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Sponsor/Company: sanofi-aventis **Drug substance**: SR46349 (eplivanserin)	**Study Identifier**: NCT00308503 **Study code**: EFC6220

Title of the study:

Efficacy and safety of eplivanserin 5mg/day on sleep maintenance insomnia: a 6 week, multicenter, randomized, double-blind, placebo controlled study.

Study center(s): International, multicenter study with 70 centers in 3 countries

Study period:

Date first subject/patient enrolled:	21-Feb-2006
Date last subject/patient completed:	20-Aug-2007

Phase of development: 3

Objectives:

The primary objective of this study was to assess the efficacy of eplivanserin 5mg/day in comparison to placebo after 6 weeks of treatment on sleep maintenance insomnia, using night polysomnography (NPSG) recordings.

The main secondary objectives were to evaluate patient's daytime functioning using the Functional Outcomes Sleep Questionnaire (FOSQ) with eplivanserin 5 mg/day as compared to placebo after 6 weeks of treatment and to evaluate the patient-reported Wake Time After Sleep Onset (pr-WASO) after 6 weeks of treatment.

Other secondary objectives were to evaluate the residual effects (using patient's morning questionnaire or psychometric tests) that may be associated with eplivanserin 5 mg/day as compared to placebo during double-blind treatment period, to compare the effect on sleep following abrupt discontinuation (after 42 nights) between eplivanserin 5 mg/day and placebo (during run-out period), to evaluate the effects on sleep architecture of eplivanserin 5 mg/day compared to placebo, to evaluate the clinical safety and tolerability of eplivanserin 5 mg/day compared to placebo, and to document plasma concentrations of eplivanserin and its pharamacologic active metabolite SR141342.

Methodology:

Multicenter, randomized, double-blind, placebo-controlled study with two parallel groups of patients

Number of subjects/patients:

Planned:	580
Randomized:	608
Treated:	608
Efficacy population	607
Safety population:	608
Pharmacokinetics population:	589

Diagnosis and criteria for inclusion:

Adult out-patients with primary insomnia based on Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition-Text Revision (DSM-IV-TR) criteria with predominant complaints of difficulty initiating or maintaining sleep for at least 1 month prior to study visit.

The patient has spent at least 6.5 hours but not more than 9.0 hours in bed each night over the preceding 2 weeks and must complain of at least 1 hour of wakefulness after sleep onset for at least 3 nights per week over the preceding month. The patient also must report an impact on daytime functioning associated with sleep maintenance insomnia as measured by question 3 of Insomnia Severity Index (ISI) at screening and randomization visit.

Based on the polysomnography (PSG) recordings during the screening nights (SNs) (SN1 and SN2) the following criteria must be present.
Mean wake time after sleep onset (WASO) calculated on SN1 and SN2≥60 min, and no SN with WASO<45 min, total sleep time (TST)≤7 hours and ≥3 hours on both SNs (SN1 and SN2), and mean latency to persistent sleep (LPS) calculated on SN1 and SN2≤30min.

Investigational product: SR46349 (eplivanserin) tablets

Dose: 5mg/day

Administration: oral, taken at dinner time

Reference therapy: Placebo tablets

Administration: oral, taken at dinner time

Duration of treatment: 6 weeks and 1 week of run-in placebo

Duration of observation: 9 weeks from screening to end of follow-up with 2 weeks run-out placebo

Criteria for evaluation:

Efficacy:

Primary endpoint:
The primary endpoint was the change from mean baseline nights (SN1/SN2) to the mean on nights (N41/N42) of polysomnography WakeTime After Sleep Onset (PSG WASO).

Main secondary endpoints:
The main secondary endpoints were change in general productivity domain of the FOSQ from baseline (Day-1) to Week 6 (Day 41) and the mean change from baseline to Week 6 of the pr-WASO

Other secondary endpoints:
Other secondary endpoints were:

- from NPSG recordings the change from the mean baseline nights (SN1/SN2) to the mean at Visit 5 nights (N41/N42) of sleep efficiency index (TST/time spent in bed), TST, Number of nocturnal awakenings (NAW), LPS, and sleep architecture: % of sleep time spent at each stage (1, 2 and 3 to 4) and during rapid eye movement (REM)
- from daily assessment of patient's morning questionnaire the mean change from baseline to Week 6 (N41/N42) of patient-reported total sleep time (pr-TST), patient-reported number of nocturnal awakenings (pr-NAW), patient-reported sleep onset latency (pr-SOL), and patient-reported quality of sleep and refreshing quality of sleep using a 4 category codification (excellent=1, good=2, fair=3 and poor=4)
- patient global impression (PGI) at Visit 5 (Week 6 [N41])
- change from baseline to Visit 5 (Day 41) of other domains of FOSQ
- Change in total score of hospital anxiety and depression (HAD) from baseline to Week 6 (N41).

Safety:

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

Pharmacokinetics:

Blood samples for the pharmacokinetic measurement were collected to describe eplivanserin and SR141342 (N-demethyl active metabolite) plasma concentrations in the targeted population. Blood samples to determine eplivanserin and SR141342 plasma

concentrations were collected on Day 20 within 2 to 3 hour post-dose (before the start of NPSG), on Days 21 and 41 before dosing and on Day 42 on awakening.

