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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00319709 **Study code**: EFC4846

Title of the study:
An eight-week, double-blind placebo controlled, multicenter study evaluating the efficacy, safety, tolerability of a fixed dose of SR58611A (350 mg q12) in elderly patients with Major Depressive Disorder (MDD).

Study centers: International, multicenter study with 33 centers in 5 countries.

Study period:

Date first patient enrolled:	25-Apr-2006
Date last patient completed:	24-Apr-2007 (acute phase)
	22-Aug-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 elderly patients with MDD.

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

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

Number of patients:	Planned: 280	Randomized: 288	Treated: 288
	Efficacy: 287 intent-to-treat (ITT)	Safety: 288	

Diagnosis and criteria for inclusion:
Male and female, out- or in-patients, 65 years 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 revision 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

Dose: 350 mg

Administration: oral BID

Reference therapy: Placebo tablets

Dose: Not applicable

Administration: oral BID

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 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 variable was the change in the clinical global impression severity of illness (CGI-1) score from baseline to Day 56. Other secondary efficacy endpoints that were assessed included MADRS scores, the Hamilton rating scale for anxiety (HAM-A), and CGI global improvement (CGI-2) scores.

Safety:

Safety assessments included clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood chemistry), vital signs (including weight), 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 (MAR) framework. The primary analysis was performed on the ITT 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 the 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. 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 288 patients randomized, the majority of patients were female (69.1%), Caucasian (99.7%) with an overall mean (±SD) age of 70.4±4.8 years. The median duration of current episode of MDD was 8.0 weeks. Demographic characteristics as well as medical history and psychiatric characteristics assessed using HAM-D, MADRS, and CGI scales were comparable across treatment groups at baseline. A total of 245 patients (85.1%) completed the acute study treatment period. The main reason for discontinuation was lack of efficacy with placebo (7.3%), and lack of efficacy and AEs with amibegron (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 the 17-item HAM-D total score. A significant difference to placebo was observed for the key secondary endpoint (CGI-1) and some of the secondary exploratory endpoints (HAM-A somatic anxiety factor score, and CGI-2 by improvement status at Day 56).

Safety results:

Three deaths were reported in this study, all in the amibegron group. One of them occurred in the acute phase and 2 in the extension phase. 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=150)	Amibegron 350 mg bid (N=138)
Patients with any TEAE (including SAEs)	45 (30.0%)	55 (39.9%)
Patients with any serious TEAE (including SAEs leading to death)	1 (0.7%)	3 (2.2%)
Patients with any TEAE leading to Death	0	1 (0.7%)
Patients permanently discontinuing treatment due to TEAE	2 (1.3%)	8 (5.8%)

During the 8-week acute phase of the study, the number of patients experiencing TEAEs was higher in the amibegron group (39.9%) compared with the placebo group (30.0%). The most frequently reported TEAEs (≥5%) with a higher incidence in the amibegron group compared with the placebo group were insomnia and nausea. Among those patients who entered the 18-week extension phase of the study, the number of patients experiencing TEAEs was higher in the placebo group (33.8%) compared to the amibegron group (26.4%).

Serious TEAEs were reported in the acute phase in 1/150 patient (0.7%) in the placebo group and in 3/138 patients (2.2%) in the amibegron group), and in the extension phase in 2/74 patients (2.7%) in the placebo group, and in 5/72 patients (6.9%) in the amibegron group). Among these serious AEs; 3 deaths (2 cardiac failures and 1 sudden death) were reported in this study. None of these deaths were considered by the Investigator as related to investigational product (IP).

Overall, psychiatric disorders were reported with a higher incidence in the amibegron group (9.4% in the acute phase and 9.7% in the extension phase) compared with the placebo group (4.7% in the acute phase and 5.4% in the extension phase).

During the acute phase, more patients in the amibegron group (8/138 patients, 5.8%) discontinued the study treatment due to a TEAEs compared with placebo (2/150 patients, 1.3%). Among those patients who entered the 18-week extension phase of the study, a higher proportion of patients from the amibegron group (7/72 patients, 9.7%) discontinued treatment due to a TEAEs compared with placebo (3/74 patients, 4.1%).

A total of 3 patients (2 with normal baseline value) in the amibegron group had alanine aminotransferase (ALT) ≥3 upper limit of normal (ULN) (maximum value at 7.5 ULN) without concomitant bilirubin increase. These abnormalities occurred between 8 and 10 weeks after the first IP intake; 2 resolved within 1 and 3 months after IP discontinuation and 1 resolved within 6 weeks while IP was continued.

During the acute phase of the study, a similar proportion of patients in the amibegron group had mild creatinine clearance changes from normal baseline compared with patients in the placebo group (13/37 patients, 35.1%versus 16/47 patients, 34.0%). During the extension 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 (12/23 patients, 52.2% versus 13/29 patients, 44.8%). However, no relevant changes from baseline in creatinine clearance were observed in any of the treatment groups. There were no relevant differences across treatment groups with regard to hematology parameters, except for monocytes and low hematocrit that were observed with a higher incidence in amibegron-treated patients compared with placebo-treated patients. No other particular safety concerns were raised with regard to other laboratory parameters or vital signs.

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 the PWC, compared with patients in the placebo group.

Issue date: 13-Feb-2009