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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00397098 **Study code**: LTE5894

Title of the study:
A double-blind, multicenter, randomized withdrawal study evaluating the efficacy and safety of amibegron (350 mg twice a day) versus placebo in the prevention of relapse of anxiety up to 1 year in patients with Generalized Anxiety Disorder improved after 12 weeks of open treatment with amibegron (350 mg twice a day).

Study centers: International, multicenter study with 42 centers in 9 countries.

Study period:

Date first patient enrolled: 06-Nov-2006

Date last patient completed: 19-Sep-2007

Phase of development: Phase 3

Objectives:
The primary objective was to assess the efficacy of SR58611 (amibegron) 350 mg twice a day (BID) compared with placebo in the prevention of relapse of anxiety in improved patients with Generalized Anxiety Disorder (GAD), over a 24- to 52-week treatment period.

The secondary objectives were to evaluate the safety and tolerability of amibegron in patients with GAD.

The study was stopped prematurely after 257 patients had been enrolled into the open-label phase due to the Sponsor's decision not to develop the compound in the GAD indication. Consequently, the analysis (as defined in the statistical analysis plan) focused on the safety and tolerability of amibegron, which is presented here.

Methodology:
This was a double-blind, placebo-controlled, randomized, parallel-group, multicenter, fixed dose withdrawal study in male and female patients with GAD. The overall study consisted of four segments:

- Segment A (1 week): drug-free screening period
- Segment B (12 weeks): open-label treatment with amibegron 700 mg/day
- Segment C (24 to 52 weeks): randomized, double-blind treatment with amibegron 700 mg/day or placebo
- Segment D (1 week): off drug safety evaluation following completion of treatment or permanent early treatment discontinuation.

Number of patients: Planned: 500 Enrolled (open-label):257 Randomized (double-blind): 115
Treated: 254 Safety: 254 (open-label), 115 (double-blind)

Diagnosis and criteria for inclusion:
Male and female patients with GAD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) with a Hamilton Anxiety rating scale (HAM-A) score ≥20 and a Montgomery-Asberg Depression Rating Scale (MADRS) score <18 at Visit 1 (Day -4) and Visit 2 (Day -1) were eligible for entry into the open-label phase. Patients who improved with a HAM-A score <11 at Visit 7 (Week 12) were eligible for entry into the double-blind phase.

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 66 weeks

Criteria for evaluation:

Efficacy:

The study was stopped prematurely and therefore sufficient data to perform an efficacy analysis were not available.

Safety:

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

Statistical methods:

Safety and tolerance data were summarized using descriptive statistics.

Two safety populations were considered for the main safety analyses: SAFE1 (total treated: "all exposed") and SAFE2. SAFE1 population consisted of all patients who took at least 1 dose of amibegron during the open-label period of the study. SAFE2 population consisted of all patients who were randomized and took at least 1 dose of double-blind study medication during the double-blind period of the study (amibegron/placebo and amibegron/amibegron).

Additionally, 2 other populations were defined. Enrolled population consisted of all patients who were dispensed amibegron during the open-label period of the study (included exposed and non-exposed patients). Not randomized population consisted of all patients in SAFE1 who took at least1 dose of open-label amibegron but were not randomized into the double-blind period of the study (amibegron/-).

All treatment-emergent AEs (TEAEs) and serious AEs (SAEs) were summarized irrespective of their relationship to study drug. The incidences of potentially clinically significant abnormalities (PCSAs) in clinical laboratory results or vital signs were calculated and presented by treatment group. Summaries of count and percentage of patients experiencing each symptom listed in the PWC, as well as mean total score and peak severity at any postbaseline visit were provided by the amibegron/placebo and amibegron/amibegron treatment groups.

Summary:

Patient disposition:

Of the 257 patients enrolled into the study, 3 patients were not exposed to study treatment. The remaining 254 patients (98.8%) were exposed to study drug during the open-label period, 152 patients (59.1%) completed this period and 115 patients (44.7%) were randomized into the double-blind period The main reason of treatment discontinuation were Sponsor's request, 45 patients (17.5%) and AEs, 20 patients (7.8%).

None of the 115 patients randomized into the double-blind period and exposed to study drug completed this study period. The main reason for treatment discontinuation was Sponsor request, 46 Patients (78.0%) in the amibegron\placebo group and 45 patients (80.4%) in the amibegron\amibegron group.

Exposure:

The overall mean duration of exposure during the open-label period was 65.8 days. A similar mean duration of exposure was noted for patients assigned to the amibegron/placebo (85.3 days) and amibegron/amibegron group (85.7 days).

Mean exposure in the double-blind period was similar in the amibegron/placebo (88.1 days) and amibegron/amibegron groups (82.3 days).

The mean duration of exposure to amibegron throughout the entire study was 168.2 days in the amibegron/amibegron treatment group. In this treatment group 33 patients (58.9%) were exposed to amibegron for 85 to 168 days and 20 patients (35.7%) of patients exposed for 169 to 252 days.

Demographics:

Baseline demographic characteristics were similar between the amibegron\placebo and amibegron\amibegron groups with the exception of gender and age. The majority of patients in both treatment groups were females (69,5% and 71.4%, respectively) and patients in the age group 18 to 49 years (78.0% and 60.7%, respetively).

