SYNOPSIS

Name of company:	sanofi-aventis
Name of finished product:	
Name of active substance(s):	Saredutant (SR48968)
Title of the study:	An Eight-Week, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety and Tolerability of One Fixed 100 mg Dose of Saredutant in Patients with Major Depressive Disorder
Investigator:	Multicenter
Study centers:	Centers in Canada, Chile, Croatia, Czech Republic, France, Germany, Mexico, and Portugal
Publications (reference):	None
Study period:	
Date first patient enrolled:	15 December 2004
Date last patient completed:	Segment B - 18 March 2006 Segment C - 26 December 2006
Phase of development:	3

Objectives:

Primary:

To evaluate the efficacy of a 100 mg fixed dose of saredutant compared to placebo in patients with major depressive disorder (MDD)

Secondary:

- To evaluate the tolerability and safety of saredutant in 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 and explore their relationships to efficacy and safety outcomes
- To evaluate the safety and tolerability of 44 weeks of additional treatment with saredutant in patients completing the initial 8-week treatment period (this will be addressed in a separate report).

Methodology:

Randomized, parallel-group, double-blind study comparing 1 fixed dose of saredutant (100 mg/day) and paroxetine (20 mg/day) with placebo

Number of patients:

Planned: 450; Randomized: 465; Treated: 464

Evaluated:

Efficacy: 461; Safety: 464; Pharmacokinetics: 450

Diagnosis and criteria for inclusion:

- Male or female patients
- 18 to 64 years of age
- Diagnosis of MDD recurrent episode as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria
- Minimum total score of 22 on the Montgomery-Asberg Depression Rating Scale (MADRS)

Investigational product:	Saredutant (SR48968C)
Dose:	100 mg once daily
Administration:	Oral capsule
Batch numbers:	Segment B: [redacted] Segment C:
Duration of treatment:	Segment A: 1 week single-blind placebo run-in period Segment B: 8 weeks double-blind period Segment C: 44 weeks double-blind extension-of-treatment period
Duration of observation:	54 weeks for periods A-C and a 1 week post treatment follow-up period

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Reference therapy:	Placebo
Dose:	One capsule once daily
Administration:	Oral capsule
Batch numbers:	Segment B: [redacted]
Reference therapy:	Paroxetine
Dose:	20 mg once daily
Administration:	Oral capsule
Batch numbers:	Segment B: [redacted]
	Segment C:

Criteria for evaluation:

Efficacy:

Primary criterion: The primary efficacy criterion was 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.

Secondary criteria:

The 4 key secondary efficacy parameters were as follows:

- Change from baseline in the Clinical Global Impression- Severity of Illness (CGI-S) score at Visit 7 (Day 56)
- Change from baseline in the HAM-D depressed mood item score (Item 1) at Visit 7 (Day 56)
- Change from baseline in the MADRS total score at Visit 7 (Day 56)

Proportion of patients with HAM-D treatment response, defined as a reduction of at least 50% in the HAM-D total score between baseline and the last available visit assessment

Safety:

- Physical examinations
- Vital signs (including weight)
- Spontaneously reported adverse events (AEs)
- 12-lead electrocardiograms (ECG)
- Clinical laboratories
- Changes in Sexual Functioning Questionnaire (CSFQ)
- Physician Withdrawal Checklist (results are presented in the extension period study report only)

Pharmacokinetics:

Plasma levels of saredutant (SR48968) and the metabolite SR49596

Pharmacokinetic sampling times and bioanalytical methods:

Sampling times

Blood samples to assess both saredutant and SR49596 plasma concentrations were to be drawn immediately after ECG evaluation performed within 2 to 4 hours after saredutant administration at Visit 4 (Day 14±3) and Visit 7 (Day 56±3) during Segment B and at Visit 8 (Day 84±3), Visit 13 (Day 224±3), and Visit 18 (Day 364±3) during Segment C, or in the occurrence of serious adverse event (SAE), overdose, confirmed QTcB ≥500 ms, or premature discontinuation.

Assays for both saredutant and SR49596

Both saredutant and SR49596 plasma concentrations were assayed using a validated liquid chromatography with tandem mass spectrometry method (DOH0511) and a limit of quantification of 0.5 ng/mL for both compounds. Paroxetine was not assayed in this study.

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Statistical methods:

Primary efficacy analysis:

Saredutant effect on the HAM-D change from baseline to 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 a random term for patient. 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 paroxetine versus placebo (assay sensitivity) was based on the Student's t-test. As a supportive analysis, change from baseline in HAM-D total score was also analyzed using an analysis of covariance (ANCOVA) model with fixed term for treatment and centered baseline HAM-D total score as covariate on the last available observation (LOCF, ie, last observation carried forward).

