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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**: NCT00252343 **Study code**: EFC5892
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, tolerability of a fixed dose of SR58611A (350 mg q12) in outpatients with Generalized Anxiety Disorder.	
Study centers: Multicenter study with a total of 34 active centers in the United States.	
Study period: Date first patient enrolled: 12-Sep-2005 Date last patient completed: 06-Feb-2007	
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 atients with Generalized Anxiety Disorder (GAD), using escitalopram 10 mg once daily (QD) as positive control. The secondary objectives were to evaluate the safety and tolerability of amibegron in patients with GAD.	
Methodology: This was a double-blind, placebo- and escitalopram-controlled, randomized, parallel-group, multicenter, fixed-dose study, planned for 360 patients (male and female patients with GAD).	
Number of patients: Planned: 360 Randomized: 360 Treated: 359 Efficacy: 348 (intent-to-treat [ITT]) Safety: 359	
Diagnosis and criteria for inclusion: Male and female outpatients, 18 years and older, suffering from GAD (according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revision text, [DSM-IV-TR] and confirmed by the Mini International Neuropsychiatric Interview [MINI] plus GAD Module), with a total score on the Hamilton Anxiety Rating Scale (HAM-A) ≥20.	
Investigational product: Amibegron tablet or matching placebo	
Dose: 350 mg BID	
Administration: oral	
Reference therapy: Escitalopram capsule or matching placebo	
Dose:: 10 mg QD	
Administration: oral	
Duration of treatment: Single-blind, run-in placebo period: 1 week. Double-blind, randomized treatment period: 8 weeks	
Duration of observation: 10 weeks (including screening, treatment periods, and follow-up)	
Criteria for evaluation:	

Efficacy:

The primary efficacy variable was the change in the 14-item HAM-A 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 were assessed, such as HAM-A somatic and psychic anxiety factor scores.

Safety:
The secondary evaluation criteria were clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood chemistry), vital signs (including weight), change in sexual functioning questionnaire (CSFQ), and physician withdrawal checklist (PWC).

Statistical methods:

Efficacy:

Primary efficacy analysis was done on the change from baseline to Day 56 in the HAM-A 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 were 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 variables were evaluated by either the chi-square test or Cochran-Mantel-Haenszel (CMH) row mean score statistics

Safety:

Safety and tolerance data were summarized (by treatment group) using descriptive statistics. The incidence of potentially clinically significant abnormalities (PCSAs) in clinical laboratory results and vital signs was presented by treatment group. The CSFQ was analyzed using the 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:

Overall at baseline, of a total of 360 patients randomized, the majority of patients were female (61.9%), Caucasian (72.8%), and with an overall mean (±SD) age of 40.3 ±13.9 years. The median duration of a current episode of GAD was 14.0 months. Demographic characteristics, as well as medical history and psychiatric characteristics assessed using the HAM-A, the Montgomery-Asberg depression rating scale (MADRS), and CGI scales were similar across treatment groups at baseline. A total of 271 patients completed the study treatment period. The main reason for discontinuation was subject's request with placebo (7.6%), subject lost to follow-up with amibegron (6.8%), and AEs with escitalopram (10.6%).

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 HAM-A total score, or on the secondary efficacy endpoints. The comparison between placebo and escitalopram, which was chosen as reference treatment, confirmed the validity of the study design and the conduct of the study.

Safety results:

An overview of treatment emergent adverse events (TEAEs) in the safety population is provided below. One serious adverse event (SAE) was reported for 1 patient in the amibegron group who experienced non-cardiac chest pain and made a full recovery. There was 1 other SAE (a non treatment emergent adverse event), which was reported for 1 patient in the placebo group who had a spontaneous abortion and made a full recovery.

	Placebo (N=119)	Amibegron 350 mg bid (N=118)	Escitalopram 10 mg qd (N=122)
Patients with any TEAE (including SAEs)	80 (67.2%)	89 (75.4%)	96 (78.7%)
Patients with any serious TEAE (including SAEs leading to death)	0	1 (0.8%)	0
Patients permanently discontinuing treatment due to TEAE	8 (6.7%)	6 (5.1%)	10 (8.2%)

The most frequently reported TEAEs during the study were headache, nausea, and dizziness that were reported with a higher incidence in the amibegron group (22.0%, 11.9%, and 11.0% of patients, respectively) compared with the placebo group (8.4%, 7.6%, and 4.2%, respectively); the frequency of headache and dizziness were also higher than in the escitalopram group (17.2% and 6.6%, respectively). A lower percentage of patients reported TEAEs related to sexual dysfunction in the amibegron group (1.7%), compared to the escitalopram (3.3%) and the placebo (4.2%) groups.

Alanine aminotransferase and aspartate aminotransferase elevations without concomitant bilirubin increases were observed in 2 patients treated with amibegron. The values returned to baseline levels within 5 weeks following the last intake of amibegron. No other particular safety concerns were raised with regard to laboratory parameters and vital signs.

Discontinuation of amibegron treatment did not cause particular withdrawal effects as assessed by the PWC scale, compared with placebo withdrawal.

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