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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00385307 **Study code**: EFC6607

Title of the study:
A multi-center, double-blind, parallel group, fixed dose, 4-arm, placebo and paroxetine controlled 8-week efficacy study of 2 oral doses of SR58611A (175 mg or 350 mg, BID) in adult outpatients with major depressive disorder.

Study centers: Multicenter study with 58 centers in the United States of America.

Study period:

Date first patient enrolled: 27-Sep-2006

Date last patient completed: 28-Nov-2007

Phase of development: Phase 3

Objectives:

The primary objective was to demonstrate the efficacy of 2 doses of SR58611 (amibegron), 175 mg or 350 mg twice a day (BID) versus placebo taken over 8 weeks as treatment for major depressive disorder (MDD).

The secondary objective was to document the clinical tolerability and safety of amibegron.

Methodology:
This was a double-blind, placebo- and paroxetine-controlled, randomized, parallel-group, multicenter, fixed dose study in male and female patients with MDD.

Number of patients:	Planned: 660	Randomized: 680	Treated: 667
	Efficacy: 658 intent-to-treat (ITT)	Safety: 669	

Diagnosis and criteria for inclusion:
Male and female out-patients, 18 to 65 years of age, suffering from MDD and presenting recurrent major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria text, (DSM-IV-TR) and assessed with the Mini International Neuropsychiatric Interview (MINI), with a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≥28, and the MADRS total score sustained above 22 throughout the screening period.

Investigational product: Amibegron tablets or matching placebo tablets

Dose: 175 mg and 350 mg

Administration: oral BID

Reference therapy: Paroxetine tablets encapsulated and matching placebo tablets

Dose: 20 mg

Administration: oral, once a day (QD)

Duration of treatment: 8 weeks

Duration of observation: 11 weeks (including screening, treatment period, and follow-up)

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the change in the 17-item Hamilton rating scale for depression (HAM-D) total score from

baseline to Day 56. The key secondary efficacy variables were the changes from baseline to Day 56 in the clinical global impression severity of illness score and the HAM-D depressed mood item score, as well as the proportion of patients with a HAM-D treatment response, defined as a reduction of ≥50% in the HAM-D total score between baseline and any postbaseline assessment. Other secondary efficacy endpoints that were analyzed, for exploratory purposes, included the HAM-D factor scores, HAM-D core items score, and the percentage of patients who demonstrated an early sustained response and remission.

Safety:

Safety was assessed by clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood chemistry), vital signs (including weight), changes in sexual functioning questionnaire (CSFQ), and physician withdrawal checklist (PWC).

Statistical methods:

Efficacy:

Primary efficacy analysis was done on the change from baseline to Day 56 in the 17-item HAM-D total score, using a mixed-effect model with repeated measures (MMRM), under the missing at random framework. The primary analysis was performed on the intent-to-treat population. The student *t* test statistics at Day 56 were used to determine the statistical significance of the comparison of amibegron versus placebo.

Secondary efficacy endpoints were analyzed using MMRM, analysis of covariance with last observation carried forward methods (LOCF ANCOVA) (quantitative variables with baseline value). Categorical secondary efficacy variables were evaluated by the chi-square test.

Safety:

Safety and tolerance data were summarized by treatment group using descriptive statistics. Incidences of potentially clinically significant abnormalities (PCSAs) in clinical laboratory results or vital signs are presented by treatment group. The CSFQ was analyzed using the LOCF ANCOVA method. Summaries of the number and percentage of patients experiencing each symptom listed in the PWC as well as mean score are provided by treatment group.

Summary:

Efficacy results:

Overall at baseline, of a total of 680 patients randomized, the majority of patients were female (65.9%) and Caucasian (72.1%) with an overall mean (±SD) age of 43.2 ± 11.5 years. The median duration of current episode of MDD was 24.0 weeks. Demographic characteristics as well as medical history and psychiatric characteristics assessed using the 17-item HAM-D, MADRS, and clinical global impression scales were comparable across treatment groups at baseline. A total of 491 patients completed the study treatment period The main reason for treatment discontinuation was: in the placebo group, subject lost to follow-up (9.8%), in the amibegron-treated groups, lack of efficacy (7.0% in the amibegron 175 mg BID group and 7.4% in the amibegron 350 mg BID group), and in the paroxetine group AEs (10.1%).

This study did not show any difference in favor of amibegron 350 mg BID or 175 mg BID treatment compared with placebo on the primary endpoint, change from baseline in the HAM-D total score, as well as on multiple secondary efficacy endpoints. A significant difference was not observed between paroxetine and placebo on the primary endpoint.

Safety results:

No deaths were reported during the study. An overview of treatment-emergent adverse events (TEAEs) reported during the study in the safety population is provided in the table below.

		Amibegron		Paroxetine
	Placebo (N=161)	**175 mg bid (N=172)**	**350 mg bid (N=171)**	**20 mg qd (N=165)**
Patients with any TEAE (including SAEs)	103 (64.0%)	116 (67.4%)	117 (68.4%)	125 (75.8%)
Patients with any serious TEAE (including SAEs leading to death)	1 (0.6%)	1 (0.6%)	6 (3.5%)	2 (1.2%)
Patients with any TEAE leading to Death	0	0	0	0
Patients permanently discontinuing treatment due to TEAE	6 (3.7%)	11 (6.4%)	10 (5.8%)	17 (10.3%)

The most frequently reported TEAEs in either amibegron group at an incidence greater than placebo, by more than 1%, were nausea, diarrhea, and upper respiratory infection. The incidence of TEAEs leading to discontinuation was similar in the 2 amibegron groups and highest in the paroxetine group. The placebo group had the lowest incidence of discontinuation due to TEAEs. For the amibegron groups, the most common causes of discontinuation were related to psychiatric disorders and nervous system disorders. Two patients were reported to have suicidal ideation, 1 in each amibegron group, and 1 patient each was reported to have suicidal ideation and suicide attempt, both in the paroxetine group.

A higher number and percentage of patients in the paroxetine group experienced sexual dysfunction TEAEs compared with patients in the placebo, amibegron 175 mg BID group, and amibegron 350 mg BID group.

During the study, 4 patients, 3 of which had normal alanine aminotransferase (ALT) values at baseline, had a PCSA for ALT (ie ≥3 ULN). Two of the patients were from the amibegron 175 mg BID group and 1 patient was from the amibegron 350 mg BID group. Of note, 1 patient in the amibegron 175 mg BID group had an ALT value ≥3 ULN, which was associated with a total bilirubin value ≥2 ULN. One patient in the paroxetine group and no patients in the placebo group had a PCSA for ALT.

The incidence of patients with mild renal impairment was higher in the amibegron 350 mg BID (19.5%) and paroxetine (18.2%) groups, compared with the amibegron 175 mg BID (14.7%) and the placebo (14.1%) groups. Most incidences of mild renal impairment were isolated. No other particular safety concerns were raised with regard to laboratory parameters and vital signs.

Following discontinuation of treatment, patients in the amibegron 175 mg BID and 350 mg BID groups did not experience particular withdrawal effects, as measured by PWC, compared to patients in the placebo group.

No dose-related effects were seen between amibegron 175 mg BID and 350 mg BID.

Issue date: 27-Feb-2009