STUDY SYNOPSIS

Title of the study: An Eight-Week, Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled Study, with Escitalopram as an Active Control, to Evaluate the Efficacy, Safety and Tolerability of a Saredutant 100 mg Dose Once Daily, in Elderly Patients with Major Depressive Disorder (EFC5574)

Investigator(s): Multicenter

Study center(s): Multiple centers in Croatia, Czech Republic, France, Mexico, Russia, Sweden, Turkey, USA

Publications (reference): Not applicable

Study period*:*
Date first patient enrolled: 18-Dec-2006
Date last patient completed: 12-Feb-2008

Phase of development*:* 3

Objectives:
Primary: To evaluate the efficacy of saredutant 100 mg once daily (OD) compared to placebo with escitalopram as an active control, in elderly patients with major depressive disorder (MDD), as assessed by a change from baseline to Visit 6 (Day 56) in the 17-item Hamilton Depression Rating Scale (HAM-D) total score

Secondary:
- To evaluate the tolerability and safety of saredutant in elderly patients with MDD
- To evaluate the efficacy of saredutant compared to placebo on disability and quality of life in patients with MDD
- To evaluate plasma concentrations of saredutant and SR49596 (inactive metabolite)
- To evaluate the safety and tolerability of 24 weeks of additional treatment with saredutant in patients completing the initial 8-week treatment period

Methodology: Multicenter, randomized, parallel-group, double-blind, placebo-controlled study

Number of patients: Planned - 375; Randomized - 393; Treated - 391
Evaluated: Efficacy - 387; Safety - 391; Pharmacokinetics - 374

Diagnosis and criteria:
Inclusion criteria*:*
- Male or female patients
- At least 60 years of age
- Diagnosis of MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria and confirmed by the Mini International Neuropsychiatric Interview

Exclusion criteria*:*
- Total score $\leq$22 on the Montgomery-Asberg Depression Rating Scale (MADRS)
- HAM-D total score $\leq$16
- Mini-Mental State Examination (MMSE) score ≤22

Investigational product: Saredutant (SR48968C) capsules
Dose: 100 mg OD with food
Administration: Oral
Batch number(s): [redacted]

Duration of treatment*:*
- Acute phase: 8 weeks
- Extension phase: 24 weeks

Patients on placebo in the Acute Phase were switched to saredutant in the Extension Phase; patients on saredutant and escitalopram remained on the same treatment in the Extension Phase.

Duration of observation*:*
34 weeks (including a 1-week single-blind placebo period, an 8-week double-blind treatment, a 24-week double-blind extension of treatment period, and a 1-week poststudy/follow-up phase)

Reference therapy*:* Escitalopram capsules
Dose: 10 mg OD with food
Administration: Oral
Batch number(s): [redacted]

Reference therapy*:* Placebo capsules
Dose: One capsule OD with food
Administration: Oral
Batch number(s): [redacted]

Criteria for evaluation:
Efficacy:
Primary: The change from baseline to Visit 6 (Day 56) in the 17-item HAM-D total score

Key Secondary:
- The change from baseline in the Clinical Global Impression (CGI) Severity of Illness score to Visit 6 (Day 56)
- The change from baseline in the HAM-D depressed mood item score to Visit 6 (Day 56)
- The change from baseline in the MADRS total score to Visit 6 (Day 56)

Safety: Safety was assessed through evaluation of the following:
- Physical examinations
- Vital signs (including weight)
- Spontaneously-reported adverse events
- 12-lead electrocardiogram (ECG)
- Clinical laboratories
- MMSE

Pharmacokinetics: Plasma levels of saredutant (SR48968) and the metabolite SR49596.

Pharmacokinetic sampling times and bioanalytical methods*:* Blood samples to assess both plasma saredutant and SR49596 concentrations were drawn immediately after ECG evaluation, 2 to 4 hours after saredutant administration (C_{max} for both compounds) on Day 14±3 (Visit 4) and Day 56±3 (Visit 6) or at the occurrence of a serious adverse event (SAE), overdose, confirmed QT interval corrected by the Bazett's formula (QTcB) ≥500 ms, or premature discontinuation.

Both plasma saredutant and SR49596 concentrations were assayed using a validated liquid chromatography with tandem mass spectrometry method (DOH0374) and a limit of quantification of 0.500 ng/mL for both compounds.

