*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| **Sponsor/Company**: sanofi-aventis<br>**Drug substance**: SR58611 (amibegron) | **Study Identifier**: NCT00825058<br>**Study code**: EFC5374 |
| **Title of the study**:<br>A double-blind, multicenter study evaluating the efficacy and safety of one fixed dose of SR58611A (700 mg per day) versus placebo and paroxetine (20 mg per day) in patients with a recurrent major depressive episode. | |
| **Study centers**: International, multicenter study with a total of 29 active centers in 7 countries. | |
| **Study period**:<br>Date first patient enrolled: 27-Nov-2003<br>Date last patient completed: 28-May-2004 (main treatment phase)<br>11-Oct-2004 (extension phase) | |
| **Phase of development**: Phase 3 (confirmatory study) | |
| **Objectives**:<br>The primary objective was to demonstrate the antidepressant efficacy (Hamilton depression rating scale [HAM-D]) of amibegron 700 mg/day compared with placebo in the treatment of patients with a recurrent major depressive episode.<br>The secondary objective was to assess the safety profile of amibegron 700 mg/d in comparison to placebo and to assess plasma concentrations of the active metabolite. | |
| **Methodology**:<br>This was a double-blind, placebo and paroxetine-controlled, randomized, parallel-group, multicenter, fixed dose study. | |
| **Number of patients**: Planned: 300 Randomized: 318 Treated: 317<br>Efficacy: 316 Safety: 317 Pharmacokinetics: 252 | |
| **Diagnosis and criteria for inclusion**:<br>Male and female in- or out-patients, 18 to 65 years of age, suffering from a recurrent major depressive episode of at least moderate intensity (DSM-IV). Patients have been hospitalized for the treatment of a previous episode; or a previous episode required antidepressant treatment(s) at the recommended dose level for at least 2 months. The duration of the current episode was of at least 6 weeks unless the severity of symptoms justified shorter duration. | |
| **Investigational product**: Amibegron 350 mg tablets or matching placebo | |
| Dose: 700 mg | |
| Administration: oral, 350 mg administered q12 h | |
| **Reference therapy**: Paroxetine or matching placebo | |
| Dose:: 20 mg once a day (QD) | |
| Administration: oral | |

**Duration of treatment**:

There was a 3 to 9-day, single-blind placebo run-in period, after which patients were randomized to the double-blind main treatment phase of the study and received either 700 mg (2 x 350 mg/d) of amibegron at 12-hour intervals (q12h), or 20 mg daily of paroxetine, or placebo (matching tablets and capsules). The main treatment phase of the study lasted a duration of 42 days (6 weeks).

**Duration of observation**:

The total duration of observation (placebo run-in period and double-blind period) was approximately 7 weeks. An optional extension phase under the same double-blind treatment conditions was proposed to all patients who improved at Week 6, for an additional 18 weeks.

**Criteria for evaluation**:

Efficacy:

Primary efficacy variable
The primary efficacy analysis was performed on the change from baseline to Week 6 of the total score of the HAM-D 17 items.

Secondary efficacy variable(s)
The secondary efficacy analysis was performed using HAM-D subscores; HAM-D responders and remitters; HAM-A total score and subscores; Montgomery and Asberg depression rating scale (MADRS) total score; clinical global impression (CGI) severity and improvement scores; patient global impression (PGI) improvement score; social and occupational functioning assessment scale (SOFAS) score.

Safety:
Safety was assessed by clinical monitoring of adverse events (AEs), laboratory parameters (hematology, blood and chemistry), physical examination findings, electrocardiogram (ECG) parameters, changes in vital signs, and body weight.

Pharmacokinetics:

Measurement of SR58878 plasma concentrations. Blood samples were collected within 1 to 3 hours following the last morning drug administration for the determination of SR58878 plasma concentrations, at Visit 4 (Day 14) and Visit 6 (Day 42) for the main study phase and at Visit 11 (Week 24) for the extension study phase or in an event of serious AE (SAE) or premature discontinuation. SR58878 plasma concentrations were assayed using a validated liquid chromatography with tandem mass spectrometry (LC/MS-MS) method with a limit of quantification (LOQ) of 4.00 ng/mL.

