SYNOPSIS

Name of company:	sanofi-aventis
Name of finished product:	
Name of active substance:	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
Investigators:	Multicenter
Study centers:	Canada, Chile, Croatia, Czech Republic, Estonia, Germany, Mexico, and Portugal
Publications (reference):	None
Study periods:	
Date first patient enrolled:	09 December 2004
Date last patient completed:	Segment B: 07 February 2006 Segment C: 29 December 2006
Phase of development:	3

Objectives:

Primary:

The primary objective of the study was to evaluate the efficacy of a 100 mg fixed dose of saredutant compared with placebo in patients with major depressive disorder (MDD).

Secondary:

The secondary objectives of the study were as follows:

Evaluate the tolerability and safety of saredutant in patients with MDD

Evaluate the efficacy of saredutant compared with placebo on disability and quality of life in patients with MDD

Evaluate plasma concentrations of saredutant and SR49596 and explore their relationships to efficacy and safety outcomes

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: 467
Treated: 466

Evaluated:

Efficacy: 462
Safety: 466
Pharmacokinetics: 452

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 (SR48968)

Dose: 100 mg once daily
Administration: Oral capsule
Batch number(s): Segment B: [redacted]
Segment C: [redacted]

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Duration of treatment: Segment B: 8 weeks
Segment C: 44 weeks

Duration of observation:
54 weeks, including a 1-week drug-free screening period, an 8-week double-blind treatment period, a 44-week double-blind extension-of-treatment period, and a 1-week post-treatment follow-up period

Reference therapy: Placebo
Dose: Placebo once daily
Administration: Oral capsule
Batch number(s): Segment B: [redacted]

Reference therapy: Paroxetine
Dose: 20 mg once daily
Administration: Oral capsule
Batch number(s): Segment B: [redacted]
Segment C: [redacted]

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:

Safety was assessed through evaluation of the following:

- Adverse events (AEs) reporting
- Standard clinical laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)
- Physical examinations
- 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 (LS) 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 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 D14 and D56 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.

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Summary:

Patient disposition, demography, and history:

Of the 467 randomized patients, 65 (13.9%) discontinued investigational product (IP) in Segment B; the most common reasons for discontinuation were disease progression/lack of efficacy (6.0%), Investigator/patient's request (3.0%) and AE (2.6%). The proportions of patients who prematurely withdrew from the study were comparable between the saredutant 100 mg and paroxetine 20 mg groups (15.2% and 16.2%, respectively), while the withdrawal rate in the placebo group was lower (10.3%). The percentage of discontinuation due to lack of efficacy was lower in the paroxetine group as compared with the percentages in the saredutant and placebo groups. The incidence of discontinuation due to an AE was higher in the paroxetine group than in the placebo and saredutant groups.

The baseline demographic characteristics (gender, race, age, weight, and body mass index) were similar across groups for the randomized population. The median age was 42 years and 74.1% were female. The study population was primarily Caucasian (55.7%) and Hispanic (44.1%).

The safety population was homogeneous for baseline psychiatric history, with a mean of 2.4 prior episodes and a mean of 5.8 months for the current major depressive episode duration.

The mean HAM-D total score at baseline was 21.6 points for each treatment group. No relevant differences between groups were found in psychiatric characteristics at baseline.

Primary efficacy results

Based on the primary analysis (MMRM), the improvement from baseline to Day 56 in HAM-D total score was statistically significant for saredutant-treated patients compared to placebo-treated patients ($p = 0.0161$).

The ANCOVA using LOCF produced similar statistically significant results ($p = 0.0327$) favoring saredutant-treated patients versus placebo-treated patients.

Paroxetine-treated patients also demonstrated a greater improvement on the HAM-D total score than placebo-treated patients. The differences were statistically significant based on both the MMRM ($p<0.0001$) and ANCOVA-LOCF analyses ($p<0.0001$).

Key secondary efficacy results

The differences between the saredutant and placebo groups were statistically significant in favor of saredutant according to analysis of the 4 key secondary endpoints using the stepdown procedures.

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Summary (continued):

A summary of the primary and key secondary efficacy results based on MMRM analysis is shown in the following table:

	Placebo (N=154)	Saredutant 100 mg (N=158)	Paroxetine 20 mg (N=150)
LS Mean change			
HAM-D total	-7.43	-9.09	-12.03
CGI-S	-1.13	-1.43	-1.86
HAM-D depressed mood item	-1.03	-1.27	-1.71
MADRS total	-10.89	-13.25	-16.83
HAM-D responders, n (%)	45 (29.2%)	65 (41.1%)	83 (56.1%)
P-values (vs. Placebo)			
HAM-D total	-	0.0161	<0.0001
CGI-S	-	0.0278	<0.0001
HAM-D depressed mood item	-	0.0308	<0.0001
MADRS total	-	0.0133	<0.0001
HAM-D responders*	-	0.0276	<0.0001

* Note: results are based on chi-square test

Safety results:

Mean treatment duration was similar among treatment groups, and the median treatment duration (56 days) was identical. The cumulative exposure was 22.3 patient years, 22.4 patient years, and 20.9 patient years, for the placebo, saredutant 100 mg, and paroxetine 20 mg groups, respectively.