Safety:

Treatment emergent adverse events

During the open-label period, a similar number of patients experienced TEAEs in each of the 3 amibegron-exposed populations, 32 patients (54.2%) in the amibegron\placebo group, 33 patients (58.9%) in the amibegron\amibegron group, and 77 patients (55.4%) in the amibegron\- group. No deaths occurred during the open-label period, and 3 patients (2.2%) in the amibegron/- group (who did not enter into the double-blind period) experienced SAEs. A total of 21 patients (8.3%) in the "all exposed" population discontinued treatment due to TEAEs, one of whom had TEAE onset during the open-label phase but discontinued study treatment during the double-blind period. The most frequently reported TEAEs in this period were headache, nausea, diarrhoea, and accidental overdose.

In the double-blind period, 1 patient experienced an SAE and 3 patients discontinued treatment due to TEAEs. The most frequently reported TEAEs in the double-blind period were headache and dry mouth. Over the entire study period, a total of 22 patients (8.7%) permanently discontinued treatment due to TEAEs. The most frequently repeated TEAEs were headache, nausea, accidental overdose, and diarrhea.

Serious adverse events

Six SAEs were reported: 1 (herpes zoster) was in a patient who failed screening and 1 (contusion) was prior to first intake of investigational product. Of the 4 which occurred during the treatment phase of the study, 3 (postprocedural infection, hypertension, and increased transaminases) occurred in the open-label period, and 1 occurred in the double-blind period (cerebrovascular accident occurring approximately 9 weeks after the patient switched from amibegron to placebo). Two of the SAEs (cerebrovascular accident and hypertension) led to permanent treatment discontinuation.

The event of increased transaminases occurred in a patient with normal liver function tests at baseline, who experienced increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), 6 days after the patient had discontinued treatment because the Sponsor decided to stop the study [ALT = 10.4 upper limit of normal (ULN), AST = 3.3 ULN, gamma-glutamyltransferase (GGT) = 1.1 ULN, alkaline phosphatase and total bilirubin were within normal ranges]. The patient was asymptomatic. Five weeks later, ALT was still elevated but below potentially clinically significant abnormality limits (1.5 ULN), and the remaining liver function tests were back within normal ranges.

Potentially clinically significant abnormalities

One patient in the amibegron/amibegron group had an increase in alkaline phosphatase ≥1.5 ULN before inclusion in the study (Day-4). In the open-label period, 1 patient had increases in AST, ALT and GGT that returned to baseline values 1.5 months after the treatment discontinuation. Three patients had increases in both AST and ALT. In the 1 case reported as an SAE, the values returned to normal 5 weeks after treatment discontinuation except for a slightly elevated ALT. For one of the other 2 patients, enzyme values returned to normal 1.5 months after treatment discontinuation and the 3rd patient was lost for follow-up. Increases in ALT only were reported in 2 patients. Values declined to normal in 1 patient 10 weeks after the first drug intake but the event resulted in premature treatment discontinuation. Values were back to borderline levels in the other patient 2.5 months later. All of these events were reported as TEAEs.

In the double-blind period, 1 Patient in the amibegron/placebo group had a total bilirubin increase ≥1.5 ULN that resulted in premature treatment discontinuation after 20 weeks of treatment. Bilirubin values decreased but were still slightly elevated 2.5 weeks after treatment discontinuation. Increase in GGT ≥3 ULN without other liver-function abnormality was reported in 1 patient in the amibegron/amibegron group who fully recovered. Both events were reported as TEAEs.

In addition to the patients with liver-function related TEAEs, 1 additional patient had on-treatment in crease in ALT ≥3 ULN that decreased with no further investigations performed, and another patient had an increase in AST ≥5 ULN that returned to normal 5 days later. For all other laboratory parameters, sporadic PCSA values were observed during the study, but no overall trend was observed.

Diastolic orthostatic hypotension occurred in 14/59 patients (23.7%) in the amibegron/placebo and 11/56 patients (19.6%) in the mibegron/amibegron group during the open-label period and in 9/57 (15.8%) and 8/56 patients (14.3%) patients, respectively, during the double-blind period. Systolic orthostatic hypotension occurred in 4/59 patients (6.8%) in the amibegron/placebo and 5/56 patients (8.9%) in the amibegron/amibegron group during the open-label treatment and in 1/57 patient (1.8%) in amibegron/placebo group during the double-blind treatment.

Supine systolic blood pressure ≤95 mmHg and a decrease ≥20 mmHg occurred in 2/59 patients (3.4%) in the amibegron/placebo and 2/56 patients (3.6%) in the amibegron/amibegron group in the open-label period, and in 1/56 patient (1.8%) in the amibegron/amibegron group during the double-blind period. A supine systolic blood pressure ≥160 mmHg and an increase ≥20 mmHg occurred in 1/59 patient (1.7%) in the amibegron/placebo group in the open-label period. None of these vital sign PCSA were reported as TEAEs.

A ≥5% weight increase occurred in 4/59 patients (6.8%) in the amibegron/placebo group and 2/56 patients (3.6%) in the amibegron/amibegron group during the open-label period, and in 7/57 (12.2%) and 3/56 (5.4%) patients, respectively, during the double-blind period. Weight decreases ≥5% occurred in 3/59 patients (5.1%) in the amibegron/placebo group and 1/56 patient (1.8%) in the amibegron/amibegron group during open-label treatment and in 3/57 (5.3%) and 4/56 (7.1%) patients, respectively, during the double-blind treatment.

In terms of peak severity at any postbaseline visit, the percentage of patients with newly emerged or worsening of PWC symptoms was generally similar in the amibegron/placebo and amibegron/amibegron groups.

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