Pharmacokinetics:

Descriptive statistics on plasma concentrations:

- 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 7, respectively) within 2 to 4 hours post dose interval, were summarized by descriptive statistics, separately for each visit.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship:

PK/PD analyses of efficacy parameters

The relationship between saredutant plasma concentrations and efficacy pharmacodynamic (PD) endpoints (ie, HAM-D total score, CGI-S score, HAM-D depressed mood item score, MADRS total score) change from baseline to Day 56 were explored by a linear 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. Graphical presentations of the individual PD variable versus plasma concentrations were provided. In addition, analysis of the relationship between saredutant plasma concentrations and the HAM-D treatment responder status to Day 56 were investigated using a t-test.

PK/PD analyses of safety parameters

Relationships between saredutant/SR49596 plasma concentrations and safety PD endpoints (QTcF, QTcB, and heart rate [HR]) measured on Day 14 and Day 56 were explored using a random coefficients regression model.

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 8.1) 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 in supine position, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria.

Summary:

Disposition, demography, and history:

Of the 465 patients who were randomized to a treatment, 464 were treated, 392 patients (84.3%) completed the Segment B study treatment period, and 73 patients (15.7%) discontinued prematurely from study treatment. The most common reasons for discontinuation were investigator or patient request, disease progression/lack of efficacy, and AEs. The proportion of patients who prematurely withdrew from the study was comparable between the saredutant 100 mg and paroxetine 20 mg groups (13.7% and 15.6%, respectively), while the withdrawal rate in the placebo group was higher (18.0%). The percentage of discontinuation due to lack of efficacy was also comparable between the saredutant 100 mg and paroxetine 20 mg groups (3.1% and 2.6%, respectively). The incidence of discontinuation due to an AE was lower in the saredutant 100 mg group (2.5%) than in the paroxetine 20 mg group (4.5%) and the placebo group (4.0%).

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Summary (continued):

Disposition, demography, and history (continued):

The baseline demographic characteristics were similar across groups for the randomized population. The majority of the patients in the study were females (73.1%), of Caucasian or Hispanic heritage (67.5% and 30.5%, respectively), and between 18 and 49 years of age (71.0%).

The safety population was homogeneous for baseline psychiatric history, with a mean of 2.6 prior episodes of MDD and a mean of 4.9 months for the current major depressive episode duration.

The mean HAM-D total score at baseline was 21.7, 22.4, and 21.9 points for the placebo, saredutant 100 mg, and paroxetine 20 mg groups, respectively. No relevant differences between groups were found in psychiatric characteristics at baseline.

Efficacy results:

Primary efficacy results

Based on the MMRM analysis, the improvement from baseline to Day 56 in HAM-D total score was not statistically significant for saredutant-treated patients compared to placebo-treated patients (p = 0.1084).

Based on ANCOVA-LOCF analysis, the improvement from baseline to Day 56 in HAM-D total score was statistically significant for saredutant-treated patients compared to placebo-treated patients (p = 0.0493).

Paroxetine-treated patients had no statistically significant improvement from baseline to Day 56 in HAM-D total score compared to placebo-treated patients based on MMRM analysis (p = 0.0588). Based on ANCOVA-LOCF analysis, the difference between paroxetine-treated patients and placebo-treated patients in HAM-D total score was statistically significant (p = 0.0473).

Key secondary efficacy results

Saredutant-treated patients had no statistically significant improvement in any of the 4 key secondary efficacy endpoints compared to placebo-treated patients based on both MMRM and ANCOVA-LOCF analyses.

Paroxetine-treated patients had statistically significant improvements in 2 of the 4 key secondary efficacy endpoints (CGI Severity of Illness score and MADRS total score) compared to placebo-treated patients based on both MMRM and ANCOVA analyses. There were no statistically significant differences between paroxetine-treated and placebo-treated patients in HAM-D depressed mood item score and HAM-D treatment response.

Safety results:

Mean treatment duration was similar among treatment groups and the median treatment duration (56 days) was identical. The cumulative exposure was 20.8, 23.9, and 21.7 patient years for the placebo, saredutant 100 mg, and paroxetine 20 mg groups, respectively.

The percentage of patients with at least one TEAE was greatest in the paroxetine 20 mg group (69.9%) and comparable between the placebo (50.7%) and saredutant 100 mg (55.9%) groups. There were no fatal outcomes. A total of 6 patients experienced SAEs: 2 patients in the placebo group, 1 patient in the saredutant 100 mg group, and 3 patients in the paroxetine 20 mg group. The proportion of patients who experienced TEAE leading to discontinuation from the study was higher in the paroxetine 20 mg group (5.9%) and placebo groups (5.3%) than in the saredutant 100 mg (1.9%) group.