Statistical methods:

Efficacy:

Main analysis

As primary analysis, the comparison of the PSG WASO change from baseline between eplivanserin versus placebo was performed at the end of double-blind (DB) treatment, on intent-to-treat (ITT) population, with a mixed-effect model with repeated measures (MMRM) approach, assuming the missing at random. 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 centered baseline PSG WASO (ie, baseline PSG WASO after having centered baseline individual values on the grand baseline mean) as continuous fixed covariate.

This model provided the baseline adjusted least-squares means (LS-means) estimates of PSG WASO at the end of treatment 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.

Supportive analysis

The supportive analysis assessed 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 centered baseline mean PSG completed WASO as covariate.

These 2 models provided the baseline adjusted LS-mean estimates at end of treatment 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.

Safety:

All safety analyses were performed on all treated population.

Adverse events

Treatment-emergent adverse events were defined as adverse events (AEs) that occurred during the DB study treatment exposure (including the day of the first DB intake) or within 5 half-lives (14 days) following the last DB intake of investigational product (IP). For summaries of all TEAEs, counts were provided by-treatment group for each preferred term within each system organ class concerned. Percentages were calculated with the number of patients from the exposed population in each group.

Laboratory, vital signs, and electrocardiogram parameters

The overall incidences of patients having at least 1 post baseline potentially clinically significant abnormality (PCSA) in laboratory parameters, vital signs parameters, and ECG parameters during DB period were summarized. For quantitative safety parameters, descriptive statistics were used to summarize results and changes from baseline values by treatment group.

Residual effects

The residual effects assessed by the sleep morning questionnaire (sleepiness in the morning and ability to concentrate in the morning) were analyzed through the change versus baseline at Week 6 using MMRM analysis.

Psychometric tests assessing sedative, psychomotor and memory effects, digit symbol substitution test and rey auditory verbal learning test (DSST and RAVLT) were analyzed using MMRM model as for primary analysis.

Rebound effect

Rebound effect was assessed by looking at the pr-WASO and pr-TST during the run-out period: for each week and the 14 days of

the run-out period, the change from baseline was analyzed with an ANCOVA adjusting for the baseline value.

Withdrawal effect

Withdrawal analyses were performed on total score of Physician Withdrawal Checklist (PWC). The changes from Day 42 (evaluation under treatment) to Day 49 and to Day 56 (run-out evaluations) were summarized using ANCOVA with the baseline (D42) value as covariate.

Pharmacokinetic:

Eplivanserin and SR141342 plasma concentrations obtained from eplivanserin-treated group were classified as "C_{max}, C12H and C_{trough}" if time interval between sampling and last dose was 2 to 8h, 10 to 14h and 18 to 24h, respectively. The occurrence of steady state was assessed graphically for both compounds by plotting C_{trough} planned to be collected on days 21 and 41 over all eplivanserin-treated patients. C_{max}, C12H and C_{trough} as well as average trough concentrations ($C_{trough, av}$) in case of steady state achievement were summarized by standard descriptive statistics, and C_{max} and $C_{trough, av}$ were summarized for overall population and by age category (<65 and ≥ 65 years) and gender.

Summary:

Disposition and baseline Characteristics:

A total of 608 patients were randomized to treatment. All patients were exposed at least once to study treatment (311 to placebo and 297 to eplivanserin 5 mg). Of these 608 patients, 49 (8.1%) discontinued the study treatment, 21 (6.8%) in the placebo group and 28 (9.4%) in the eplivanserin group. The main reason for discontinuation was "other reason" in the placebo group (7 patients, 2.3%) and AEs in the eplivanserin group (14 patients, 4.7%).
More than half of the treated population was female (55.1%). Mean ± SD age for the whole population was 52.7±14.3 years, ranging from 18 to 85 years with 22.9% of the patients ≥65 years of age.

Efficacy results:

Primary endpoint

On N41/N42, the adjusted mean PSG WASO decreased (improved) from baseline by 22:06 min:sec in the placebo group and by 25:43 min:sec in the eplivanserin 5mg group, with no significant difference between treatment groups (LS mean = -3:37 min:sec, not significant). It should be noted that at N20/N21, the difference between treatment groups for PSG WASO was -6:25 min:sec [95%CI: -12:20 to -0:29].

Main secondary endpoints

The primary analysis did not reach the statistical significance level at 5 %. As this was a hierarchical step down procedure further conclusions could not be made on the significance of main secondary endpoints.
After 6 weeks of treatment, LS mean difference from placebo was -0.01 [95%CI: -0.08 to 0.06] for the general productivity score of the FOSQ and -2:43 min:sec [95%CI: -8:18 to 2:52] for the pr-WASO.