**Statistical methods**:

Efficacy:

Efficacy variables were evaluated in an intent-to-treat (ITT) population using both the observed-case (OC) and last observation carried forward (LOCF) approaches. Primary efficacy analysis was done on the change from baseline in the HAM-D 17-item total score at the final visit of the double-blind treatment period using analysis of covariance (ANCOVA). Secondary efficacy endpoints were analyzed using ANCOVA for continuous endpoints, and Fisher's exact test or Cochran-Mantel-Haenszel (CMH) test for categorical endpoints.

Safety:

Safety analysis was done on the exposed (treated) population. Treatment emergent AEs (TEAEs) during the main treatment and extension periods were summarized by system organ class and preferred term, grouped by treatment. Mean changes from baseline were summarized using descriptive statistics for laboratory test variables, vital signs, and ECG data. Incidences of potentially clinically significant abnormalities (PCSAs) in laboratory test results, vital signs or ECG data were presented by treatment group.

Pharmacokinetics:

Descriptive statistics and statistical analysis were performed with SR58878 plasma concentrations observed within 1 to 3 hours following amibegron administration. Plasma levels on Day 14 (Visit 4), Day 42 (Visit 6) and Week 24 (Visit 11) were summarized using descriptive statistics separately by visit.
Analysis of steady state was evaluated using ANOVA method comparing concentrations at Day 42 with those at Day 14. If the difference between concentrations at both days was not statistically different, then steady state was considered achieved by Day 14.

The influence of covariates, such as gender, weight, and age were evaluated by examining correlations between concentrations, and weight and age, and by using the ANOVA method for gender using data from Visit 4 (Day 14) and Visit 6 (Day 42). Relationship between plasma concentrations and safety parameters (ECG parameters) measured at Visit 4 (Day 14) and Visit 6 (Day 42) were explored using linear regression techniques.

**Summary**:

Efficacy results:

Overall at baseline, of a total of 318 patients randomized, the majority of patients were female (71.9%), Caucasian (99.4%) with an overall mean age (standard deviation [SD]) of 44.0 years (10.6). The mean number (SD) of previous episodes of MDD was 2.8 (2.1), the mean duration of current episode 92.8 days (71.9). Mean (SD) total scores for HAM-D and MADRS were 26.0 (2.7) and 30.8 (5.1), respectively. Demographic characteristics as well as medical history were similar across treatment groups. A total of 40 (12.6%) patients discontinued treatment. The main reasons for treatment discontinuation were lack of efficacy (19 patients, 6.0%), Investigator/subject's request (11 patients, 3.5%), and AEs (8 patients, 2.5%). Discontinuations related to lost to follow-up and other occurred as single incidences (0.3%).

On the primary efficacy endpoint in the ITT population, amibegron 700 mg/day was associated with a significantly greater decrease in the mean change from baseline of the total score of the 17-item HAM-D total score, compared with placebo (-13.31 [7.18] versus -11.12 [7.17], respectively, difference in mean changes: -2.18, 95% CI = [-3.96, -0.41], p = 0.016). Paroxetine was used as an active control in this study and showed a marginally significant improvement compared with placebo (-13.17 [7.18] versus -11.12 [7.17], respectively, difference in mean changes: -2.05, 95% CI = [-4.24, 0.14], p = 0.066), but the study was not powered to detect a statistical difference between placebo and paroxetine. The magnitude of the effect was comparable to amibegron.

The difference between amibegron and placebo was greater in more severely depressed patients (ITT patients with baseline HAM-D total score >25: amibegron: (-15.63 [7.86] versus placebo: -11.86 [7.86], difference in mean changes: -3.78, 95% CI = [-6.47, -1.08], p = 0.006). The analysis of the HAM-D total score in the ITT population showed that the percentages of early onset responders was greater with amibegron compared with placebo (29.2% versus 17.1%, respectively, p = 0.026). No significant difference was observed in percentages of responders and remitters at last visit, and in sustained responders.

