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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00535340 **Study code**: EFC5895

Title of the study:
An eight-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of fixed dose of SR58611A 350 mg twice a day in elderly patients with Generalized Anxiety Disorder with an optional twenty-four week extension.

Study centers: International, multicenter study with 14 centers in 5 countries.

Study period:

Date first patient enrolled: 16-Mar-2007

Date last patient completed: 29-Aug-2007

Phase of development: Phase 3

Objectives:
The primary objective was to demonstrate the efficacy of SR58611 (amibegron) 350 mg twice a day (BID) compared to placebo in elderly patients with Generalized Anxiety Disorder (GAD), as assessed by a change from baseline to Visit 7 (Day 56) in the 14-item Hamilton Anxiety Rating Scale (HAM-A) total score.

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

The study was stopped prematurely after 55 patients had been randomized, 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.

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

Number of patients: Planned: 270 Randomized: 55 Treated: 55
Safety: 55

Diagnosis and criteria for inclusion:
Patients at least 60 years of age diagnosed with GAD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria diagnosed by a psychiatrist and supported by the Mini International Neuropsychiatric Interview (MINI) plus Generalized Anxiety Disorder module.

Investigational product: Amibegron tablet

Dose: 350 mg BID

Administration: oral, BID

Reference therapy: placebo

Dose: Not applicable

Administration: oral, BID

Duration of treatment: Double-blind randomized treatment period: 8 weeks (acute treatment period) + 24-weeks (optional extension treatment period).

Duration of observation: 10 weeks for those patients who did not enter the extension, and 34 weeks for those patients who entered the extension.

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), laboratory parameters (hematology, blood chemistry), vital signs (including weight), and physician withdrawal checklist (PWC).

Statistical methods:

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 count and percentage of patients experiencing each symptom listed in the PWC, as well as mean score, were provided by treatment group.

Summary:

As the study was prematurely terminated, the focus of the report and presentation of the data concern the randomized of the safety population only, defined as Randomized population - All patients randomized to receive study medication who had been assigned a treatment number by the Interactive Voice Response System, and Safety population - All patients who were randomized and took at least 1 dose of double-blind study medication.

Patient disposition:

Of the 55 randomized elderly patients, 24 completed the main study treatment period, 60% (12/2) patients in the placebo group and 34.3% (12/35) patients in the amibegron group. Of the patients completing the main study treatment period, 12 patients (7 in placebo and 5 in amibegron) entered the extension period but no one completed this period. The main reason for patient discontinuation of the acute and extension periods was Sponsor's request, 55.0% (11/20) patients in the placebo group and 40.0% (14/35) patients in the amibegron group and Subject request, 10.0% (2/20) patients in the placebo group and 11.4% (4/35) patients in the amibegron group. Discontinuation due to AEs was reported for 5% (1/20) placebo patient and 17.1% (6/35) amibegron patients and lack of efficacy was the reason for discontinuation of 5% (1/20) placebo patient and 11.4% (4/35) amibegron patients.

Exposure:

The mean ± SD exposure of patients (safety population) in the acute and extension phase was 57.6 ± 38.3 days for the placebo group and 44.2 ± 31.2 days for the amibegron group.

Demographics:

Demographic characteristics of the safety population at baseline were similar with respect to race, age, bodyweight and body mass index except for gender with more females (69.1%) than males (30.9%).

Safety:

A similar percentage of patients in the placebo (35.0%) and amibegron (34.3%) groups experienced TEAEs. No deaths occurred, and 1 patient in the amibegron group experienced a serious AE – a panic attack. One patient (5.0%) in the placebo group and 6 patients (17.1%) in the amibegron group discontinued study treatment because of TEAEs.

In terms of individual TEAEs by preferred term, 2 (5.7%) patients each in the amibegron group experienced dizziness, headache, vision blurred, dry mouth, increases in transaminases, and insomnia. Other TEAEs were reported by not more than in 1 patient. In the placebo group, the most frequently reported TEAE was dry mouth (3 patients, 15.0%), followed by headache (2 patients, 10.0%). All other TEAEs in the placebo group were reported by not more than in 1 patient.