Other secondary endpoints

The analyses of the other secondary endpoints showed that, after 6 weeks of treatment, eplivanserin 5 mg compared with placebo:

- decreased the number of awakenings, both measured by PSG recording (LS mean difference = -1.82, 95%CI: -2.39 to-1.25) and reported by patients (LS mean difference = -0.25, 95%CI: -0.43 to -0.08)
- did not increase sleep duration, as measured by PSG recording (LS mean difference = 1.18 min:sec, 95%CI: -5:27 to 8:02) or reported by patients (LS mean difference = 6:23 min:sec, 95%CI: -5:32 to 18:18)
- did not affect sleep induction, both measured by PSG recording (LS mean difference for PSG LPS= 1:04 min:sec, 95%CI: -2:12 to 4:20) or reported by patients (LS mean difference for pr-SOL= -0:45 min:sec, 95%CI: -3:12 to 1:42)
- increased the quality of sleep (LS mean difference = -0.09, 95%CI: -0,17 to -0,00) but not the refreshing quality of sleep (LS mean difference = -0.05, 95%CI: -0.13 to 0.04)
- did not affect the total score of the FOSQ or of the 4 other domains
- increased the percentage of time spent in sleep stages 3 & 4 (slow wave sleep [SWS]) (LS mean difference = 3.13%, 95%CI: 2.06 to 4.20) at the expense of stages 1 and 2 which were decreased (LS mean difference = -2.22%, 95%CI: -2.76 to -1.68 and -1.21%, 95%CI: -2.43 to 0.01, respectively)

- did not affect REM sleep (LS mean difference = 0.28, 95%CI: -0.42 to 0.98)
- did not change the levels of depression and anxiety as measured on hospital anxiety and depression scale (HADS) (LS mean difference = 0.19, 95%CI: -0.24 to 0.61 and 0.36, 95%CI: -0.11 to 0.82, respectively).

In addition, after 6 weeks of treatment, eplivanserin 5 mg was superior to placebo regarding the "aid to sleep" (PGI-item 1; 58.3% of the patients considered that eplivanserin helped them sleep versus 46.4% of the patients for placebo) and "the duration of sleep" (PGI-item 3; 54.3% of the patients considered that eplivanserin increased the duration of sleep versus 44.7% of the patients for placebo). On the other hand, eplivanserin 5 mg was not different from placebo regarding "sleep induction" (PGI-item 2) and "medication strength" (PGI-item 4).

Exploratory analyses showed that the effect of eplivanserin on sleep maintenance was more pronounced in the elderly (patients ≥65 years) with a mean decrease of PSG WASO of 14:47 min:sec in the eplivanserin group compared with 7:30min:sec in the placebo group (LS mean difference = - 7.16 min:sec, 95%CI: -19:20 to 4:48) after 6 weeks of treatment. In the subpopulation of patients aged <65 years the LS mean difference between the treatment groups was -2:55min:sec, 95%CI: -9:41 to 3:52.

Safety results:

The percentage of patients who had at least 1 TEAE was higher in the eplivanserin group (43.4%) compared with the placebo group (39.9%). In the eplivanserin group the most frequently reported TEAEs with an incidence ≥1% (and at least 1% higher than the placebo group) were: dry mouth, constipation, abdominal pain, stomach discomfort, rash and nasal congestion. In the placebo group the most frequently reported TEAEs with an incidence ≥1% (and at least 1% higher than the eplivanserin group) were: headache, nausea, back pain and abnormal dreams.

Four patients (1.3%) in the eplivanserin group versus none in the placebo group reported SAEs. No particular pattern to the occurrence of these SAEs was detected. No deaths were reported in the study. The number of patients who discontinued treatment due to AEs was higher in the eplivanserin group (4.7%) than in placebo group (1.6%).

The percentage of patients with PCSA for orthostatic systolic blood pressure (SBP) was higher in the eplivanserin group (7.2%) compared with the placebo group (4.3%). In the eplivanserin group the majority of cases were transient on treatment and asymptomatic except for 1 case, which was associated with dizziness and fall leading to study treatment discontinuation. The percentage of patients with glucose level ≥11 mmol/L (unfasted) or ≥7 mmol/L (fasted), was higher in the eplivanserin group (6.2%) compared with the placebo group (4.0%). The percentage of patients with PCSAs values for weight increase≥5%, were also higher in the eplivanserin group (6.3%) compared with the placebo group (2.8%). However, the mean changes from baseline for all 3 parameters were not clinically relevant. Sporadic PCSAs in laboratory and ECG values were observed in both treatment groups without clinical relevance.

There was no evidence of symptoms related to residual effect (after each night of treatment), rebound effect (collected from the run-out period) or withdrawal effect from eplivanserin.

Pharmacokinetic results:

Eplivanserin and SR141342 C_{trough} on Days 21 and 41 were similar suggesting that steady state was reached within 3 weeks for both compounds. Mean eplivanserin and SR141342 C_{trough} and C_{max} values observed in the present study are consistent with exposures previously reported in healthy subjects. As previously observed in phase I studies, higher (20 to 30%) plasma concentrations of both eplivanserin and SR141342 are observed in patients ≥65 years as compared to patients <65 years and in female patients as compared with male patients, both genders being fairly represented in each age group.

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