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Sponsor/Company: sanofi-aventis **Drug substance**:SR46349 (eplivanserin)	**Study Identifier**: NCT00679900 **Study code**: EFC10480

Title of the study:

Comparison of the safety and efficacy of eplivanserin and lormetazepam in the treatment of insomnia characterized by sleep maintenance difficulties. A 4 week, randomized, double-blind, comparative, parallel-group study.

Study center(s): International, multicenter study with 40 centers in 8 countries

Study period:

Date first subject/patient enrolled:	24-Apr-2010
Date last subject/patient completed:	09-Mar-2009

Phase of development: 3

Objectives:

The primary objective of this study was to compare the potential for next-day residual effects of eplivanserin 5 mg/day and lormetazepam 1 mg/day by measuring the sleepiness in the morning using the patient's sleep questionnaire during 4 weeks of treatment in patients with chronic primary insomnia and sleep maintenance difficulties.

The secondary objectives were to compare the clinical safety of both products including the potential for rebound insomnia and withdrawal symptoms after treatment discontinuation, to compare the efficacy of both products on subjective sleep parameters (patient reported (pr)-Wake time After Sleep Onset (WASO), pr-Total Sleep Time (TST), pr-Number of Awakenings (NAW), pr-Sleep Onset Latency (SOL), Quality of Sleep (QoS), refreshing QoS), and to compare the effects of both products on patient's daytime functioning using the Functional Outcome Sleep Questionnaire (FOSQ) and the Sleep Impact Scale (SIS) after 4 weeks of treatment.

Methodology: Multicenter, randomized, double-blind, comparative study with two parallel groups

Number of subjects/patients:

Planned:	266
Randomized:	283
Treated:	283
Efficacy population:	278
Safety population:	283

Diagnosis and criteria for inclusion:

Outpatients, 18 years of age and above with primary insomnia according to Diagnostics and Statistical Manual of Mental Disorders, 4th Edition-Text Revision (DSM-IV-TR)SR46349 (eplivanserin) tablets criteria. The patient must have complained of at least 1 hour of wakefulness for at least 3 nights per week during the preceding month, must have spent at least 6.5 hours and not more than 9 hours in bed (time in bed = TIB) trying to sleep, each night during the preceding 2 weeks. Based on patient's sleep questionnaire administered each morning during the run-in period, patients must have had the following (calculated on at least 4 nights): a mean pr-WASO ≥45 min, mean pr-TST <7 hours and >3 hours, and a mean pr-SOL ≤30 min.

Investigational product: SR46349 (eplivanserin)

Dose: 5mg/day

Administration: oral, every night immediately at bedtime

Reference therapy: Lormetazepam

Dose: 1mg/day

Administration: oral, every night immediately at bedtime

Duration of treatment: 4 weeks

Duration of observation: 7 weeks

Criteria for evaluation:

Safety:

Primary safety endpoint:
The primary endpoint of this study was safety related to potential next day residual effect “sleepiness in the morning” from the patient's sleep questionnaire.

Secondary safety endpoints:
Secondary endpoints were the ability to concentrate from the patient's sleep questionnaire, rebound effect measured by pr-WASO and pr-SOL on patient's sleep questionnaire during the run-out phase, and withdrawal effects measured on physician withdrawal checklist (PWC) during the run-out phase.

Other secondary endpoints:
Other secondary endpoints were the occurrence of treatment emergent adverse events (TEAEs), laboratory evaluations, vital signs, electrocardiograms (ECGs) and physical examination.

Efficacy:

Efficacy endpoints
Efficacy endpoints were pr-WASO, pr-TST, pr-NAW, pr-SOL, Qos and refreshing QoS from the patient’s sleep questionnaire, Patient Global Impression self-report (PGI), Clinical Global Impression (CGI-I), Functional Outcomes of Sleep Questionnaire (FOSQ), and Sleep Impact Scale (SIS).

