These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00252356 **Study code**: EFC5041

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 and tolerability of a fixed dose of SR58611A (350 mg q12) in outpatients with MDD.

Study centers: Multicenter study with 38 centers in 2 countries (United States of America, Canada).

Study period:

Date first patient enrolled:	08-Sep-2005
Date last patient completed:	27-Jan-2007 (acute phase)
	23-May-2007 (extension phase)

Phase of development: Phase 3

Objectives:

The primary objective was to assess the efficacy of SR58611 (amibegron) 350 mg twice daily (BID) compared to placebo in patients with major depressive disorder (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 patients with MDD.

Number of patients: Planned: 450 Randomized: 468 Treated: 467
Efficacy: 455 intent-to-treat (ITT) Safety: 467

Diagnosis and criteria for inclusion:

Out-patients, at least 18 years years-old, suffering from MDD, and presenting a recurrent major depressive episode (MDE) according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision (DSM-IV-TR) criteria and assessed with the Mini International Neuropsychiatric Interview (MINI), and with a Montgomery and 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, and urinalysis), vital signs (including weight), physician withdrawal checklist (PWC), and changes in sexual functioning questionnaire (CSFQ).

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 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), 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 tolerability 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 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:

A total of 468 patients were randomized. Overall, at baseline, the majority of patients were female (66.9%), Caucasian (81.2%) with an overall mean (±SD) age of 44.6±12.9 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 HAM-D, MADRS, and CGI scales were comparable across treatment groups at baseline. A total of 344 patients completed the acute phase of the study. The main reasons for discontinuation were lack of efficacy for the placebo group (8.9%), subject lost to follow-up for the amibegron 350 mg BID group (7.7%) and AEs for the escitalopram group (9.0%).

This study did not show any difference in favor of amibegron 350 mg BID, when compared with placebo, on the primary efficacy endpoint, the change from baseline at Day 56 in the HAM-D total score. No differences in favor of amibegron 350 mg BID, when compared with placebo, were found on multiple secondary efficacy endpoints.

The significant difference between escitalopram and placebo on the primary efficacy endpoint confirmed the validity of the study.

Safety results:

No deaths were reported during the entire study (acute and extension phases). An overview of treatment emergent adverse events (TEAEs) reported in the safety population during the acute phase of the study is provided in the table below.

	Placebo (N=157)	Amibegron 350 mg BID (N=156)	Escitalopram 10 mg QD (N=154)
Patients with any TEAE (including SAEs)	100 (63.7%)	104 (66.7%)	114 (74.0%)
Patients with any serious TEAE (including SAEs leading to death)	1 (0.6%)	3 (1.9%)	3 (1.9%)
Patients permanently discontinuing treatment due to TEAE	11 (7.0%)	6 (3.8%)	16 (10.4%)

During the acute phase of the study, the most frequently reported TEAEs (≥5%) with a higher incidence in the amibegron 350 mg BID group compared with the placebo group were constipation, headache, and upper respiratory tract infection. The frequency of constipation and upper respiratory tract infection were lower in the escitalopram group, compared with the amibegron 350 mg BID group. No amibegron 350 mg BID and placebo patients reported AE of suicidal ideation, compared with 1 escitalopram patient.

Among those patients who entered the 18-week extension phase of the study, the number of patients experiencing TEAEs were similar across all treatment groups (35/64 patients, 54.7% in the placebo group, 37/72 patients, 51.4% in amibegron group, and 44/80 patients, 55.0% in the escitalopram group) and were lower compared with the incidences reported during the acute phase. Few patients had serious TEAEs (2/72 patients, 2.8% patients in the amibegron group and 1/80 patient, 1.3% in the escitalopram group). Approximately 3 months after starting study drug, 1 patient in the amibegron group who was taking naproxen concomitantly, experienced a serious TEAE of drug induced hepatitis [alanine aminotransferase (ALT) was 50.7 upper limit of norma (ULN) and bilirubin was 3.2 ULN]. The patient recovered 7 weeks after discontinuing amibegron and naproxen. Two patients in each treatment group discontinued due to TEAEs.

During the extension phase of the study, TEAEs with an incidence ≥5% in the amibegron 350 mg BID group and with an incidence that was higher than the placebo group, were headache, upper respiratory tract infection, and insomnia. There were no AEs of suicidal ideation.

During the acute phase of the study, 3/135 patients, 2.2% (2 patients had a normal baseline ALT) in the amibegron 350 mg BID group had an on treatment ALT value ≥3 ULN, versus 1/136 patient, 0.7% (abnormal baseline ALT) in the placebo group and 2/141 patients, 1.4% (1 patient had a normal baseline ALT) in the escitalopram group. None of them had an ALT value ≥10 ULN and none had an ALT value that was ≥3 ULN and associated with a total bilirubin value that was ≥2 ULN. For the 2 amibegron patients, the PCSA was reported as a TEAE. The escitalopram patient was reported to have a serious AE. All patients were reported to have recovered.

During the extension phase of the study, 2/65 patients, 3.1% (both had normal baseline ALT) in the amibegron 350 mg BID group had an on treatment ALT value ≥3 ULN, versus 0/59 patient in the placebo group and 1/74 patient, 1.4% (abnormal baseline) in escitalopram group. For the amibegron 350 mg BID patients, 1 had an ALT value ≥5 ULN and 1 had an ALT value ≥10 ULN. Both amibegron 350 mg BID patients were also reported to have normal baseline AST values and on treatment AST values ≥3 ULN. One patient was reported to have an associated TEAE and the other was reported to have a serious TEAE of drug induced hepatitis as described above. Both patients were reported to have recovered.

During the acute phase of the study, mild creatinine clearance changes from normal baseline values were comparable for the 3 treatment groups. During the extension phase of the study, mild creatinine clearance changes were greater in the escitalopram group, compared with the amibegron and placebo groups. Only placebo patients had mild creatinine clearance changes that started in the acute phase and continued into the extension phase. There were few differences across treatment groups with regard to hematology parameters in both the acute and extension phases. More patients in the amibegron group had PCSAs in orthostatic hypotension compared with the placebo group (10/155 patients, 6.5% versus 6/150 patients, 4.0%, respectively) during the acute phase. This was also true for the extension phase. In the amibegron group, the incidence of orthostatic hypotension was slightly higher during the extension phase, compared with the incidence reported during the acute phase (8.6% versus 6.5%, respectively). No other particular safety concerns were raised with regard to other laboratory parameters and vital signs.

During both, the acute and extension phase, a lower percentage of patients experienced TEAE related to sexual dysfunction in the amibegron 350 mg BID 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 350 mg BID group did not experience particular withdrawal effects, as measured by PWC, compared with patients in the placebo group.

Issue date: 13-Feb-2009