The percentage of patients with at least 1 TEAE was greater in the paroxetine 20 mg group (68.6%) than in the placebo (58.7%), or saredutant 100 mg (57.0%) groups. Overall, 9 patients experienced a total of 9 treatment-emergent SAEs during the study (4 patients in the placebo group, 1 in the saredutant 100 mg group (myocardial ischemia assessed as not related to IP by the Investigator), and 4 in the paroxetine 20 mg group). There were no fatal outcomes. The proportion of patients who experienced TEAEs that led to study drug discontinuation was higher in the paroxetine 20 mg group (8.5%) than in the placebo (2.6%) or saredutant 100 mg (3.8%) groups.

	Placebo (N=155)	Saredutant 100 mg (N=158)	Paroxetine 20 mg (N=153)
Patients with any TEAE (including TESAEs)	91 (58.7%)	90 (57.0%)	105 (68.6%)
Patients with any TESAE	4 (2.6%)	1 (0.6%)	4 (2.6%)
All Deaths	0	0	0
Patients permanently discontinuing treatment due to TEAE	4 (2.6%)	6 (3.8%)	13 (8.5%)

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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:

- Headache: placebo (11.6%), saredutant 100 mg (15.2%), and paroxetine 20 mg (19.6%)
- Dry mouth: placebo (3.9%), saredutant 100 mg (7.0%), and paroxetine 20 mg (7.8%)

The majority of TEAEs were of mild or moderate intensity. In the saredutant 100 mg group, the intensity of TEAEs reported in ≥5% of patients and at a greater rate than in the placebo group were as follow:

- Headache: 10 (6.3%) cases were of mild intensity, 11 (7.0%) were moderate, and 3 (1.9%) were severe
- Dry mouth: all 11 (7.0%) cases were of mild intensity

No cases of suicide attempt or completed suicide were reported.
The proportion of sexual dysfunction TEAEs was highest in the paroxetine 20 mg group (6.5%) versus the placebo (0.0%) and saredutant 100 mg (1.3%) groups.

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 (AST), and total bilirubin PCSAs was low overall and similar across treatment groups. Elevations of ALT were mild [<5 X upper limit of the normal range (ULN)] and asymptomatic. No patient had ALT ≥3 X ULN associated with total bilirubin ≥34 μmol/L (≥2 X ULN).

None of the QTcF values was ≥500 ms or represented an increase of >60 ms from baseline. Two patients had a prolonged QTcF interval (male>450 ms or female >470 ms), 1 patient (0.6%) in the saredutant 100 mg group with a prolonged QTcF value at baseline and 1 patient (0.7%) in the paroxetine 20 mg group. Saredutant treatment was associated with a 2 bpm mean increase in heart rate. Mean changes from baseline for HR at the last visit were as follows: placebo (-0.2 bpm), saredutant 100 mg (1.9 bpm), and paroxetine 20 mg (-1.4 bpm). Saredutant treatment was associated with a small mean decrease in QTcF. Mean changes from baseline for QTcF at the last visit were as follows: placebo (-1.8 ms), saredutant 100 mg (-1.4 ms), and paroxetine 20 mg (-2.0 ms).

The mean CSFQ total score change from baseline indicated improvement for each treatment group, with greatest improvement in the saredutant 100 mg group. In the saredutant 100 mg group, there was an apparent difference by gender, with CSFQ improvement noted among the female patients, but not among the male patients.

Pharmacokinetic results:

Plasma concentrations (ng/mL) of saredutant after 14-day (mean coefficient of variation [CV%]: 38.2 [94]) and 56-day (mean [CV%]: 46.3 [81]) repeated once daily administration of saredutant were similar. Plasma concentrations (ng/mL) of SR49596 after 14-day (mean [CV%]: 5.29 [102]) and 56-day ([mean [CV%]: 6.34 [73]) repeated once daily administration of saredutant were similar. These results suggested that steady state was reached on Day 14 for both compounds.

Pharmacokinetic/pharmacodynamic results:

Statistically significant relationships (estimates of slopes significantly different from zero, $p<0.05$) were found between changes from baseline to D56 in score of efficacy parameters and saredutant plasma concentrations, indicating that higher plasma concentrations were associated with an increased response.

A statistically significant relationship between improved HAM-D treatment responder status and higher saredutant plasma concentration was also shown ($p = 0.0077$).

Based on estimates of the slopes that were not significantly different from zero ($p>0.05$), there were no significant relationships between saredutant or SR49596 plasma concentrations and the change from baseline in QTcF and HR.

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Summary (continued):

Conclusions:

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