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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Drug substance(s): SR48968/Saredutant	Study Identifiers: NCT Number: NCT00629551 EudraCT Number: 2007-003863-31 Study code: EFC10438
Title of the study: An eight-week, double-blind study to evaluate the efficacy, safety, and tolerability of two fixed doses of saredutant (100 mg and 30 mg) once daily in combination with paroxetine 20 mg once daily compared to saredutant placebo in combination with paroxetine 20 mg once daily in patients with major depressive disorder (EFC10438)	
Study center(s): Approximately 75 centers from the US, Chile, Estonia, Germany, Mexico, Russia, South Africa, and South Korea.	
Study period: Date first patient enrolled: 22/02/2008 Date last patient completed: 27/02/2009	
Phase of development: 3	

Objectives:

Primary:

- To evaluate the efficacy of 2 fixed doses of saredutant (100 mg and 30 mg) once daily in combination with paroxetine 20 mg OD compared to saredutant placebo in combination with paroxetine 20 mg once daily in patients with major depressive disorder (MDD), as assessed by the change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the 17-item Hamilton Depression Rating Scale (HAM-D) total score
- To evaluate the effect of 2 fixed doses of saredutant (100 mg and 30 mg) once daily in combination with paroxetine 20 mg once daily compared to saredutant placebo in combination with paroxetine 20 mg once daily on sexual function in patients with MDD, as assessed by the change from baseline Visit 2 (Day -1) to Visit 7 (Day 56) in the Changes in Sexual Functioning Questionnaire (CSFQ) total score

Secondary:

- To evaluate the tolerability and safety of 2 fixed doses of saredutant (100 mg and 30 mg) once daily in combination with paroxetine 20 mg once daily in patients with MDD.

Methodology: This was an eight-week, multinational, multicenter, randomized, double-blind, parallel-group study design, in which two fixed doses of saredutant (100 mg and 30 mg) and placebo were administered in combination with paroxetine 20 mg. The study consisted of three phases: (a) Screening phase was a one-week, placebo, single-blind period, (b) Randomization phase was an 8-week, double-blind period, and (c) Post-study phase was a one-week, drug-free, safety follow-up period.

At entry into the randomization phase, patients were to be randomized in a 1:1:1:1 ratio to one of the following 4 groups: saredutant 100 mg + paroxetine 20 mg, saredutant 30 mg + paroxetine 20 mg, saredutant placebo + paroxetine 20 mg, and saredutant placebo + paroxetine 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 subjects :	Planned: 820 (205 patients/group) Randomized: 825 Treated: 819
Evaluated:	Efficacy : 809 Safety: 819

Diagnosis and criteria for inclusion:

Inclusion criteria:

- Male or female
- 18 to 65 years of age
- Diagnosis of MDD, recurrent, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM IV TR) criteria (296.3) and confirmed by the semi-structured Mini International Neuropsychiatric Interview (MINI)

Exclusion criteria:

- Montgomery-Asberg Depression Rating Scale (MADRS) total score of less than 24
- HAM-D total score of less than 18

Study treatments

Investigational medicinal product(s): Saredutant (SR48968)

Formulation: capsule

Route(s) of administration: oral

Dose regimen: 100 mg and 30 mg once daily, fed conditions

Noninvestigational medicinal product(s): paroxetine

Formulation: capsule

Route(s) of administration: oral

Dose regimen: 20 mg once daily, fed conditions

Duration of treatment: 9 weeks (including 1 week of single-blind placebo treatment and 8 weeks of double-blind treatment)

Duration of observation: 10 weeks (including Screening Phase, Randomized Treatment Phase, and Post-study Phase)

Criteria for evaluation:

Efficacy:

Primary endpoints:

- The change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the 17item HAM-D total score in the intent-to-treat (ITT) population.
- The change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the CSFQ total score in the ITT population.

Secondary endpoint:

The main secondary efficacy endpoints were:

- The change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the Clinical Global Impression (CGI) Severity of Illness score
- The change from baseline Visit 2 (Day –1) to Visit 7 (Day 56) in the HAM-D depressed mood item score
- The percentage 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:

Primary endpoint:

- Change in CSFQ total score

Secondary endpoints

- Sexual functioning status
- Level of sexual functioning (low / normal) based on threshold scores for sexual functioning on the CSFQ total score
- Physical examination
- Adverse events
- Clinical laboratory evaluations
- Vital signs (blood pressure, heart rate)
- Electrocardiograms
- Physician withdrawal checklist (PWC)

Pharmacokinetics: Plasma concentrations of saredutant and its inactive metabolite SR49596, and plasma concentration of paroxetine.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Sampling times:

Plasma concentrations of saredutant, SR49596 (inactive metabolite), and paroxetine were assessed at Visit 4 (Day 14), Visit 5 (Day 28), Visit 6 (Day 42), and Visit 7 (Day 56). Predose 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 paroxetine. An ECG was performed 2 to 4 hours postdose on Day 14 and 56; postdose 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, of overdose, or of confirmed QTcB>500 msec.

