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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00252330 **Study code**: EFC5116

Title of the study:
An eight-week, double-blind placebo controlled, multicenter study with Escitalopram- (10 mg qd) as positive control, evaluating the efficacy, safety, tolerability of a fixed dose of SR58611A (350 mg q12) in outpatients with Major Depressive Disorder (MDD).

Study centers: Multicenter study with 48 centers in 2 countries

Study period:

Date first patient enrolled: 14-Sep-2005

Date last patient completed: 04-Jan-2007 (acute phase)
10-May-2007 (extension phase)

Phase of development: Phase 3

Objectives:

The primary objective was to assess the efficacy of a fixed dose of SR58611 (amibegron), 350 mg twice daily (BID) compared to placebo in patients with MDD, using escitalopram, 10 mg once daily (QD) as positive control.

The secondary objective was to evaluate the tolerability and safety of amibegron in patients with MDD.

Methodology:

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

Number of patients: Planned: 450 Randomized: 476 Treated: 474
Efficacy: 466 intent-to-treat (ITT) Safety: 474

Diagnosis and criteria for inclusion:

Male and female out-patients, 18 year-old or more, suffering from MDD and presenting recurrent Major Depressive Episode (MDE) 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), and with a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≥22.

Investigational product: Amibegron tablets or matching placebo tablets

Dose: 700 mg

Administration: oral, 350 mg administered q12 h

Reference therapy: Escitalopram capsule or matching placebo capsule

Dose:: 10 mg once a day (QD)

Administration: oral

Duration of treatment:

Single-blind run-in placebo period: 1 week - Double-blind randomized treatment period: 8 weeks (acute treatment period) + 18 weeks (optional extension treatment period).

Duration of observation:

10 weeks (including screening, single-blind and acute double-blind treatment periods and follow-up) for those patients who did not enter the extension and 28 weeks for those patients who entered the extension.

Criteria for evaluation:

Efficacy:

The primary efficacy analysis the change in the 17-item Hamilton rating scale for depression (HAM-D) total score from baseline to Day 56. The key secondary efficacy variable was the change in the clinical global impression (CGI) severity of illness score from baseline to Day 56. Other secondary efficacy endpoints that were assessed included MADRS, Hamilton rating scale for anxiety (HAM-A), and CGI improvement scores.

Safety:

Safety was assessed by clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood chemistry, urinalysis), 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 ITT population. The Student t test statistics at Day 56 was used to determine the statistical significance in 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), or LOCF ANOVA methods (quantitative variables without baseline value). Categorical secondary efficacy variables were evaluated by either the chi-square test or Cochran-Mantel-Haenszel row mean score statistics.

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, were presented by treatment group. The CSFQ was analyzed using the LOCF ANCOVA method. Summaries of the count and percentage of patients experiencing each symptom listed in the PWC as well as mean score were provided by treatment group.

Summary:

Efficacy results:

Overall at baseline, of a total of 476 patients randomized, the majority of patients were female (65.3%), Caucasian (77.1%) with an overall mean (±SD) age of 44.2±12.2 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 17-item HAM-D, MADRS and CGI scales were comparable across treatment groups at baseline. A total of 351 patients completed the acute study treatment period. The main reason for discontinuation was AEs with placebo (8.1%), lack of efficacy with amibegron (10.6%) and AEs as well as subject's request with escitalopram (5.8% each).

This study did not show any difference in favor of the amibegron 350 mg BID treatment compared with placebo on the primary endpoint, change from baseline in HAM-D total score, as well as on the secondary efficacy endpoints. The comparison between placebo and escitalopram confirmed the validity of the study design and the conduct of the study.