	Placebo (N=150)	Saredutant 100 mg (N=161)	Paroxetine 20 mg (N=153)
Patients with any TEAE (including TESAEs)	76 (50.7%)	90 (55.9%)	107 (69.9%)
Patients with any TESAE	2 (1.3%)	1 (0.6%)	3 (2.0%)
All Deaths	0	0	0
Patients permanently discontinuing treatment due to TEAE	8 (5.3%)	3 (1.9%)	9 (5.9%)

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Summary (continued):

Safety results (continued):

Treatment-emergent AEs occurring at an incidence ≥5% in the saredutant 100 mg group with a greater incidence than in the placebo group and presented by decreasing order of frequency in the saredutant 100 mg group were as follows:

- Dry mouth: placebo (6.0%), saredutant 100 mg (8.1%), and paroxetine 20 mg (10.5%)
- Back pain: placebo (1.3%), saredutant 100 mg (6.8%), and paroxetine 20 mg (2.0%)
- Dizziness: placebo (5.3%), saredutant 100 mg (6.2%), and paroxetine 20 mg (4.6%)

The majority of TEAEs were of moderate intensity. The intensity of dry mouth, back pain, and dizziness in the saredutant 100 mg group were as follows:

- Dry mouth: mild - 10 patients (6.2%); moderate - 3 patients (1.9%); severe - 0 patients (0.0%)
- Back pain: mild - 5 patients (3.1%); moderate - 4 patients (2.5%); severe -1 patient (1.2%)
- Dizziness: mild - 6 patients (3.7%); moderate - 4 patients (2.5%); severe - 0 patients (0.0%)

Suicide was attempted by 2 patients: 1 patient in the placebo group and 1 patient in the saredutant 100 mg group. Both suicide attempts were considered SAEs and the investigational product was discontinued; only the attempt in the saredutant 100 mg group was considered related to treatment.

The number of patients reporting sexual dysfunction TEAEs was the same in the paroxetine 20 mg group (3 patients, 2.0%) and the saredutant 100 mg group (3 patients, 1.9%). No patients in the placebo group reported sexual dysfunction TEAEs. There were no clinically relevant differences in laboratory parameters values and vital signs between treatment groups.

The proportion of patients with alanine transaminase (ALT), aspartate transaminase, and total bilirubin PCSAs was low overall and similar across treatment groups. Elevations of ALT were mild (<3 X upper limits of normal [ULN]) and asymptomatic. No patient had ALT ≥3 X ULN associated with total bilirubin ≥34 μmol/L (≥2 X ULN).

The incidence of patients with prolonged QTcF PCSAs was low and comparable across groups. None of the QTcF values were ≥500 ms or represented an increase of >60 ms from baseline. Five patients had prolonged QTcF intervals (male >450 ms or female >470 ms)—3 (1.9%) patients in the saredutant 100 mg group and 2 (1.4%) patients in the paroxetine 20 mg group. In the saredutant group, QTcF prolongation occurred in 3 male patients, all of whom had prolonged QTcF values at baseline. Saredutant treatment was associated with a slight decrease in mean heart rate. Mean changes from baseline for HR at the last visit were as follows: placebo (1.8 bpm), saredutant 100 mg (-0.3 bpm), paroxetine 20 mg (-0.6 bpm). Saredutant treatment was also associated with a small mean decrease in QTcF. Mean changes from baseline for QTcF at the last visit were as follows: placebo (0.6 ms), saredutant 100 mg (-0.3 ms), and paroxetine 20 mg (-0.3 ms).

Mean change from baseline in the total score for the CSFQ was greater in the saredutant 100 mg group than in the placebo and paroxetine 20 mg groups, indicating greater improvement with saredutant 100 mg. Across all subjects, the difference between saredutant and placebo was significant (p=0.048), with greater improvement seen in male patients (p=0.0305; saredutant versus placebo).

Pharmacokinetic results:

Plasma concentrations (ng/mL) of saredutant after 14-day (mean [coefficient of variation, CV%]: 36.1 [61]) and 56-day (mean [CV%]: 37.5 [63]) repeated once daily administration of saredutant were similar. Plasma concentrations (ng/mL) of SR49596 after 14-day (mean [CV%]: 5.25 [77]) and 56-day (mean [CV%]: 5.03 [67]) repeated once daily administration of saredutant were similar. These results suggest that steady state was reached on Day 14 for both compounds.

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Summary (continued):

Pharmacokinetic/pharmacodynamic 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 plasma concentrations.

No statistically significant relationship between QTcF changes from baseline and saredutant or SR49596 plasma concentrations was observed (estimates of slopes not significantly different from zero, p>0.05). A statistically significant relationship between the decrease from baseline in HR and saredutant (p=0.0252) or SR49596 (p=0.0486) plasma concentrations was observed.

Conclusions:

[redacted]

Date of report: 28-Jan-2008