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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00825019 **Study code**: EFC5379

Title of the study:
A double-blind, multicenter study evaluating the efficacy and safety of one fixed dose of SR58611A (700 mg/day) versus placebo and paroxetine (20 mg/day) in patients with a recurrent major depressive episode.

Study centers: Multicenter study with 25 centers in the United States of America.

Study period:

Date first patient enrolled:	08-Sep-2003
Date last patient completed:	01-Oct-2004 (main treatment phase)
	28-Dec-2004 (extension phase)

Phase of development: Phase 3 (confirmatory study)

Objectives:
The primary objective was to demonstrate the antidepressant efficacy on the Hamilton depression rating scale (HAM-D) of amibegron (SR58611) 700 mg/day compared to placebo in the treatment of patients with a recurrent major depressive episode.

The secondary objective was to assess the safety profile of amibegron 700 mg/d in comparison to placebo and to assess plasma concentrations of the active metabolite.

Methodology:
This was a double-blind, placebo and paroxetine-controlled, randomized, parallel-group, multicenter, fixed dose study.

Number of patients: Planned: 300 Randomized: 307 Treated: 306
Efficacy: 298 Safety: 306 Pharmacokinetics: 100

Diagnosis and criteria for inclusion:
Male and female out-patients, 18 to 65 years of age, suffering from a recurrent major depressive episode of at least moderate intensity (DSM-IV). Patients have been hospitalized for the treatment of a previous episode; or a previous episode required antidepressant treatment(s) at the recommended dose level for at least 2 months. The duration of the current episode is of at least 6 weeks unless the severity of symptoms justifies shorter duration.

Investigational product: Amibegron 350 mg tablets or matching placebo

Dose: 700 mg

Administration: oral, 350 mg administered q12 h

Reference therapy: Paroxetine or matching placebo

Dose:: 20 mg once a day (QD)

Administration: oral

Duration of treatment:
There was a 3 to 9-day, single-blind placebo run-in period, after which patients were randomized to the double-blind main treatment phase of the study and received either 700 mg (2 x 350 mg/d) of amibegron at 12-hour intervals (q12h), or 20 mg daily of paroxetine, or placebo (matching tablets and capsules). The main treatment phase of the study lasted a duration of 42 days (6 weeks).

Duration of observation:
The total duration of observation (placebo run-in period and double-blind period) was approximately 7 weeks. An optional extension phase under the same double-blind treatment conditions was proposed to all improved patients for an additional 4.5 months.

Criteria for evaluation:

Efficacy:

Primary efficacy variable
The primary efficacy analysis was performed on the change from baseline of the total score of the HAM-D 17 items.

Secondary efficacy variable(s)
Secondary efficacy analysis was performed using: HAM-D subscores, HAM-D responders and remitters, HAM-A total score and subscores, Montgomery-Asberg Depression Rating Scale (MADRS) total score, clinical global impression (CGI) severity and improvement scores, patient global impression (PGI) improvement score, social and occupational functioning assessment scale (SOFAS) score.

Safety:
Safety was assessed by clinical monitoring of adverse events (AEs), Arizona Sexual Experience Scale (ASEX), laboratory parameters (hematology, blood chemistry, and urinalysis), physical examination findings, electrocardiogram (ECG) parameters, changes in vital signs, and body weight.

Pharmacokinetics:

Measurement of SR58878 plasma concentrations. Blood samples were collected within 1 to 3 hours following the last morning drug administration for the determination of SR58878 plasma concentrations at Visit 4 (Day 14 ±2) and Visit 6 (Day 42 ±4) for the main study phase and at Visit 11 (Week 24 ±1) for the extension study phase or in an event of serious AE (SAE) or premature discontinuation. SR58878 plasma concentrations were assayed using a validated liquid chromatography with tandem mass spectrometry (LC/MS-MS) method with a limit of quantification of 16 ng/mL.

Statistical methods:

Efficacy:
Efficacy variables were evaluated in an intent-to-treat (ITT) population using both the observed-case (OC) and last observation carried forward (LOCF) approaches. Primary efficacy analysis was done on the change from baseline in the HAM-D 17 item total score at the final visit of the double-blind treatment period using ANCOVA. Secondary efficacy endpoints were analyzed using analysis of variance (ANOVA) for continuous endpoints, and Fisher's exact test or Cochran-Mantel-Haenszel (CMH) test for categorical endpoints.

Safety:
Safety analysis was done on the treated population. Treatment-emergent AEs (TEAEs) during the double-blind treatment and extension periods were summarized by system organ class and preferred term, grouped by treatment. Mean changes from baseline were summarized using descriptive statistics for laboratory test variables, vital signs, and ECG data. Incidences of potentially clinically significant abnormalities (PCSAs) in laboratory test results, vital signs or ECG data were presented by treatment group. Changes from baseline in ASEX total score and core items were analyzed using ANOVA.

Pharmacokinetics:
Descriptive statistics and statistical analysis were performed with SR58878 plasma concentrations observed within 1 to 3 hours following amibegron administration. Plasma levels on Day 14 (Visit 4), Day 42 (Visit 6) and Week 24 (Visit 11) were summarized using descriptive statistics separately by visit.
Analysis of steady state was evaluated using ANOVA method comparing concentrations at Day 42 with those at Day 14. If the difference between concentrations at both days was not statistically different, then steady state was considered achieved by Day 14.