Statistical methods*:*
Primary efficacy analysis: The change from baseline to Day 56 in the HAM-D total score was assessed by a mixed-effect model for repeated measurements (MMRM) under the missing at random framework, with fixed terms for treatment, visit, treatment-by-visit interaction. The centered baseline score and centered baseline score-by-visit interaction were also included in the model as continuous fixed covariates. The difference between saredutant and placebo groups at Day 56 was estimated using the baseline-adjusted least-squares means computed within the mixed-model framework. Statistical significance of saredutant versus placebo (primary efficacy comparison) and escitalopram versus placebo (assay sensitivity) was based on the Student's t-test.

Supportive analysis: An analysis of covariance with the missing data imputed by carrying the last observation forward (ANCOVA-LOCF) approach was performed on the primary efficacy variable. The last available observation of change from baseline in HAM-D total score for a patient during the Acute Phase was modeled with factors for treatment (saredutant 100 mg, escitalopram 10 mg, and placebo) and centered baseline as covariate. Estimates of differences between saredutant 100 mg versus placebo (and escitalopram 10 mg versus placebo) were calculated along with the associated 95% confidence intervals (CIs) and p-values. In an exploratory manner, an ANCOVA-observed cases approach was also performed.

Pharmacokinetics: Saredutant and SR49596 individual plasma concentrations for the safety population, assessed from blood samples drawn on Day 14 ± 3 and Day 56 ± 3 (Visits 4 and 6, respectively) within 2 to 4 hours post dose interval, were summarized by descriptive statistics, separately for each visit. Descriptive statistics were also provided for the age subgroups (<65, 65-74, ≥75) since there was a significant influence of age on concentrations.

Statistical methods (continued)*:*

Pharmacokinetic/pharmacodynamic (PK/PKD) relationship:

Populations analyzed were as follows: For pharmacokinetic/pharmacodynamic (PK/PD)-efficacy - ITT population for whom PK sampling was done within 2-4 hrs after dosing at Visit 6 (D56+/-3); for PK/PD-ECG: safety population for whom PK sampling was done within 2-4 hrs after dosing at Visit 4 & Visit 6 and after ECG measurement.

PK/PD analyses of efficacy and ECG parameters

The relationship between saredutant C_{max}, and HAM-D total score and CGI-S score change from baseline to Day 56 were explored by a linear regression model. Relationships between saredutant/SR49596 C_{max} and safety PD endpoints (QTcF, QTcB, and heart rate) were explored across visits (4 and 6) using a mixed-effect model with repeated measures. For each PD endpoint, the regression coefficient, 95% CI and the p-value were derived from the model, and were used as relevant measures to evaluate the significance of the PK/PD relationship. In addition, analysis of the relationship between saredutant Cmax and the HAM-D treatment responder status was investigated using a t-test.

PK/PD analyses were also done separately on each age subgroup (<65, 65-74, $\geq$ 75), since there was a significant influence of age on plasma concentrations.

Safety: Safety and tolerability were assessed by review of individual values and descriptive statistics. Adverse events were coded using the Medical Dictionary of Regulatory Activities (Version 10.1) and were classified according to chronological criteria. Treatment-emergent adverse events (TEAEs) were listed and summarized using counts and percents. Abnormalities of hematology and biochemistry parameters, and vital signs in supine position, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria.

Summary:

Patient disposition, demographics and baseline characteristics:

A total of 393 patients were randomized into the Acute Phase of the study; 391 were exposed to the double-blind investigational product (IP). All exposed patients received the treatment to which they were randomized.

Of the randomized patients, 60 (15.3%) patients withdrew from study treatment in the Acute Phase. The most common reasons for discontinuation were adverse event (5.6%), lack of efficacy (4.6%), or subject's request (3.6%). The proportions of patients who prematurely withdrew from the study were comparable between the escitalopram 10 mg and the placebo groups (17.3% and 16.1%, respectively), while the withdrawal rate in the saredutant 100 mg group was lower (13.5%).

Baseline demographic characteristics [gender, race, age, weight, creatinine clearance and body mass index] were similar across groups for the randomized population. The patients in the study comprised of mostly females (73.3%), and the median age was 68 years. The majority of the patients were Caucasian (79.6%).

The safety population was similar across treatment groups for most aspects of baseline psychiatric history, with a mean of 3.70 prior episodes of depression and a mean of 6.29 months for the current major depressive episode duration. The proportion of patient with previous suicide attempts was higher in the saredutant group, compared to other groups. No relevant differences between groups were found in psychiatric characteristics at baseline; the mean HAM-D total score at baseline was 22.89 points.

Efficacy results:

For the primary endpoint (change from baseline to Day 56 in HAM-D total score) no statistically significant improvement was seen in either treatment group compared to placebo based on the primary analysis (MMRM) and the secondary analysis (LOCF-ANCOVA). The difference between escitalopram 10 mg and placebo was also not statistically significant (-1.00 points; p-value = 0.2940; however the interpretation of this p-value should take into account the unbalanced nature of the randomization between placebo and escitalopram treatment groups).

