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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00345098 **Study code**: LTE5376
Title of the study: A double-blind, multi-center, multinational, randomized withdrawal study evaluating the efficacy and safety of SR58611A (350 mg q12) versus placebo in the prevention of depression relapse up to 1 year in patients with Major Depressive Disorder improved after 12 weeks of open treatment with SR58611A (350 mg q12).	
Study centers: International, multicenter study with 65 centers in 13 countries	
Study period: Date first patient enrolled: 15-May-2006 Date last patient completed: 01-Feb-2008	
Phase of development: Phase 3	
Objectives: The primary objective was to demonstrate that in depressed patients who improve after 12 weeks treatment with SR58611 (amibegron) 700 mg/day, the time to relapse for depressive symptoms is longer in the amibegron group than in the placebo group during a 24 to 52 week double-blind treatment period (amended by Protocol Amendment No. 01). The secondary objective was to assess the safety and tolerability of amibegron 350 mg twice daily (BID) in patients with depressive disorders.	
Methodology: This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, fixed-dose withdrawal study in male and female patients with Major Depressive Disorder (MDD) following a 12-week open-label amibegron treatment.	
Number of patients:Planned: 800 Enrolled:704 (open label) Randomized: 452 (double blind) Treated: 703 Efficacy: 451 intent-to-treat (ITT) Safety: 703 (open label), 452 (double blind)	
Diagnosis and criteria for inclusion: Patients 18 years or older, diagnosed with recurrent MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) with at least 1 Major Depressive Episode (MDE) over the past 5 years in addition to the current episode, a current episode between 4 weeks and 2 years duration, and a Montgomery-Asberg depression rating scale (MADRS) total score ≥28 were eligible for entry into the open-label phase on Day -1. Patients were randomized into the double-blind phase on Week 12 if they had a MADRS total score <12 (amended by Protocol Amendment No. 01).	
Investigational product: amibegron tablets	
Dose: 350 mg	
Administration: oral, BID	
Reference therapy: placebo tablets	
Dose: Not applicable	
Administration: oral, BID	

Duration of treatment:

Open-label treatment period: 12 weeks. Randomized double-blind period: 24 to 52 weeks.

Duration of observation:

Up to 16 months (including a 1-week screening period, a 12-week open-label treatment period, a 24- to 52-week double-blind treatment period, and a 1-week off-drug safety evaluation following completion of treatment or permanent early treatment discontinuation).

Criteria for evaluation:

Efficacy:

The primary efficacy variable, evaluated during the double-blind treatment period, was the time to relapse, with relapse defined as any one of the following criteria (amended by Protocol Amendment No. 01): MADRS score $\geq$17 confirmed at a subsequent visit 2 weeks later unless the patient dropped out; any dropout for lack of efficacy according to the Investigator's decision based on his/her knowledge of the patient; the prescription/use of alternative or additional treatments (pharmacological or nonpharmacological) for relief of psychiatric symptoms; any suicide attempt/suicide.

The secondary efficacy variables were the changes from baseline (Week 12) to the last available evaluation in Clinical Global Impression (CGI) severity of illness, in MADRS total score and in Hamilton Anxiety Rating scale (HAM-A) total score and subscores.

Safety:

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

Statistical methods:

Efficacy:

Efficacy variables were evaluated based on the ITT population. For the primary analysis, the log Rank test was used to test the null hypothesis of equality of relapse hazard for patients in the amibegron group relative to those in the placebo group. The type I error for rejecting null hypothesis was 5% using a 2-sided test. No covariates were included in the primary model. The cumulative proportion of patients who did not experience relapse over time was estimated using the Kaplan-Meier method. Survival curves displaying these estimates are provided by treatment group.

The secondary efficacy variables were modeled using an analysis of covariance (ANCOVA) with treatment group as the fixed effect and baseline value (Week 12) as the covariate.

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. 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:

Of the 704 patients enrolled in the open-label phase of the study, the majority were females (70.5%), Caucasian (92.8%), with a mean (±SD) age of 47.5 ±11.6 years. The median duration of the current episode of MDD at baseline was 10.0 weeks in the overall population, with a median time of 1.4 years between the last and the current episode of MDD. The psychiatric characteristics at baseline, assessed using CGI, MADRS, and HAM-A scales, were comparable across treatment groups.

The study showed a significant difference in favor of amibegron 350 mg BID compared with placebo on the primary efficacy endpoint, the time to relapse (log-rank p=0.0017). The Kaplan-Meier estimates of percentage of relapse at 6 and 10 months were lower in the amibegron group than in the placebo group (6 months: 16.9% and 24.7%, respectively; at 10 months: 21.1% and 35.9%, respectively).