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

	Placebo (N=161)	Amibegron 350 mg BID (N=161)	Escitalopram 10 mg QD (N=152)
Patients with any TEAE (including SAEs)	97 (60.2%)	104 (64.6%)	114 (75.0%)
Patients with any serious TEAE (including SAEs leading to death)	4 (2.5%)	6 (3.7%)	2 (1.3%)
Patients permanently discontinuing treatment due to TEAE	13 (8.1%)	9 (5.6%)	10 (6.6%)

Among those patients who entered the 18-week extension phase of the study, the incidences of TEAEs were similar across all treatment groups (56.7% in placebo, 53.9% in amibegron and 55.7% in escitalopram) and were lower compared with the incidences reported during the acute phase. Few patients had serious TEAEs (2/67 patients, 3.0% in the placebo group, 2/76 patients, 2.6% in the amibegron group, and 1/97 patient, 1.0% in the escitalopram group). A higher proportion of patients from the amibegron group (7/76 patients) discontinued treatment due to an AE compared with placebo (1/67 patients) or escitalopram (3/97 patients).

During the 8-week acute phase of the study, the most frequently reported TEAEs (≥5%) with a higher incidence in the amibegron group compared with the placebo group were nausea, diarrhea, dry mouth, and upper respiratory tract infection, and upper respiratory tract infection, nasopharyngitis, and influenza during the extension phase.

Overall, psychiatric disorders were reported with a comparable incidence in the placebo and the amibegron groups. Three cases of suicidal ideation were reported in the amibegron group versus none in the placebo group and 1 in the escitalopram group.

During the entire study, 6 patients had alanine aminotransferase (ALT) ≥3 upper limit of normal (ULN) including 2 patients receiving amibegron, both with normal baseline values, and 4 patients receiving placebo, of whom 2 had normal baseline values. Increased ALT ≥3 ULN was associated with total bilrubin ≥2 ULN in 1 patient from the placebo group, compared with no patients from the amibegron and the escitalopram groups. In the amibegron-treated patients, these abnormalities in ALT occurred at the end of the 8-week treatment period and were reported as AEs. Both patients entered the extension phase of the study; 1 patient discontinued the treatment and recovered within 2.5 months after the onset of the AE (ie, 2 months after treatment discontinuation), and the other patient recovered within 4 months after the onset of the AE. In the 2 placebo-treated patients with normal baseline value, these abnormalities occurred during the extension phase of the study and were reported as SAEs.

During the entire study, no PCSAs in creatinine clearance were reported in the amibegron group. During the acute phase of the study, more patients in the amibegron group had mild creatinine clearance changes from normal baseline compared with patients in the placebo group (7/129 patients versus 2/127 patients). This was also true during the extension phase of the study (6/61 patients in the amibegron group, of whom 3 patients already had abnormal renal function during the acute phase versus 2/60 patients in the placebo group). However no relevant changes from baseline in creatinine and creatinine clearance were observed in any of the treatment groups. There were no differences across treatment groups with regard to other laboratory parameters, except for eosinophils and decrease in hemoglobin that were observed with a higher incidence in amibegron-treated patients compared with placebo-treated patients, in both, the acute and extension phase.

During both, acute and extension phase, a lower percentage of patients experienced TEAE related to sexual dysfunction in the amibegron or the placebo group compared with the escitalopram group.

Following abrupt discontinuation of treatment during the acute or the extension phase, patients in the amibegron group did not experience particular withdrawal effects, as measured by PWC, compared with patients in the placebo group.

During the extension phase, more patients in the amibegron group had PCSAs in orthostatic hypotension compared with the placebo and the escitalopram groups (17.3% versus 6.0% and 8.4%, respectively) and the incidence in the amibegron group was slightly higher compared with the incidence reported during the acute phase (17.3% versus 12.7%). No relevant changes from baseline in orthostatic systolic blood pressure were observed in any treatment groups. No other particular safety concerns were raised with regard to other vital sign parameters.

Four pregnancies were reported during the study that resulted in spontaneous abortion in 1 patient (amibegron group), elective abortion in 2 patients (placebo and escitalopram groups) and in at term live newborn delivery in 1 patient (placebo group).

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