With regards to the key secondary variables, for CGI-S score and the MADRS total score, neither treatment group showed a significant improvement compared to placebo. For the HAM-D depressed mood item score, the saredutant group showed no significant improvement compared to placebo, whereas the escitalopram group showed a significant improvement based on both MMRM analysis (0.31 points, p = 0.0363) and ANCOVA-LOCF analysis (0.30 points, p = 0.0389).

Summary (continued):

***Safety results**:*

Mean treatment duration was similar among treatment groups, and the median treatment duration (56 days) was identical. Cumulative exposure was 20.7 patient years, 23.4 patient years, and 11.2 patient years, for the placebo, saredutant 100 mg, and escitalopram 10 mg groups, respectively.

The percentage of patients with at least 1 TEAE was greater in the escitalopram 10 mg group (55.0%) than in the placebo (50.7%), or saredutant 100 mg (42.9%) groups. Overall, 7 patients experienced TESAEs (2 patients in the placebo group, 2 in the saredutant 100 mg group, and 3 in the escitalopram 10 mg group). There were no fatal outcomes. The proportion of patients who had a TEAE that led to study treatment discontinuation was higher in the escitalopram 10 mg group (10.0%) than in the placebo (4.7%) or saredutant 100 mg (4.3%) groups.

	Placebo (N=148)	Saredutant 100 mg (N=163)	Escitalopram 10 mg (N=80)
Patients with any TEAE (including TESAEs)	75 (50.7%)	70 (42.9%)	44 (55.0%)
Patients with any serious TEAE	2 (1.4%)	2 (1.2%)	3 (3.8%)
Patients with any TEAE leading to Death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	7 (4.7%)	7 (4.3%)	8 (10.0%)

n (%) = number and percentage of patients with at least one TEAE.
TEAE: Treatment emergent adverse events.

The only TEAE by preferred term occurring at an incidence $\geq$ 5% in the saredutant 100 mg group and with a greater incidence than in the placebo group was headache: saredutant 100 mg, 6.1%; escitalopram 10 mg, 6.3% and placebo, 5.4%. In the saredutant group, 3.7% of the cases of headache were mild, 1.6% were moderate and 0.6% (one case) were severe in intensity.

No cases of suicidal ideation, suicide attempt or completed suicide were reported.

The incidence of TEAEs related to sexual dysfunction was comparable in the escitalopram (1.3%) and the saredutant (1.2%) groups (0% for the placebo group).

The incidence of cardiac TEAEs was low and was comparable between the saredutant and placebo groups (3.1% vs. 2.7%, respectively). No cardiac TEAEs were seen in the escitalopram group.

The incidence of hepatobiliary TEAEs was low and comparable across groups (saredutant, 0.6% [one case of aspartate transaminase, AST, increased considered not related to IP], placebo, 1.4% and escitalopram, 1.3%).

Mean vital signs and laboratory parameters were comparable for both treatment groups and did not indicate any clinically relevant trends over time.

The proportion of patients with ALT, AST, and total bilirubin PCSAs was low overall and similar across treatment groups. No patient had alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN).

Mean change from baseline at Day 56 for QTcF was –2.7 ms for saredutant vs. –0.8 ms for placebo and –0.4 for escitalopram. No patient in any group had QTcF values ≥ 500 ms during the Acute Phase. The incidence of prolonged QTcF (females, >470 ms; males >450 ms) was 5.1% in the saredutant 100 mg group, 2.6% in the escitalopram group and 1.4% in the placebo group. One patient in the saredutant group (0.6%) had QTcF increased from baseline >60 ms, and one patient in the escitalopram group (1.3%) had QTcF increased from baseline >60 ms.

There were no significant differences between saredutant and placebo in QTcF adjusted by age or by baseline creatinine clearance.

No significant changes from baseline were seen in the MMSE total score in any of the treatment groups.

Summary (continued):

Pharmacokinetic results:

Saredutant and SR49596 C_{max} were similar over Days 14 and 56 suggesting that steady conditions were reached by Day 14 for both compounds.

Exploratory PK/PD analysis failed to demonstrate a significant relationship between saredutant C_{max} and efficacy endpoints. However, there was a positive correlation between QTcF change from baseline and saredutant and SR49596 C_{max}.

When analyzed by age subgroup a significant positive correlation was seen only between SR49596 C_{max} and the increase from baseline in QTcF only in the ≥ 75 years subgroup.

Conclusions:

[redacted]

Date of report: 18-Aug-2008