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 Patients with Generalized Anxiety Disorder (EFC5583)

Investigator(s): Multicenter

Study center(s): 40 centers in Belgium, Canada, Finland, France, Italy, Sweden, and Turkey

Publications (reference): None

Study period:
Date first patient enrolled: 04 December 2006
Date last patient completed: 01 April 2008

Phase of development: Phase 3

Objectives:

Primary:

- To evaluate the efficacy of saredutant 100 mg once daily (OD) compared to placebo with escitalopram as an active control, in patients with generalized anxiety disorder (GAD), as assessed by a change from baseline to Visit 7 (Day 56) in the 14-item Hamilton Anxiety Rating Scale (HAM-A) total score

Secondary:

- To evaluate the tolerability and safety of saredutant in patients with GAD
- To evaluate the efficacy of saredutant compared to placebo on disability and quality of life in patients with GAD
- To evaluate plasma concentrations of saredutant and SR49596 (inactive metabolite)

Methodology: Multinational, multicenter, randomized, parallel-group, double-blind study, comparing 1 fixed dose of saredutant 100 mg OD to placebo, using escitalopram 10 mg OD as an active control

Number of patients: Planned: 360 patients (120 patients/group); Randomized: 365; Treated: 361
Evaluated: Efficacy: 357; Safety: 361; Pharmacokinetics: 343

Diagnosis and criteria for inclusion:

Inclusion criteria:

- Male or female
- At least 18 years of age
- Diagnosis of GAD as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision criteria and confirmed by the Mini International Neuropsychiatric Interview Plus GAD module

Exclusion criteria:

- Minimum total score of less than 22 (<22) on the 14-item HAM-A
- Total score of 18 or higher (≥18) on the Montgomery-Asberg Depression Rating Scale (MADRS)

Investigational product: Saredutant (SR48968C)
Dose: 100 mg OD
Administration: Oral capsule, fed conditions
Batch number(s): [redacted]

Duration of treatment: 9 weeks, including 1 week of placebo treatment and 8 weeks of double-blind treatment
Duration of observation: (a) Screening Phase: 1-week, placebo, single-blind treatment period
(b) Acute Phase: 8-week, double-blind treatment period
(c) Post-study Phase: 1-week, drug-free, follow-up period
All phases: 10 weeks

Reference therapy: Escitalopram
Dose: 10 mg OD
Administration: Oral capsule, fed conditions
Batch number(s): [redacted]

Reference therapy: placebo
Dose: Placebo OD
Administration: Oral capsule, fed conditions
Batch number(s): [redacted]

Criteria for evaluation:

Efficacy:

Primary endpoint: The primary efficacy endpoint was the change from baseline to Visit 7 (Day 56) in the 14-item HAM-A total score.

Secondary endpoints:

The key secondary efficacy endpoint was the change from baseline to Visit 7 (Day 56) in the Clinical Global Impression-Severity of Illness (CGI-S) score.

The other secondary efficacy endpoints were:

- Changes from baseline in the HAM-A factor scores (psychic and somatic anxiety) and item scores (anxious mood and tension) at Visit 7 (Day 56)
- Clinical Global Impression-Improvement (CGI-I) score at Visit 7 (Day 56)
- Percentage of patients demonstrating a treatment response defined as a reduction of at least 50% in the HAM-A total score between baseline and Visit 7 (Day 56)
- Percentage of patients demonstrating a sustained treatment response defined as a reduction of at least 30% in the HAM-A total score between baseline and Visit 3 (Day 7) or Visit 4 (Day 14) that is maintained to Visit 7 (Day 56)
- Percentage of patients demonstrating clinical remission defined as a HAM-A total score of <8 at Visit 7 (Day 56)
- Percentage of patients with clinical remission defined as a CGI-I score of 1 (very much improved) at Visit 7 (Day 56)
- Change from baseline in the MADRS total score at Visit 7 (Day 56)
- Change from baseline in the Patient Health Questionnaire (PHQ-15) total score at Visit 7 (Day 56)
- Change from baseline in the Sheehan Disability Scale (SDS) total score at Visit 7 (Day 56)
- Change from baseline in the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) total score at Visit 7 (Day 56)
- Change from baseline in the Q-LES-Q-SF item 15 (satisfaction with medication) and item 16 (overall life satisfaction and contentment during the past week) scores at Visit 7 (Day 56)
- Change from baseline in the Endicott Work Productivity Scale (EWPS) total score at Visit 7 (Day 56)
- Percentage of patients who improved (score of 1 or 2), were unchanged (score of 3, 4, or 5), or worsened (score of 6 or 7) on the CGI-I score at Visit 7 (Day 56)
- Shift from baseline in PHQ-15 somatic symptom severity at Visit 7 (Day 56)