The influence of covariates, such as gender, weight, and age were evaluated by examining correlations between concentrations, and weight and age, and by using the ANOVA method for gender using data from Visit 4 (Day 14) and Visit 6 (Day 42). Relationship between plasma concentrations and safety parameters (ECG parameters) measured at Visit 4 (Day 14) and Visit 6 (Day 42) were explored using linear regression techniques.

Summary:

Efficacy results:

Overall at baseline, of a total of 307 patients randomized, the majority of patients were female (69.6%), Caucasian (72.2%) with an overall mean age (SD) of 40.5 years (11.0). The mean number (SD) of previous episodes of MDD was 2.2 (1.4), the mean duration of current episode 230.6 days (156.5). Mean (SD) total scores for HAM-D and MADRS were 22.9 (3.8) and 30.0 (5.7), respectively. Demographic characteristics as well as medical history were similar across treatment groups. A total of 68 patients (22.1%) discontinued treatment. The main reasons for treatment discontinuation were, subject lost to follow-up (26 patients, 8.5%), investigator/subject's request (18 patients, 5.9%), AEs (14 patients, 4.6%), lack of efficacy (7 patients, 2.3%), other (2 patients, 0.7%), and poor compliance to protocol (1 patient, 0.3%).

The results of this study show that there were no differences between amibegron 700 mg/day and placebo over a 6-week period of treatment for the primary efficacy endpoint 17-item HAM-D total score and any of the key secondary efficacy endpoints in MDD (HAM-D depressed mood score, MADRS total score, CGI severity score).

The difference between the paroxetine and placebo groups in the change from baseline in the primary endpoint was not statistically significant either. The study was not powered to detect a statistical difference between placebo and paroxetine. However, the marginal reduction observed with paroxetine in the change of HAM-D total score versus placebo does not allow considering the study valid for drawing any efficacy conclusions.

Secondary analyses (analyses of covariance using baseline HAM-D total score or countries are covariates) and a sensitivity analysis of covariance using a mixed effect model with repeated measures and baseline HAM-D total score as a covariate, showed similar results to the primary analysis.

Safety results:

An overview of TEAEs in this study is provided in the table below.

	Placebo (N=121) n (%)	**SR58611A 700 mg (N=124) n (%)**	**Paroxetine 20 mg (N=61) n (%)**
Patients with any TEAE (including SAEs)	75 (62.0)	72 (58.1)	40 (65.6)
Patients with any SAE (including SAEs leading to death)	0 (0.0)	2 (1.6)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Patients permanently discontinuing treatment due to AE	4 (3.3)	7 (5.6)	3 (4.9)

During the main treatment phase, the percentage of AEs in the amibegron 700 mg group (58.1%) was lower than in the placebo group (62.0%) and paroxetine 20 mg group (65.6%). There were no deaths and the 2 SAEs reported (bronchitis and worsening of depression) were in the amibegron 700 mg group. A total of 14 patients discontinued the study treatment due to an AE: 7 patients from the amibegron 700 mg group, 3 patients from the paroxetine group, and 4 placebo patients. The most frequently reported TEAEs in the amibegron 700 mg group were headache and nausea. Most of these events were mild to moderate in intensity. With regard to vital signs, there were no significant differences between groups, as well as with regard to the assessment of sexual dysfunction.

The total incidence of alanine aminotransferase (ALT) >2 upper limit of normal (ULN) was similar between the amibegron 700 mg and placebo groups (0.9%). Values were lower than 3 ULN and there were no associated increases in bilirubin (≥34 µmol/L).

During the extension phase, the percentage of AEs in the amibegron 700 mg group (62.2%) was comparable to the placebo group (63.0%), and lower than in the paroxetine 20 mg group (65.2%). No deaths occurred during the extension phase. There was 1 SAE observed in the amibegron 700 mg group (asthma). A total of 6 patients discontinued the study treatment due to an AE: 3 patients from the amibegron 700 mg group and 3 patients from the placebo group. The most frequently reported TEAEs in the

amibegron 700 mg group were upper respiratory tract infection. These events were mild to moderate in intensity. Body weight was increased in more patients from the amibegron 700 mg group than from the placebo group.

One patient had ALT>2 ULN in the amibegron 700 mg group and in the placebo group during the extension phase, without associated PCSA in bilirubin.

For both, the main treatment and extension phases of the study, there were no significant differences between the amibegron 700 mg group, the paroxetine 20 mg group, or the placebo group with regard to ECG, liver function, white blood cell, or red blood cell and platelets PCSAs. In addition, there were no prolonged QTcB- and no QTcF-interval increases from baseline observed in the amibegron 700 mg group.

Pharmacokinetic results:

Overall, SR58878 plasma concentrations were consistent between the three visits. SR58878 steady state was attained on Day 14 (p=0.0609). Overall, no difference between male and female subjects was observed, as seen in the male to female ratio estimate (1.09). No relationship was observed between SR58878 plasma concentrations and weight (p=0.991) or age (p=0.107).

Pharmacokinetic/Pharmacodynamic relationship:

Based on estimates of the slope, not significantly different from zero, there was no significant relationship between change from baseline in QTcB- and QTcF-interval and SR58878 plasma concentrations.

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