Amibegron was superior, or tended to be superior to placebo in the following secondary efficacy endpoints measured in the ITT population: HAM-D depressed mood item score (p = 0.028), melancholia HAM-D item score (p = 0.031) and core items factor scores (p = 0.067); HAM-A total score (p = 0.010), MADRS total score (p = 0.058), CGI severity and improvement scores (p = 0.011 and p = 0.025, respectively), PGI improvement score (p = 0.074), SOFAS total score (p = 0.058), HAM-D anxiety/somatization (p = 0.011), retardation (p = 0.022), and sleep disturbance factor scores (p = 0.067). No significant improvement was observed on HAM-D cognitive disturbance factors scores.

Safety results:

An overview of TEAEs in this study is provided in the table below.

| | **Placebo (N=123) n (%)** | **SR58611A 700 mg (N=131) n (%)** | **Paroxetine 20 mg (N=63) n (%)** |
|---|---|---|---|
| Patients with any TEAE (including SAEs) | 38 (30.9) | 49 (37.4) | 26 (41.3) |
| Patients with any SAE (including SAEs leading to death) | 0 (0.0) | 3 (2.3) | 0 (0.0) |
| Deaths | 0 (0.0) | 1 (0.8) | 0 (0.0) |
| Patients permanently discontinuing treatment due to AE | 1 (0.8) | 5 (3.8) | 2 (3.2) |

During the main treatment phase, the percentage of AEs in the amibegron 700 mg group (37.4%) was lower than in the paroxetine group (41.3%), but higher than in the placebo group (30.9%). The death (suicide) and the 2 other SAEs (hyperglycemia and suicide attempt) observed during the main treatment phase were in the amibegron 700 mg group. A total of 8 patients discontinued from study treatment due to an AE: 5 patients from the amibegron 700 mg group, 2 patients from the paroxetine group and 1 placebo patient. The most frequently (>5%) reported TEAEs in the amibegron 700 mg group were headache (10.7%) and nausea (9.9%) compared with the paroxetine (6.3% and 14.3%, respectively) or placebo (10.6% and 3.3%, respectively) groups. Both of these events were mild to moderate in intensity.

The total incidence of alanine aminotransferase (ALT) PCSAs was higher in the amibegron 700 mg group (3.9%) when compared with the paroxetine 20 mg group (1.6%) and placebo group (0%).

Two of the 5 patients with postbaseline PCSA increases from the amibegron 700 mg group reported normal baseline values. Both of these patients reported increases in ALT values of ≥3 ULN (3.2 and 12.2 ULN), without an associated increase in bilirubin.

During the extension phase, the percentage of AEs in the amibegron 700 mg group (21.3%) was lower than both the paroxetine (42.4%) and placebo treated groups (24.2%). No deaths or SAE occurred during the extension phase of the study. A total of 10 patients discontinued from study treatment due to an AE: 5 patients from the amibegron 700 mg group and 5 patients from the paroxetine group. The most frequently reported TEAE in the amibegron 700 mg group was headache (6.7%). Body weight increase (≥7%) was observed at a lower incidence and body weight decrease (≥7%) was observed at a higher incidence in the amibegron 700 mg group compared with the other treatment groups.

The total incidence of ALT PCSAs was high in the placebo group (6.1%) when compared with the amibegron 700 mg group (2.8%) and paroxetine 20 mg group (3.2%).

No clinically relevant differences between treatment groups with regard to white blood cells, red blood cell, platelet, vital sign, or ECG PCSAs were observed during the main treatment and extension phases of the study. There were no other notable safety findings.

Pharmacokinetic results:

Overall, SR58878 plasma concentrations were consistent between the 3 visits. SR58878 steady state was statistically reached by Day 14 ($p = 0.656$). Overall, no difference between male and female patients was demonstrated ($p = 0.760$). No relationship was revealed between SR58878 plasma concentrations and weight ($p = 0.235$) or age ($p = 0.473$).

Pharmacokinetic/Pharmacodynamic relationship:

There was no relationship between QTcF- or QTcB-interval change from baseline and SR58878 plasma concentrations as shown by nonsignificant changes from baseline of the slopes ($p>0.05$).

**Issue date:** 27-Feb-2009