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Sponsor/Company: sanofi-aventis **Drug substance**: SR58611 (amibegron)	**Study Identifier**: NCT00855530 **Study code**: LTS4848

Title of the study:
A fifty-two-week multicenter, open-label study evaluating the long-term safety and tolerability of SR58611A 350 mg q12 in patients with Major Depressive Disorder.

Study centers: International, multicenter study with 43 centers in 11 countries

Study period:

Date first patient enrolled: 28-Sep-2005

Date last patient completed: 18-Jul-2007

Phase of development: Phase 3

Objectives:

The primary objective was to evaluate the long-term safety and tolerability of SR58611 (amibegron) in patients with MDD.

The secondary objective was to determine plasma concentrations of SR58878 (the active metabolite of amibegron) for pharmacokinetic population analyses, to evaluate the quality of life (QoL) in patients with MDD, and to evaluate the efficacy of amibegron in patients with MDD.

Methodology:

This was an open-label, fixed-dose, multinational, multicenter, Phase 3 study in male and female patients with MDD.

Number of patients: Planned: 500 Enrolled: 527 Treated: 523
Efficacy: 517 intent-to-treat (ITT) Safety: 523

Diagnosis and criteria for inclusion:

Male and female outpatients ≥18 years of age, with MDD as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria and confirmed by the semi-structured Mini International Neuropsychiatric Interview, recurrent episode for at least 1 month prior to entry into the study, and with a total score ≥18 on the 17-item Hamilton Depression rating scale (17-item HAM-D).

Investigational product: amibegron tablets

Dose: 350 mg

Administration: oral, BID

Reference therapy: Not aoolicable

Duration of treatment:

Open-label treatment period: 12 weeks. Randomized double-blind period: 24 to 52 weeks.

Duration of observation:

Up to 16 months (including a 1-week screening period, a 12-week open-label treatment period, a 24- to 52-week double-blind treatment period, and a 1-week off-drug safety evaluation following completion of treatment or permanent early treatment discontinuation).

Criteria for evaluation:

Safety:

Safety was assessed by clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood chemistry), vital signs (including weight), physical examinations, and physician withdrawal checklist (PWC).

Efficacy:

All efficacy variables were secondary endpoints in this study. Efficacy was evaluated using the 17-item Hamilton Depression rating scale (HAM-D), Clinical Global Impression (CGI), Sheehan Disability Scale (SDS), QoL Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), Medical Outcomes Study Short Form-36 (SF-36), and Endicott Work Productivity Scale (EWPS). The Q-LES-Q-SF, SF-36 and EWPS were performed in selected countries only.

Pharmacokinetics:

The concentration of SR58878 was determined for the purpose of developing a population pharmacokinetics model. Single blood samples (6 mL) were collected from each patient premorning dose at Week 2 (trough level), 1 to 2 hours postmorning dose at Week 4 (maximal concentration), 4 to 8 hours postmorning dose at Week 8 and anytime postmorning dose at Week 24.

Statistical methods:

All analyses were presented by age group (adult: 18 to 64 years; elderly: ≥65 years of age) and overall.

Safety:

Safety and tolerability data were summarized using descriptive statistics. Incidences of potentially clinically significant abnormalities (PCSAs) in clinical laboratory results and vital signs were presented by age group. Summaries of the count and percentage of patients experiencing each symptom listed in the PWC as well as mean score were provided by age group.

Efficacy:

Analysis of efficacy data was descriptive only. Efficacy variables were evaluated for the ITT population.

Summary:

Safety results:

An overview of treatment emergent adverse events (TEAEs) in the safety population is provided in the table below.

	Amibegron 350 mg bid		
	Adult (N=484)	Elderly (N=39)	Overall (N=523)
Patients with any TEAE (including SAEs)	400 (82.6%)	31 (79.5%)	431 (82.4%)
Patients with any serious TEAE (including SAEs leading to death)	33 (6.8%)	5 (12.8%)	38 (7.3%)
Patients with any TEAE leading to Death	0	0	0
Patients permanently discontinuing treatment due to TEAE	77 (15.9%)	10 (25.6%)	87 (16.6%)

In total, 38 patients (7.3%) had TEAEs reported as serious; 33 adult patients (6.8%) and 5 elderly patients (12.8%). The most frequently reported TEAEs during the study were headache (21.4%), accidental overdose, intake in excess defined as a dosing above 2 tablets/day or 700 mg/day (21.4%), nausea (13.6%), influenza (9.6%), dizziness (9.2%), nasopharyngitis (9.2%), insomnia (8.8%), somnolence (6.1%), diarrhea (6.1%), back pain (6.1%), abdominal pain upper (5.9%), and gastritis (5.2%).

Elevations in alanine aminotransferase (ALT) ≥3 upper limit of normal (ULN) were observed in 21 patients without concomitant bilirubin increase ≥2 ULN. Of these, 16 patients (14 adult and 2 elderly patients) had normal baseline values. Most of the initial ALT elevations occurred within the first 2 months of treatment.

During the study, the number of patients with mild renal impairment (creatinine clearance ≥50 and ≤80 mL/min) was 24.4% in adult patients (115/472) and 72.2% in elderly patients (26/36). Furthermore, more than half of these patients already had mild renal impairment at baseline (66/115 adult patients and 21/26 elderly patients). When considering the adult patients with normal renal function at baseline who developed mild renal impairment during the study, the majority of these patients were between 45 and 64 years of age. These findings are consistent with the decline in renal function with age. One patient (55 years old) had mild renal impairment at baseline that became severe during the study but returned to baseline level while the study treatment was continued.

The most frequently reported PCSAs in vital signs during the study was orthostatic hypotension, both in diastolic and systolic blood pressure. No other particular safety concerns were raised with regard to other laboratory parameters and vital signs. Following discontinuation of treatment, patients did not experience withdrawal effects, as measured by PWC.

Efficacy results:

A total of 527 patients were assigned to receive amibegron 350 mg BID. The majority of the patients were female (76.3%) and most of the patients were Caucasian, with a similar racial mix for both age groups. The mean age was 42.7 ± 11.3 years in the adult patients and 70.4 ± 4.2 years in the elderly patients. Overall, the median duration of the current episode of MDD was 13.0 weeks, with a median time of 2.0 years between the current and last episode. A total of 266 patients completed the study treatment period. The main reason for discontinuation was AEs (16.1%), lack of efficacy (12.3%), and patient's request (11.0%).

All secondary efficacy endpoints and QoL parameters showed a postbaseline improvement as compared with baseline. There was a trend for the improvement in these parameters increasing throughout the study. The benefit of treatment was apparent in both, adult and elderly patients.

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