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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)			**Study Identifier**: NCT00432614 **Study code**: EFC6224
Title of the study: A multi-national, multi-center, double blind, placebo-controlled, parallel group, fixed dose efficacy and safety study of SR58611A 350 mg twice daily vs. placebo in adults with Major Depressive Disorder on concomitant treatment with escitalopram 10 mg/d.			
Study centers: International, multicenter study with 52 centers in 13 countries.			
Study period: Date first patient enrolled: 24-Jan-2007 Date last patient completed: 22-Feb-2008			
Phase of development: Phase 3			
Objectives: The primary objective was to compare, after 8 weeks, the efficacy of amibegron versus placebo in patients with Major Depressive Disorder (MDD) who are on concomitant treatment with escitalopram 10 mg/day. The secondary objective was to document clinical safety and tolerability of the association of amibegron versus placebo both on concomitant treatment with escitalopram 10 mg/day through comparison between treatment groups on spontaneously reported adverse events (AEs), physical examination, and measurement of weight, temperature, heart rate, blood pressure, and routine clinical laboratory tests.			
Methodology: This was a multinational, multicenter, randomized, double-blind, 3 parallel group, fixed-dose, placebo-controlled, Phase 3 study in male and female patients with MDD.			
Number of patients:	Planned: 500 Efficacy: 500 intent-to-treat (ITT)	Enrolled: 510 Safety: 506	Treated: 506
Diagnosis and criteria for inclusion: Male and female adult in- or out-patients (18 to 65 years of age) with MDD, as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision criteria (DSM-IV-TR).			
Investigational product: Amibegron tablets and matching placebo tablets			
Dose: 350 mg			
Administration: oral twice daily (BID)			
Reference therapy: Escitalopram capsules and matching placebo capsules			
Dose: 10 mg			
Administration: oral once a day			
Duration of treatment: Double-blind randomized treatment period of 8 weeks			
Duration of observation: 12 weeks (including screening, treatment period, and follow-up)			

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the mean change in the 17-item Hamilton Depression rating scale (17-item HAM-D) total score, from baseline to Day 56. The key secondary efficacy variables were the speed of response, which was based on time to first response (the response is defined as the improvement of at least 50% versus baseline for the 17-item HAM-D total score), and the change in Clinical Global Impression, severity of illness score (CGI-1), from baseline to Day 56. Other secondary efficacy endpoints that were assessed included change from baseline in the 17-item HAM-D depressed mood item score, proportion of patients with 17-item HAM-D treatment response, percentage of patients demonstrating an early sustained response, and percentage of patients demonstrating clinical remission.

Safety:

Safety assessments included clinical monitoring of AEs, laboratory parameters (hematology, blood chemistry and urinalysis), vital signs measurements, body weight, oral temperature, physical examinations, and the Physician's Withdrawal Checklist (PWC).

Statistical methods:

Efficacy:

The primary analysis was based on the ITT population. The primary efficacy analysis was done on the change in the 17-item HAM-D total score, from baseline to Day 56, using a mixed-effect model with repeated measures (MMRM), under the missing at random framework. Student t-test statistics were used to determine the statistical significance of the primary efficacy comparison of amibegron versus placebo, both on top of escitalopram, and for the comparison of placebo on top of escitalopram versus placebo alone for assessing assay sensitivity.

Time to fist response was compared using log-rank test between escitalopram + amibegron versus escitalopram + placebo, and CGI-1 was analyzed using analysis of covariance (ANCOVA) only.

Safety:

Safety and tolerability data were summarized by treatment group using descriptive statistics. Incidences of potentially clinically significant abnormalities (PCSAs) in clinical laboratory results and vital signs were presented by treatment group. 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 510 patients were randomized and the majority of the patients were female (64.1%), Caucasian (76.3%), with an overall mean (±SD) age of 43.1 ±11.9 years at baseline. The median duration of the current episode of MDD was 16.0 weeks. Demographic characteristics as well as medical history and psychiatric characteristics assessed using 17-item HAM-D and CGI-1 scales were comparable across treatment groups at baseline. A total of 420 (82.4%) patients completed the study treatment period. The main reason for discontinuation was AEs in the escitalopram + placebo treatment group (7.8%) and in the escitalopram + amibegron treatment group (5.9%), and lack of efficacy (9.8%) in the placebo treatment group.

Based on the MMRM analysis, there was no evidence of a difference in the 17-item HAM-D total score from baseline to Day 56 between the escitalopram + amibegron treatment group and the escitalopram + placebo treatment group (mean difference of -0.30; p=0.6865). This result was confirmed by ANCOVA last observation carried forward (LOCF) analysis (mean difference of -0.60; p-0.4631). The significant difference between the escitalopram + placebo treatment group versus the placebo treatment group confirmed the assay sensitivity of the study (mean difference of -3.22; p=0.0005).

No significant differences were observed between the escitalopram + amibegron treatment group and the escitalopram + placebo treatment group for the key secondary endpoints (time to first response and CGI-1) or for any of the other secondary criteria. Significant differences between the escitalopram + placebo treatment group and the placebo treatment group were observed for all the secondary efficacy endpoints.

Safety results:

No deaths were reported in the study. Five patients reported serious adverse events (SAEs) such as liver function test abnormal, lipoma, intestinal strangulation, acute hepatitis, and intervertebral disc protrusion. An overview of treatment emergent adverse events (TEAEs) in the safety population is provided in the table below.

	Placebo (N=102)	Escitalopram 10 mg qd Placebo (N=202)	Escitalopram 10 mg qd Amibegron 350 mg bid (N=202)
Patients with any TEAE (including SAEs)	64 (62.7%)	140 (69.3%)	149 (73.8%)
Patients with any serious TEAE (including SAEs leading to death)	1 (1.0%)	3 (1.5%)	1 (0.5%)
Patients permanently discontinuing treatment due to TEAE	6 (5.9%)	16 (7.9%)	12 (5.9%)

The most frequently reported TEAE during the study was nausea. This was reported at a higher incidence in the escitalopram + amibegron treatment group (29.2%) compared with the escitalopram + placebo treatment group (23.8%) and the placebo treatment group (6.9%). Other frequently reported TEAEs included diarrhea, headache and dizziness, all of which were reported at a similar incidence in the escitalopram + amibegron treatment group and the escitalopram + placebo treatment group. The incidence of these events was lower in the placebo treatment group compared with the other 2 treatment groups.

Elevations in alanine aminotransferase (ALT) ≥3 upper limit of normal (ULN) were observed in 5 patients including 1 patient in the placebo treatment group and 4 patients in the escitalopram + amibegron treatment group. All 5 patients had normal baseline values. Increased ALT ≥3 ULN was associated with total bilirubin ≥2 ULN in 1 patient who was in the placebo treatment group. For 3 of the patients treated with escitalopram + amibegron, these abnormalities in ALT occurred at the end of the 8-week treatment period.

During the study a similar proportion of patients treated with escitalopram + placebo and with escitalopram + amibegron had mild creatinine clearance changes from normal baseline (12/169 patients, 7.1% and 13/175 patients, 7.4%, respectively). The ~~incidence~~ number of patients with mild creatinine clearance changes from normal baseline was lower in the placebo treatment group (2/92 patients, 2.2%). No other particular safety concerns were raised with regard to laboratory parameters and vital signs.

Following abrupt discontinuation of treatment, patients treated with escitalopram + placebo or with escitalopram + amibegron did not experience particular withdrawal effects, as measured by PWC, compared with patients in the placebo treatment group.

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