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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00332891 **Study code**: EFC5891
Title of the study: An 8-week, double-blind, placebo-controlled, multicenter study with paroxetine (20 mg q24) as positive control, evaluating the efficacy and safety of 2 fixed doses of SR58611A (175 mg q12 and 350 mg q12) in outpatients with Generalized Anxiety Disorder.	
Study centers: International, multicenter study with a total of 31 active centers in 5 countries.	
Study period: Date first patient enrolled: 03-Mar-2006 Date last patient completed: 19-Apr-2007	
Phase of development: Phase 3	
Objectives: The primary objective was to assess the efficacy of 2 fixed doses of SR58611A (amibegron) 175 and 350 mg twice daily (BID) compared to placebo in patients with Generalized Anxiety Disorder (GAD) using paroxetine (20 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 paroxetine-controlled, randomized, parallel-group, multicenter, 2 fixed dose-study in male and female patients with GAD.	
Number of patients: Planned: 480 Randomized: 508 Treated: 507 Efficacy: 506 (intent-to-treat [ITT]) Safety: 507	
Diagnosis and criteria for inclusion: Male and female outpatients, 18 to 65 years old, 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 175 mg tablet or matching placebo	
Dose: 175 mg BID and 350 mg BID	
Administration: oral	
Reference therapy: Paroxetine capsule or matching placebo	
Dose:: 20 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 secondary efficacy variables were evaluated by either the chi-square test or Cochran- Mantel-Haenszel row mean score statistics.

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. 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:

A total of 508 patients were randomized; the majority of patients were female (68.7%), all Caucasian with an overall mean (±SD) age of 41.2 ±11.0 years at baseline. The median duration of current episode of GAD was 8.0 months. Demographic characteristics as well as medical history and psychiatric characteristics assessed using HAM-A, Montgomery and Asberg depression rating scale (MADRS) and CGI scales were similar across treatment groups at baseline. A total of 476 patients completed the study treatment period. The main reason for discontinuation was AEs with placebo (4.6%), amibegron 350 mg BID (2.4%), and paroxetine (3.1%) and subject's request with amibegron 175 mg BID (2.4%).

Using the MMRM method, a reduction of 1.78 points in the HAM-A total score was observed in the group treated with amibegron 350 mg BID, compared with placebo (p=0.0420). Although the estimate obtained from LOCF ANCOVA method for this comparison was of similar magnitude compared to the results from MMRM, it was not significant (difference from placebo of -1.80, p=0.0566).

Using the MMRM method, no evidence of a difference in the HAM-A total score was observed in the group treated with amibegron 175 mg BID compared with placebo (mean difference -1.15, p= 0.1895). This result was confirmed by LOCF ANCOVA analysis (difference from placebo of -1.37 p=0.1473.

The significant difference observed between paroxetine and placebo on the primary endpoint confirmed the validity of the design and conduct of the study.

No difference between amibegron 350 mg BID and placebo, and amibegron 175 mg BID and placebo was observed for the key secondary endpoint (CGI severity of illness score).

Significant difference with placebo was observed for HAM-A psychic anxiety factor, HAM-A treatment response, CGI global Improvement score, and MADRS total score in the group treated with amibegron 350 mg BID, and SDS total score in the group treated with amibegron 175 mg BID.

Safety results:

An overview of treatment emergent adverse events (TEAEs) in the safety population is provided in the table below. Three serious adverse events (SAE) were reported for 2 patients in the placebo group who experienced coronary artery insufficiency, coronary artery stenosis, and cerebrovascular accident.

	Placebo (N=130)	Amibegron 175 mg bid (N=126)	Amibegron 350 mg bid (N=125)	Paroxetine 20 mg qd (N=126)
Patients with any TEAE (including SAEs)	42 (32.3%)	36 (28.6%)	53 (42.4%)	59 (46.8%)
Patients with any serious TEAE (including SAEs leading to death)	2 (1.5%)	0	0	0
Patients permanently discontinuing treatment due to TEAE	5 (3.8%)	1 (0.8%)	3 (2.4%)	3 (2.4%)

The most frequently reported TEAEs during the study were nausea and headache, which were reported with a lower or similar incidence in amibegron 175 mg BID compared with placebo and paroxetine groups. The incidences of nausea and headache in amibegron 350 mg BID were higher compared with placebo and lower compared to the paroxetine group. No patient experienced a TEAE related to sexual dysfunction in either of the amibegron groups compared with 4 patients receiving paroxetine. A significant improvement in the change of total CSFQ score from baseline to last visit in the global population was observed between amibegron 350 mg BID and placebo groups.

Overall, the creatinine clearance changes, except for the normal baseline population, were higher in placebo than in the amibegron groups. During the study, among the patients that presented normal creatinine clearance, more patients in the amibegron 175 mg BID and amibegron 350 mg BID groups had mild renal impairment compared with patients in the placebo group (4.8%, 11%, and 3%, respectively). No other particular safety concerns were observed with regard to laboratory parameters and vital signs.

Following discontinuation of treatment, patients in the amibegron 175 mg BID and amibegron 350 mg BID groups did not experience particular withdrawal effects, as measured by PWC, compared to patients in the placebo group.

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