There was a significant difference in favor of amibegron 350 mg BID compared with placebo on all secondary exploratory endpoints (change from baseline in CGI severity of illness, MADRS and HAM-A total scores, HAM-A somatic anxiety and psychic anxiety factor scores).

Safety results:

Overviews of the treatment-emergent adverse events (TEAEs) reported during the open-label and the double-blind phases of the study are presented in the tables below.

Overview of TEAEs during the open-label phase – n (%)

	Amibegron\ Placebo (N=232)	Amibegron\ Amibegron (N=220)	Amibegron\- (N=251)	All exposed (N=703)
Patients with any TEAE (including SAEs)	94 (40.5%)	90 (40.9%)	142 (56.6%)	326 (46.4%)
Patients with any serious TEAE (including SAEs leading to death)	2 (0.9%)	0	16 (6.4%)	18 (2.6%)
Patients with any TEAE leading to death	0	0	1 (0.4%)	1 (0.1%)
Patients permanently discontinuing treatment due to TEAE	0	1 (0.5%)	43 (17.1%)	44 6.3%)

Overview of TEAEs during the double-blind phase – n (%)

	Amibegron\ Placebo (N=232)	Amibegron\ Amibegron (N=220)
Patients with any TEAE (including SAEs)	84 (36.2%)	99 (45.0%)
Patients with any serious TEAE (including SAEs leading to death)	4 (1.7%)	5 (2.3%)
Patients with any TEAE leading to death	0	1 (0.5%)
Patients permanently discontinuing treatment due to TEAE	6 (2.6%)	6 (2.7%)

Two deaths were reported during the study, 1 during the open-label phase (completed suicide, amibegron/- group) and 1 during the double-blind phase (laryngeal neoplasm and intestinal obstruction, amibegron/amibegron group).

During the open-label phase, a total of 326 patients (46.4%) reported TEAEs, especially headache (13.2%) and nausea (9%). Eighteen patients (2.6%) experienced serious adverse events (SAEs). Four patients were reported with SAEs associated with liver enzyme increase, 2 patients with SAEs of myocardial infarction, and 2 patients with SAEs of suicide attempt. Forty-four patients (6.3%) discontinued treatment due TEAEs, especially nausea (11 patients, 1.6%).

During the double-blind phase, 99 patients (45.0%) in the amibegron group reported TEAEs compared with 84 patients (36.2%) in the placebo group. The most frequently reported TEAEs were headache (8.6%) and insomnia (5.5%) in the amibegron group and headache (6.0%) in the placebo group. Five patients (2.3%) experienced SAEs in the amibegron group compared with 4 patients (1.7%) in the placebo group. One patient in each group was reported with an SAE of suicide attempt. One patient in the amibegron group was reported with an SAE of myocardial infarction. Six patients in each group permanently discontinued treatment due to TEAEs.

Two cases of pregnancy were reported during the study. One patient exposed to amibegron for approximately 12 days during the open-label phase (amibegron/- group) delivered a full-term infant with 2 identified congenital abnormalities (atrial septal defect and pulmonary artery stenosis). On 21 August 2008, the second patient (amibegron/placebo group, double-blind phase) gave birth to a healthy boy.

A total of 11 patients had on-treatment elevations in alanine aminotransferase (ALT) values ≥3 times the upper limit of normal (ULN) during the study, 8 during the open-label phase, and 3 during the double-blind phase. Most of the initial ALT elevations occurred within the first 2 months of treatment. During the open-label phase, 2 patients with elevated ALT and aspartate aminotransferase (AST) ≥20 ULN, and total bilirubin ≥2 ULN were reported with SAEs of hepatitis and toxic hepatitis, 1 patient with elevated ALT and AST ≥10 ULN was reported with an SAE of increased hepatic enzyme, and 4 patients with elevated ALT ≥5 ULN were reported with liver function related-TEAEs. During the double-blind phase, elevations in ALT values were <5 ULN, infrequent, transient, not associated with increase in total bilirubin ≥2 ULN, and normalized without treatment discontinuation in both groups (2 patients in the amibegron group, and 1 patient in the placebo group).

For all other laboratory parameters, sporadic PCSAs were observed during the study, but no overall trend was observed. Most of the cases of renal impairment observed during the study were mild, and the majority of the patients with on-treatment renal impairment already had renal impairment at baseline. No patients with a normal renal function at baseline experienced moderate or severe renal impairment. The PCSA in vital signs the most frequently observed during the study was diastolic orthostatic hypotension. As measured with the PWC, patients did not experience withdrawal effects after the discontinuation of amibegron.

Issue date: 17-Feb-2009