Assays for saredutant, SR49596, and paroxetine:

Plasma samples were assayed for saredutant, SR49596 (inactive metabolite), and paroxetine 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 paroxetine.

Statistical methods:

The changes from baseline to Day 56 in HAM-D and CSFQ total scores were analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach under the missing at random framework. The primary comparisons are between saredutant 100 mg + paroxetine and paroxetine alone and saredutant 30 mg + paroxetine and paroxetine alone groups. Comparison between paroxetine alone and placebo groups was performed for assay sensitivity.

The mixed-effects model included fixed categorical effects for treatment, visit, gender, baseline CSFQ status (normal/low), and treatment-by-visit interaction, and the continuous fixed covariate of centered baseline score (corresponding to the variable being analyzed) and centered baseline score-by-visit interaction. Patient-specific random effects were modeled as part of the within-patient correlation structure. 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 leastsquares 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 100 mg + paroxetine 20 mg or saredutant 30 mg + paroxetine 20 mg versus paroxetine 20 mg alone (primary efficacy comparisons) and the comparison of paroxetine 20 mg alone 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 four levels (placebo, saredutant 100 mg + paroxetine, saredutant 30 mg + paroxetine, and paroxetine alone) 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 for saredutant 100 mg + paroxetine versus paroxetine alone, 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.

The incidence of TEAEs, AEs with an outcome of death, serious adverse events (SAEs), and AEs leading to treatment discontinuation are tabulated by counts and percentages within each treatment group. The incidences of on-treatment Potentially Clinically Significant Abnormalities (PCSA) were tabulated by counts and percentages within each treatment group for liver function and ECG parameters. QTc interval from ECG tracings was derived using both Fridericia (QTcF) and Bazett (QTcB) correction methods. Descriptive statistics for QTcF and QTcB parameters for each treatment group and visit were also provided.

Summary:

Population characteristics: A majority of study patients were female and of Caucasian heritage, with a median age of 41 years. Except for a smaller proportion of patients with HAM-D total scores > 25 in the saredutant 30 mg + paroxetine group, psychiatric profiles prior to study drug exposure were similar across treatment groups. Between 20% and 26% of patients in any treatment group discontinued prematurely from study treatment. Adverse event, subject request, and lack of efficacy were the most documented reasons for discontinuation.

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: -11.42 points for placebo group, -13.71 points for paroxetine alone group, -14.29 points for saredutant 30 mg + paroxetine group, and -13.88 points for saredutant 100 mg + paroxetine group.

The difference between the paroxetine alone and placebo groups was significant (LS-Mean difference = -2.29, p-value = 0.0028), thereby demonstrating assay sensitivity of active treatment versus placebo. The results of the supportive ANCOVA-LOCF analysis were consistent with the MMRM primary analysis for co-primary endpoints.

On average, patients in all treatment groups showed improvement in sexual function (positive change from baseline); improvement was greatest in the placebo group. There were no differences between the saredutant 100 mg + paroxetine, saredutant 30 mg + paroxetine, and paroxetine alone groups and between paroxetine alone and the placebo groups based on the raw assessment of p-values.

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: CGI Severity of Illness score, HAM-D depressed mood item score, and HAM-D treatment responders.

Safety results:

Overall incidences in the active treatment groups (saredutant 100 mg + paroxetine, saredutant 30 mg + paroxetine and paroxetine alone) were similar, and greater than in the placebo group. Nausea and headache were the most frequently reported AEs; incidences of nausea were greater in all active treatment groups than in the placebo group. Of note, nervous system event rates were higher in non-placebo groups mainly due to higher reports of somnolence. In addition, incidences in gastrointestinal disorders were higher in non-placebo groups due to appreciably higher cases of nausea. Two patients in each active treatment group had ALT values > 3xULN. Maximum values were all < 5xULN and not associated with total bilirubin values > 2xULN.

No patient treated with saredutant 100 mg + paroxetine or saredutant 30 mg + paroxetine had QTcF value > 500 msec or an increase from baseline in QTcF value > 60 msec. Four patients treated with saredutant 30 mg + paroxetine and 2 patients treated with saredutant 100mg + paroxetine had prolonged QTcF values. Of the 6 patients who had prolonged QTcF values, 4 were females (maximum value 476 msec) and 2 were males (maximum value 452 msec). Two patients (1 male, 1 female) had prolonged values at baseline and values in 4 patients (2 males, 2 females) were no longer prolonged at final visit.

Two patients had suicidal ideation in saredutant 30 mg + paroxetine group. There were no patient deaths during the study.

Because of early discontinuation of the study no analysis was done on pharmacokinetic data for the purpose of this study.

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