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Sponsor/Company: sanofi-aventis **Drug substance**: SR46349 (eplivanserin)	**Study Identifier**: NCT00805350 **Study code**: EFC10844

Title of the study:
Efficacy and safety of eplivanserin 5mg/day in insomnia characterized by sleep maintenance difficulties: a 6-week, randomized, double-blind, placebo-controlled, polysomnography study

Study center(s): International, multicenter study with 57 centers in 7 countries

Study period:

Date first subject/patient enrolled:	01-Dec-2008
Date last subject/patient completed:	05-Jun-2009

Phase of development: 3

Objectives:

The primary objective was to assess the efficacy of eplivanserin 5mg/day in comparison to placebo after 6 weeks of treatment on sleep maintenance of insomniac patients, as measured by Polysomnography Wake Time After Sleep Onset (PSG-WASO) and Polysomnography Number of Awakenings (PSG-NAW).

The secondary objectives were to evaluate the effects of eplivanserin 5mg/day as compared with placebo on:

- other sleep parameters measured by PSG recordings (Total Sleep Time – PSG-TST, Sleep Efficiency – PSG-SE, Latency to Persistent Sleep – PSG-LPS) and reported by patients (Wake Time After Sleep Onset – pr-WASO, Number of Awakenings – pr-NAW, Total Sleep Time – pr-TST, QoS and Refreshing Quality of Sleep – RQoS)
- sleep architecture
- daytime functioning using the Sleep Impact Scale (SIS)
- patient's impression of treatment effects using the Patient's Global Impression questionnaire
- the potential for next-day residual effects (using patient's morning questionnaire and psychometric tests)
- the potential for rebound insomnia following abrupt discontinuation of treatment
- the effect of treatments on the quality of life of patients with primary insomnia using the SF-36 Health Survey
- the clinical safety and tolerability of eplivanserin 5mg/day compared with placebo.

Methodology:

Randomized, double-blind, placebo controlled study with 2 parallel groups

Number of subjects/patients:

Planned:	600
Randomized:	637
Treated:	636
Efficacy population:	636
Safety population:	636

Diagnosis and criteria for inclusion:

Adult patients with primary insomnia based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition – text revisions (DSM-IV-TR) with difficulty initiating or maintaining sleep, or non restorative sleep for at least 1 month preceding the study visit, and having clinically significant distress or impairment in social, occupational or other important areas of functioning.

Investigational product: SR46349 (eplivanserin) tablets

Dose: 5mg/day

Administration: oral, every night at dinner time

Reference therapy: Placebo tablets

Administration: oral, every night, at dinner time

Duration of treatment: 6 weeks

Duration of observation: 9 weeks

Criteria for evaluation:

Efficacy:

Primary efficacy endpoints
Primary efficacy endpoints were change from baseline of mean PSG-WASO on N41/N42 and change from baseline of mean PSG-NAW on N41/N42.

Secondary efficacy endpoints
Secondary efficacy endpoints were other PSG sleep parameters:

- PSG-TST, PSG-SE (TST/Time in Bed), PSG-LPS
- sleep architecture: percentage of sleep time spent in each sleep stage (1, 2, 3-4/SWS, REM), shift to stage 1, shift to wake, stage 1 + WASO, (stages 3&4/stage 1 + WASO)
- patient-reported sleep parameters
- patient Global Impression (PGI)
- sleep Impact Scale (SIS)
- SF-36 Health Survey

Additional analysis included responder rate.

Safety:

Safety evaluation criteria were occurrence of treatment emergent adverse events (TEAEs), laboratory evaluations, vital signs, electrocardiograms (ECGs), next-day residual effect, rebound and withdrawal effects.

Statistical methods:

Efficacy:

All efficacy analyses were performed on the intent-to-treat (ITT) population.

Primary efficacy endpoints

Main analysis
The analysis of primary efficacy endpoints is described for PSG-WASO. The same analysis was performed for the co-primary endpoint PSG-NAW.

The comparison of the PSG WASO change from baseline between eplivanserin versus placebo was performed at week 6 on the ITT population with a mixed effect model with repeated measures (MMRM) approach assuming the missing at random framework. This model ran using SAS Mixed procedure with an unstructured correlation matrix to model the within patient errors. Parameters were estimated using restricted maximum likelihood method with the Newton Raphson algorithm. Denominator degrees of freedom were estimated using Satterthwaite's approximation. This model included the fixed categorical effects of treatment, visit (mean of nights N20/N21 and mean of nights N41/N42), and treatment by visit interaction, as well as the mean baseline nights of PSG WASO as continuous fixed covariate. This model provided the baseline adjusted least-squares means (LS-means) estimates of PSG WASO at week 6 by treatment group, as well as the difference of these estimates versus placebo with their corresponding standard errors, degrees of freedom, Student t test statistics and associated 95% confidence intervals.

Multiplicity issue

To handle the multiplicity of the two co-primary endpoints analyzed (PSG-WASO and PSG-NAW at Week 6), a Hochberg's procedure was used as follows: if the worst comparison (largest p-value) was significant at 5% level, then the two comparisons (PSG-WASO and PSG-NAW) were declared significant, if the worst comparison was non-significant at 5% level, the significance of the best comparison (smallest p-value) was evaluated at the 2.5% level.

Supportive analysis

To assess the sensitivity of the primary analysis, supportive analyses of covariance (ANCOVA) were conducted based on the 2 following strategies "Last observation carried forward (LOCF)" and "Observed cases (OC)". These analyses used treatment factor as fixed effect with 2 levels (eplivanserin and placebo) and mean baseline nights of PSG WASO as covariate. These 2 models provided the baseline adjusted least-squares mean (LS-mean) estimates at week 6 by treatment group, as well as the difference of the estimate versus placebo with their corresponding standard error, Student t test statistics and associated 95% confidence interval.