Safety: Safety was assessed through evaluation of the following:

- Adverse event (AE) reporting
- Standard clinical laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)
- Physical examinations
- Physician Withdrawal Checklist (PWC)
- Changes in Sexual Functioning Questionnaire (CSFQ)

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

Pharmacokinetic sampling times and bioanalytical methods:

Sampling times: Blood samples to assess both plasma saredutant and SR49596 concentrations were to be drawn immediately (within 20 minutes) after ECG evaluations, 2 to 4 hours after saredutant administration (maximal concentration [C_{max}] for both compounds) on Day 14±3 (Visit 4) and Day 56±3 (Visit 7) or at the occurrence of a serious adverse event (SAE), overdose, confirmed QTcB ≥ 500 ms, or premature discontinuation.

Assays for both saredutant and SR49596: Both plasma saredutant and SR49596 concentrations were assayed using a validated liquid chromatography with tandem mass spectrometry method (DOH0374) and a limit of quantification (LOQ) of 0.5 ng/mL for both compounds. Plasma concentrations below LOQ were set to LOQ/2 (ie, 0.25 ng/mL) for patients in the saredutant 100-mg group. Escitalopram was not assayed in this study.

Statistical methods:

Primary efficacy analysis: Saredutant effect on the HAM-A change from baseline to Visit 7 (Day 56) was assessed by a mixed-effect model for repeated measurements (MMRM) under the missing at random framework, with fixed terms for treatment, visit, and treatment-by-visit interaction, and modeling the random effects for patients as part of the within-patient error correlation structure. 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 Visit 7 (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. As a supportive analysis, change from baseline in HAM-A total score was also analyzed using an analysis of covariance (ANCOVA) model with fixed term for treatment and centered baseline HAM-A total score as covariate on the last available observation (LOCF, ie, last observation carried forward).

Pharmacokinetics: Individual saredutant and SR49596 C_{max} observed on Day 14±3 and Day 56±3 (Visits 4 and 7, respectively) were summarized by standard descriptive statistics, separately for each visit.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship: The relationship between saredutant C_{max}, and HAM-A 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 [HR]) were explored across visits (4 and 7) using a random coefficients regression model. For each PD endpoint, the regression coefficient, 95% confidence interval, 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 C_{max} and the HAM-A treatment responder status was investigated using a t-test.

Safety: Safety and tolerability was assessed by the 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, vital signs, and ECG parameters were assessed using potentially clinically significant abnormality criteria, and were tabulated by counts and percents.

Summary:

Patient disposition, demography, and history: Of the 365 randomized patients, 55 (15.1%) patients withdrew from study treatment: 17 (13.5%) from the placebo group, 18 (14.4%) from the saredutant 100 mg group, and 20 (17.5%) from the escitalopram 10 mg group. The majority of these withdrawals were due to lack of efficacy and AEs. Withdrawals due to lack of efficacy were similar in the placebo and escitalopram 10 mg groups (5.6% and 5.3%, respectively) and lower in the saredutant 100 mg group (4.0%). Withdrawals due to AEs were higher in the escitalopram 10 mg and saredutant 100 mg groups (7.9% and 5.6%, respectively) compared to the placebo group (3.2%).

Baseline demographic characteristics (gender, race, age, weight, and body mass index) were similar across treatment groups for the randomized population. The mean age was 41.6 years, and 66.0% were female. The study population was primarily Caucasian (98.1%).

Summary (continued):

Patient disposition, demography, and history (continued):

In terms of baseline psychiatric history, the mean duration of current episode was 21.5 months across all treatment groups in the randomized population, with a shorter duration in the saredutant 100 mg group (18.7 months) compared to the escitalopram 10 mg (21.4 months) and placebo (24.5 months) treatment groups. The mean age at onset of first treatment was 35.7 years across all treatment groups.

The mean HAM-A total score at baseline was similar across treatment groups (27.8 points for placebo, 28.0 points for the saredutant 100 mg group, and 28.5 points for the escitalopram 10 mg group). No relevant differences between groups were found in psychiatric characteristics at baseline.

Primary efficacy results: Analysis of the primary efficacy endpoint (change from baseline to Day 56 in HAM-A total score) did not show a statistically significant difference between the saredutant 100 mg and placebo groups according to the prespecified primary analysis (MMRM). A statistically significant greater reduction was observed in the escitalopram 10 mg group compared to placebo, confirming the assay sensitivity of the trial. Supportive analysis based on ANCOVA-LOCF did not show statistically significant differences for either the saredutant 100 mg or escitalopram 10 mg groups versus placebo.

