 56); proportion of patients demonstrating a treatment response, defined as a reduction of at least 50% in HAM-D total score between baseline and any post-baseline assessment.

Safety: The primary safety endpoint was the change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the CSFQ total score in the ITT population. Other endpoints taken from the CSFQ included the proportions of patients in each category of sexual functioning status at the end of the study and the change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the CSFQ subscale scores.

Other safety endpoints included physical examinations, vital signs, spontaneously-reported adverse events, electrocardiograms (ECG), clinical laboratories, and the Physician Withdrawal Checklist (PWC).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pre-dose trough samples were taken 20 to 28 hours after the Day 13, 27, 41 and Day 55 doses to assess plasma concentrations of saredutant, SR49596 (inactive metabolite) and escitalopram. An ECG was performed 2-4 hours post-dose on Day 14 and 56; post-dose peak samples were taken immediately (not exceeding 20 minutes) after the ECG to assess plasma concentrations of saredutant and SR49596 (inactive metabolite) concentrations. In addition, plasma samples were also taken immediately (not exceeding 20 minutes) after the ECG in the event of early termination from the study, in the event of overdose, or confirmed QTcB>500 msec.

Plasma samples were assayed for saredutant, SR49596 (inactive metabolite), and escitalopram using fully validated LC-MS/MS assays with limits of quantification of 0.5 ng/mL for both saredutant and SR49596 and 0.2 ng/mL for escitalopram.

Statistical methods:

The change from baseline to Day 56 in the 17-item HAM-D and CSFQ total scores was analyzed in the Intent-to-Treat (ITT) population using a mixed-effect model with repeated measures analysis under the missing at random framework. The primary comparison is between the saredutant 100 mg + escitalopram 10 mg and escitalopram 10 mg alone groups. Comparison between escitalopram 10 mg alone and placebo groups was performed for assay sensitivity.

The mixed-effect model included fixed terms for treatment, visit, gender, baseline CSFQ status, and treatment-by-visit interaction, and continuous fixed covariate of centered baseline score (corresponding to the variable being analyzed) and centered baseline score-by-visit interaction. The Intent-To-Treat (ITT) population consisted of all randomized patients who received at least 1 dose of double-blind study medication and provided any post-baseline efficacy data.

All available post-baseline evaluations were used to calculate the baseline-adjusted least squares means (LS-Means) estimates at Day 56 by treatment group, along with the estimated treatment differences and 95% confidence intervals. Student t-tests were used to determine the statistical significance of saredutant + escitalopram versus escitalopram (primary efficacy comparison) and the comparison of escitalopram versus placebo (assay sensitivity). A step-down procedure was used for the co-primary comparisons to control the overall type-I error rate at 0.05 level.

As a supportive approach, an analysis of covariance (ANCOVA) using the treatment factor as a fixed effect with three levels (placebo, saredutant + escitalopram, and escitalopram) and the centered baseline as covariate on the last available observation, also called last observation carried forward (LOCF), was also performed.

If both co-primary endpoints (HAM-D and CSFQ total scores) were declared statistically significant at the 5% level, the key secondary endpoints were to be subjected to a similar hierarchical testing procedure. The test procedure would terminate as soon as an endpoint was found not statistically significant at the level of 0.05.

Safety and tolerability was based upon the review of individual values and summary statistics for the each treatment group. Incidences of treatment-emergent adverse events (TEAEs), AEs with an outcome of death, serious adverse events (SAEs), and AEs leading to treatment discontinuation were tabulated by patient counts and percentages. Abnormalities in clinical laboratories, vital signs, and ECGs were based on the definitions for potentially clinically significant abnormalities (PCSAs) and were tabulated by patient counts and percentages.

Summary:

Population characteristics: A majority of patients were female (approximately 67% across groups) and of Caucasian heritage (68.1 to 74.4% across groups) with a median age of 43 years and a median weight of 77 kg. Mean number of previous psychiatric episodes ranged from 3.44 to 4.55 across groups, and patients who had attempted suicide or were hospitalized for depression were lower in the placebo group (range of 5.6% to 11.6% and range of 6.5% to 10.8%, respectively). Mean duration of current episode, family history of depression, baseline HAM-D total scores, and baseline CSFQ total scores were relatively stable across groups.

Efficacy results: The estimated mean changes from baseline to Day 56 in the co-primary efficacy endpoint, the HAM-D total score, based on the MMRM analysis were: -10.29 points for placebo, -13.01 points for escitalopram 10 mg alone, and -12.44 points for saredutant 100 mg + escitalopram 10 mg.

MMRM results at Day 56 revealed that patients treated with saredutant, in combination with escitalopram, did not show a statistically significant greater improvement in the symptoms of depression compared to escitalopram alone (LS-Mean difference = 0.57, pvalue = 0.4272). However, the escitalopram alone group showed a statistically significant greater improvement compared to the placebo group (LS-Mean difference = -2.72, p-value = 0.0002). A supportive analysis on last assessed visit using ANCOVA-LOCF confirmed these findings.

A hierarchical procedure to test for the co-primary efficacy endpoints (HAM-D and CSFQ total scores) was carried out. Since the primary efficacy comparison from the Day 56 MMRM analysis of HAM-D total score was not statistically significant, no inferential assessment can be made for CSFQ.

The termination of the hierarchical testing of the co-primary endpoints from the previous section precluded the hierarchical testing of the following key secondary endpoints: CGIS Severity of Illness score, HAM-D depressive mood item score, and HAM-D treatment responders.

Safety results: Incidence rates of patients experiencing any TEAEs in the active treatment groups (saredutant + escitalopram and escitalopram alone) were similar, and both were greater than that of the placebo group. Nausea and headache were the most frequently reported AEs. Of note, gastrointestinal event rates were higher in non-placebo groups mainly due to higher reports of nausea and diarrhea. In addition, incidences in psychiatric disorders were higher in non-placebo groups due to appreciably higher cases of decreased libido.

No patient treated with saredutant + escitalopram had QTcF value > 500 msec. One female and 1 male patient treated with saredutant + escitalopram had prolonged QTcF values (477 msec and 451 msec, respectively). Two female patients treated with saredutant + escitalopram had a clinically relevant increase from baseline in QTcF (96 msec and 64 msec, respectively). However, only the former had an absolute elevation in QTcF (477 msec). Changes from baseline in QTcF interval at last assessed visit were similar between the saredutant + escitalopram and escitalopram alone groups (-2.9 msec for placebo, and 1.4 msec for both saredutant + escitalopram and escitalopram alone groups).

No patients treated with saredutant + escitalopram had an ALT value > 3xULN. There were no patient deaths during the study.

“No analysis was done on the PK data for the purposes of this study.”

Issue date: 16-Jun-2016