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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00266747 **Study code**: EFC5893
Title of the study: An eight-week, double-blind, placebo-controlled, multicenter study with paroxetine (20 mg q24) as positive control, evaluating the efficacy, safety and tolerability of a fixed dose of SR58611A (350 mg q12) in outpatients with Generalized Anxiety Disorder.	
Study centers: International, multicenter study with 35 centers in 7 countries.	
Study period: Date first patient enrolled: 27-Dec-2005 Date last patient completed: 18-Jan-2007	
Phase of development: Phase 3	
Objectives: The primary objective was to assess the efficacy of a fixed dose of SR58611A (amibegron) (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, fixed dose study in male and female patients with GAD.	
Number of patients: Planned: 360 Randomized: 366 Treated: 366 Efficacy: 364 (intent-to-treat [ITT]) Safety: 366	
Diagnosis and criteria for inclusion: Male and female out-patients, 18 to 65 year old, suffering from GAD (according to the diagnostic and statistical manual of mental disorders, 4th edition text revision, [DSM-IV-TR] and confirmed by the mini international neuropsychiatric interview [MINI] plus GAD module), and with a Hamilton Anxiety Rating Scale (HAM-A) total score of ≥20.	
Investigational product: Amibegron tablet or matching placebo	
Dose: 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 Improvement severity score (CGI-1), from baseline to Day 56. To support this analysis, other secondary efficacy endpoints were assessed such as HAM-A somatic and psychic anxiety factor scores.

Safety:

Clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood chemistry), vital signs (including weight), changes 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 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 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 366 patients randomized, the majority of patients were female (66.9%), Caucasian (92.3%) with an overall mean (±SD) age of 40.8 ± 12.3 years. The median duration of current episode of GAD was 10.0 months. Demographic characteristics as well as medical history and psychiatric characteristics assessed using HAM-A, MADRS and CGI scales were similar across treatment groups at baseline. A total of 307 patients completed the study treatment period. The main reason for discontinuation was lack of efficacy with placebo (16.4%) and amibegron (5.0%) and AEs with paroxetine (8.1%).

Using the MMRM method, a significant reduction of 2.31 points in the HAM-A total score was observed in the group treated with amibegron, compared with placebo (p =0.0260). This was supported by the results of the LOCF ANCOVA analysis (difference from placebo of -2.68, p=0.0107). The comparison between placebo and paroxetine, which was chosen as active control, confirmed the sensitivity of the study.

No significant difference between amibegron and placebo was observed for the key secondary endpoint (CGI severity of illness score).

Improvement in all exploratory secondary parameters was observed with amibegron treatment; significant difference with placebo was observed for HAM-A somatic and psychic anxiety factors, CGI global Improvement score, PHQ-15, and EWPS total scores.

Safety results:

During the study, the incidence of patients experiencing TEAEs was lower in the amibegron group (48.3%) compared with both placebo and paroxetine groups (56.6 and 72.6%, respectively). No deaths or SAEs were reported during the study. One patient in the amibegron group discontinued the study treatment due to an AE (anxiety disorder), compared with 7 patients in the placebo group and 11 patients in the paroxetine group (see Table below).

	Placebo (N=122)	Amibegron 350 mg bid (N=120)	Paroxetine 20 mg qd (N=124)
Patients with any TEAE (including SAEs)	69 (56.6%)	58 (48.3%)	90 (72.6%)
Patients with any serious TEAE (including SAEs leading to death)	0	0	0
Patients permanently discontinuing treatment due to TEAE	7 (5.7%)	1 (0.8%)	11 (8.9%)

The most frequently reported TEAEs in the amibegron group were headache and nausea that were reported with a lower or similar incidence compared with the placebo group. One patient receiving placebo and 1 patient receiving amibegron each experienced a TEAE related to sexual dysfunction (libido decreased) compared with 14 patients receiving paroxetine.

Transaminase elevations (ALT≥3 ULN) without concomitant bilirubin increases were observed in 3 patients (1 patient receiving placebo and 2 patients receiving amibegron), all with normal baseline values. In the 2 amibegron-treated patients, these abnormalities were reported at the end of the 8-week treatment period. One of the amibegron patients recovered within the month following investigational product (IP) discontinuation and for the other patient, transaminases values were still increased at the last available assessment (3 days after the last IP intake).

During the study, more patients in the amibegron group had mild creatinine clearance changes from normal baseline compared with patients in the placebo group (12/115 patients versus 6/115 patients). No other particular safety concerns were raised with regard to laboratory parameters and vital signs. There were no differences across treatment groups with regard to hematology parameters, except for eosinophils and monocytes.

Following abrupt discontinuation of treatment, patients in the amibegron group experienced fewer of the withdrawal effects than patients treated with placebo or paroxetine.

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