Key secondary efficacy results: Analysis of the key secondary efficacy endpoint (change from baseline to Visit 7 [Day 56] in CGI-S score), did not show a statistical difference between saredutant and placebo, and escitalopram showed a statistical improvement based only on the MMRM analysis.

Significant differences between the saredutant 100 mg and placebo groups were not observed with any of the other secondary endpoints. Escitalopram showed significant improvements for a number of the other secondary endpoints including HAM-A factor (psychic anxiety) and item (anxious mood and tension) scores, CGI-I scores, MADRS scores, Q-LES-Q-SF scores, EWPS scores, and clinical remission based on CGI-I scores.

Safety results: Mean treatment duration was similar among treatment groups, and the median treatment duration (56 days) was identical. The cumulative exposure was 17.7, 17.6, and 15.2 patient years for the placebo, saredutant 100 mg, and escitalopram 10 mg groups, respectively.

The percentage of patients with at least 1 TEAE was highest in the escitalopram 10 mg group (71.7%), followed by the saredutant 100 mg group (64.5%) and the placebo group (55.6%). Overall, 2 patients experienced treatment-emergent serious adverse events (TESAEs) (1 in the saredutant 100 mg group, and 1 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 (9.7%) than in the placebo (3.2%) or saredutant 100 mg (7.3%) groups.

	Placebo (N=124)	Saredutant 100 mg (N=124)	Escitalopram 10 mg (N=113)
Patients with any TEAE (including TESAEs)	69 (55.6%)	80 (64.5%)	81 (71.7%)
Patients with any serious TEAE	0	1 (0.8%)	1 (0.9%)
All deaths	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	4 (3.2%)	9 (7.3%)	11 (9.7%)

Headache was the most frequently reported TEAE. Dry mouth was the only TEAEs reported in ≥5% of patients in the saredutant 100 mg group, and with a greater incidence than in the placebo group. Of those saredutant patients with dry mouth TEAEs, 8 cases were mild and 1 case was moderate. Nausea was most prominent in the escitalopram 10 mg group. The incidence of cardiovascular TEAEs was low and was highest in the placebo group. There were 5 hepatobiliary TEAEs reported in 4 patients in the saredutant 100 mg group. The proportion of patients with TEAEs related to sexual dysfunction was highest in the escitalopram 10 mg group.

One saredutant patient experienced an alanine aminotransferase (ALT) value ≥3 times the upper limit of the normal range (ULN) which was reported as serious. The maximum value was 10.02 ULN, and was not associated with total bilirubin ≥2 ULN. This patient also had elevated aspartate aminotransferase (AST) values (maximum of 6.78 ULN), and borderline alkaline phosphatase (ALP) (1.02 ULN) and gamma glutamyl transpeptidase (GGT) (1.18 ULN) values.

Summary (continued):

Safety results (continued):

No saredutant-treated patients experienced a prolonged QTcF value (females: >470 ms; males: >450 ms) or an increase from baseline >60 ms. Treatment with saredutant was associated with a 2.6 beats per minute mean increase in HR and a small mean decrease in QTcF (-3.3 msec).

Assessment of the PWC total score showed that patients who withdrew from escitalopram 10 mg had a worsening of symptoms while small changes were noted in the placebo and saredutant 100 mg groups.

In the CSFQ analysis, an improvement in sexual functioning (a greater positive score) was observed in the saredutant 100 mg group, and a worsening in sexual functioning was observed in the escitalopram 10 mg group, although none of these changes were significantly different from placebo.

Pharmacokinetic results: Saredutant C_{max} on Days 14 and 56 were similar (mean, coefficient of variation: 35.9 [75] and 38.8 [88] ng/mL, respectively), and those of the metabolite, SR49596, were also comparable (5.29 [86] and 5.10 [92] ng/mL on Days 14 and 56, respectively), suggesting that steady state was reached within 2 weeks for both compounds.

Pharmacokinetic/Pharmacodynamic relationship results: No statistically significant relationship (estimates of slopes not significantly different from zero, p>0.05) was found between changes in efficacy scores and saredutant C_{max}. No difference in saredutant C_{max} was observed between HAM-A treatment responder and nonresponder groups. No statistically significant relationship between QTcF and HR changes from baseline and saredutant or SR49596 C_{max} was observed.

Conclusions:

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Date of report: 19-Sep-2008