Most TEAEs were mild or moderate in intensity. Severe TEAEs were reported by 3 (8.6%) patients administered amibegron (trigeminal neuralgia, abdominal pain, insomnia) and 1 (5.0%) patient administered placebo (insomnia). All patients fully recovered from TEAEs (11 amibegron and 6 placebo patients) or recovered with sequelae (1 amibegron and 1 placebo patient, each of whom reported insomnia).

Transaminase increases were reported as a TEAE in 2 patients; for one of these patients (in the amibegron group) the transaminases increase was >3 ULN.

The amibegron-treated patient who experienced a panic attack reported as an SAE discontinued treatment, as did the amibegron-

treated patient with a potentially clinically significant abnormality (PCSA) of increased transaminases.

One patient in the amibegron group with normal baseline value had increased transaminase values (ALT, 3.3 ULN and AST, 2.9 ULN respectively, on Day 7), which was reported as a TEAE and led to treatment discontinuation. The values returned to normal within 2 months after the last dose of investigational product. Two placebo patients with normal baseline values had high alkaline phosphatase levels of 1.6 ULN (1 patient) and high bilirubin level of 1.6 ULN (1 patient). None of these PCSA led to treatment discontinuation.

Mild impairment in creatinine clearance (50 to 80 mL/min) was reported in 15/32 (46.9%) patients in the amibegron group compared to 11/19 (57.9%) in the placebo group, and moderate impairment (30 to 49 mL/min) in 4/32 (12.5%) patients in the placebo group]. The majority of these elderly patients, 17/19 in the amibegron group and 13/16 in the placebo group had abnormal creatinine clearance at baseline and some other patients with normal baseline values developed mild renal impairment during the study, which is known and consistent with the decline in renal function with age.

Metabolism abnormalities were reported for 5 amibegron-treated patients, with 4 patients with high glucose values (≥7 mmol/L fasted or ≥11.1 mmol/L unfasted), and 1 patient with low glucose values (≤3.9 mmol/L).

A small number of patients (4 in the placebo and 2 in the amibegron) had elevated white blood cell counts (eosinophil, monocytes, and basophils), and 1 patient in the placebo and 2 patients in the amibegron group had low red blood cell and platelet counts, and all 3 patients had low hematocrit values.

Diastolic orthostatic hypotension occurred in 4/20 (20.0%) patients in the placebo group and 9/35 (25.7%) patient in the amibegron group and systolic orthostatic hypotension was reported in 4/20 (20.0%) placebo-treated and 8/35 (22.9%) amibegron-treated patients. Elevated and decreased supine blood pressure occurred rarely in both treatment groups and 1 patient in the amibegron group had elevated diastolic blood pressure on-treatment. One amibegron-treated patient had mild hypotension that was reported as a TEAE, received corrective therapy and recovered. Another patient with elevated supine diastolic blood pressured, which was reported as a TEAE led to premature treatment discontinuation.

Weight increases occurred in 1/19 (5.3%) patient in the placebo and 1/33 (3.0%) patients in the amibegron group and a weight decrease in 1/19 (5.3%) patient in the placebo group.

A similar percentage of placebo- and amibegron-treated patients experienced at least 1 newly emerged or worsened PWC symptom at the first postbaseline (36.8% and 37.0%, respectively) and second postbaseline (47.4% and 40.0%, respectively) visits. However, at the third and fourth postbaseline visits, a lower percentage of amibegron patients (28.0% and 20.0%, respectively) than placebo patients (42.1% and 47.4%, respectively) experienced symptoms measured by the PWC. The peak severity of symptoms, assessed with the PWC total score, at any postbaseline visit was 9.7 ±6.8 in the amibegron group and 12.5 ±10.6 in the placebo group (mean changes from baseline, 0 and -1.5, respectively).

Issue date: 04-Dec-2008