Secondary efficacy endpoints

The mean change from baseline of most of other PSG variables, the weekly mean change from baseline of patient's morning sleep questionnaire variables and the change from baseline of each sub-score of SIS were analyzed on the ITT population using the same model as for primary analyses (MMRM). The remaining PSG parameters were summarized using descriptive statistics treatment group at baseline, on nights N20/N21 (Week 3) and N41/N42 (Week 6) based on each patient of the raw data averaged on pair of PSG nights and on the corresponding change from baseline.

For PGI scales, the count and percentage of each category were described by group at each evaluation (Week 3, Week 6) using OC strategy. The count and percentage of favorable responses were provided; analysis was performed using Chi square test to compare percentage of favorable responses (for each of the 4 questions) versus unfavorable ones.

The change from baseline of the SF36 sub-scores and summary scores were carried out with ANCOVA at Week 6 (LOCF strategy) using the treatment group as fixed-effect and the baseline value as covariate.

Safety

All safety analyses were performed on the all treated population.

Adverse events

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that occurred from first dose of double-blind study medication up to 14 days after the last dose of double-blind study medication. For summaries of all TEAEs, counts were provided by treatment group for each preferred term within each SOC concerned. Percentages were calculated with the number of patients from the all treated population in each group.

Laboratory, vital signs, and electrocardiogram parameters

Summaries of patients with at least one treatment emergent potentially clinically significant abnormality (PCSA) for laboratory, ECG, vital signs parameters were provided by treatment group taking into account any abnormalities from the day after the first dose of double blind study medication up to 14 days after last dose of double blind study medication. For quantitative safety parameters, descriptive statistics (at baseline, by visit for vital signs and at worst values) were used to summarize results and changes from baseline values by treatment group. Percentages were calculated with the number of patients from the all treated population in each group.

Residual effects

The weekly mean change from baseline to week 6 of the Sleepiness in the morning and ability to concentrate in the morning were analyzed on the all treated patients using the same model (MMRM) as for primary analysis.

DSST and RAVLT were performed on the all treated patients and were analyzed at both timepoints (morning and afternoon) on the change from the mean baseline on days (SD1/SD2) to the mean on days (D41/D42) (Week 6) using the same model as for primary analysis (MMRM).

Rebound effect

Rebound analyses were performed on all treated patients, who performed the run-out period (who completed the double-blind period and received at least one dose of single-blind placebo) using an ANCOVA with the mean baseline value as covariate, based on OC strategy.

Summary:

Disposition and baseline Demographics:

A total of 637 patients were randomized, 636 patients were treated and 315 patients received placebo and 321 received eplivanserin 5 mg. Of these 636 patients, 38 (6.0%) withdrew from the study, 22 (7.0%) in the placebo group and 16 (5.0%) in the eplivanserin group. The main reason for discontinuation was "other reason" in the placebo group (17 patients, 5.4%) and AE in the eplivanserin group (7 patients, 2.2%). At baseline, the 2 treatment groups were comparable for demographics and sleep characteristics. As expected, the study population exhibited major sleep maintenance difficulties (mean PSG-WASO >90 minutes and no or few difficulties with sleep initiation (mean PSG-LPS ≤17 minutes).

Efficacy results:

Analysis of the co-primary efficacy endpoints showed that eplivanserin 5mg/day at week 6 improved sleep maintenance by decreasing PSG NAW (LS Mean change from baseline of -3.16). The difference versus placebo was -1.62, p<0.0001. However, no difference was detected between the two groups on PSG-WASO at week 6 (LS Mean difference of -2:30 min:sec, p = 0.4118). Nevertheless, the study reached the primary objective, the demonstration of sleep maintenance as the difference versus placebo of the change from baseline of one of the co-primary endpoints was significant.

Among the various secondary endpoints, PSG-WASO and PSG-NAW at 3 weeks were decreased (improved) on eplivanserin as compared to placebo (for PSG-WASO: LS Mean difference = -5:57 min:sec, p = 0.0356; for PSG-NAW: LS Mean difference = -1.33, p<0.0001). Patient reported WASO showed consistent results with PSG-WASO (LS Mean difference higher at week 3 than at week 6 and in favor to eplivanserin 5mg/day). No difference was observed between the two groups on PSG-LPS at either week 3 or week 6. Results for other patient reported sleep parameters showed improvement versus baseline at week 3 and at week 6 for the number of awakenings, total sleep time, sleep quality and sleep refreshing quality with a difference versus placebo in favor of eplivanserin 5mg/day. Daytime functioning as measured by SIS scales improved from baseline in both groups with a difference versus placebo in favor of eplivanserin 5mg/day for all subscales at week 3 and at week 6. The SF-36 parameters showed a small difference in favor of eplivanserin for the vitality score and the mental component summary score with all other parameters showing no or negligible differences between groups.

Safety results:

Treatment emergent adverse events were reported in 32.7% of patients on eplivanserin 5mg/day and in 24.8% of patients on placebo. Three patients, all in the placebo group experienced SAEs, 2 patients during the emergence observation and one patient approximately 6 weeks after the last drug intake (post treatment). Two patients, both in the placebo group experienced SAEs with fatal outcome, one during the emergence observation and the second approximately 6 weeks after the last drug intake. None of the patient in the eplivanserin group experienced SAEs. Seven patients, 1 in the placebo group and 6 in the eplivanserin group discontinued double-blind treatment due to TEAE. No clinically relevant findings were observed in laboratory values, vital signs and ECG parameters.

No residual effect, assessed by psychometric tests (DSST and RAVLT) in the morning and in the afternoon, was observed at week 6 and no rebound insomnia, as defined by a worsening versus baseline on pr-WASO, was observed after discontinuation of eplivanserin.

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