Statistical methods:

Safety:

Primary safety endpoint

The primary endpoint was the change from baseline to Day 28 of the mean VAS “sleepiness in the morning”, averaged on a weekly basis, in the all treated population.

Primary analysis
As primary analysis, the comparison of the change from baseline to Day 28 of the mean VAS “sleepiness in the morning” between eplivanserin 5mg/day versus Lormetazepam 1mg/day was performed using a mixed-effect model with repeated measures (MMRM) under the missing at random framework in the all treated population.

Assessment of treatment by subgroup interaction
To assess the homogeneity of the treatment effects across various subgroup factors, treatment interaction with subgroups defined by demographics characteristics was assessed. The MMRM method was used to assess the impact of treatment-by-subgroup interactions at Day 28 for each subgroup factor separately.

Supportive analyses
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)”.

Secondary safety endpoints

Secondary safety endpoints were other measures of the next day’s residual effect. The “ability to concentrate” was analyzed using the same model as the primary safety analysis (MMRM).

Rebound effect

The rebound effect was assessed using the change from baseline of pr-WASO and pr-SOL at each time point of the run-out (daily for the first week, averaged on the second week) and analyzed using an analysis of covariance with the baseline value as covariate.

Withdrawal effect

The withdrawal effect was assessed by calculating the total score of the physician withdrawal checklist (PWC). The change from Day 28 to Day 42 of the total score was analyzed with an ANCOVA with the baseline value as covariate based on the OC strategy.

Adverse events

Treatment-emergent adverse events (TEAEs) were defined as AEs, which occurred between the first double-blind intake of study drug and 14 days (five half-lives) after the last double-blind administration of the study drug. Events present before the first double-blind dose of study drug that worsened in intensity or become serious during the period defined above were considered as TEAE. Events occurring the day of the first double-blind intake were considered as TEAEs. For summaries of all TEAEs, counts were provided by-treatment group for each preferred term within each system organ class (SOC) concerned. Percentages were calculated with the number of patients from the exposed population in each group. Serious adverse events (SAEs) and AEs leading to treatment discontinuation were tabulated by treatment group.

Laboratory, vital signs, and ECG parameters

Summaries of patients having at least 1 treatment-emergent potentially clinically significant abnormality (PCSA) for laboratory, ECG, and vital sign parameters were provided taking into account any abnormalities during treatment period.

For quantitative safety parameters, descriptive statistics were used to summarize results and changes from baseline values by treatment group. Summaries were presented using the worst on-treatment value for central laboratory and ECG parameters as well as evaluations by planned visit during the double-blind treatment period for vital sign parameters. All safety analyses were performed on the all treated double-blind population.

Efficacy endpoints

The efficacy variables from patient's sleep questionnaire (change from baseline to Day 28 of pr- WASO, pr-TST, pr-NAW, pr-SOL, QoS and refreshing QoS) were analyzed using the same model (MMRM) as for primary safety analysis.

The change from baseline to Day 28 on each of the sub-scores and total score from FOSQ and SIS were analyzed using an ANCOVA using treatment factor as fixed effect with 2 levels (eplivanserin and lormetazepam) and with the baseline as covariate, based on LOCF strategy. No interaction was included in the model.

For PGI and CGI scales the count and percentages of each category were described by group at each evaluation. Analyses were performed using Chi square test to compare the percentage of favorable responses at the end of double-blind treatment versus unfavorable ones.

Additional analysis

In order to better understand the data in terms of clinical relevance, responder analysis using combined criteria have been performed. The responders rate were evaluated based on separate and combined responder definitions including the main patient-reported criterion pr-WASO and respectively a secondary patient-reported criterion, either the ability to concentrate or the sleepiness in the morning.

Summary:

Disposition and baseline Demographics:

A total of 413 patients were screened, of whom 283 patients were randomized. The main reason for non-randomization was "inclusion/exclusion criteria not respected" (28.6%). Both treatment groups were comparable regarding demographic data. The median age of patients was 52.0 years and 12.4% of patients were elderly ($\geq$65 years). Two third of patients were female. More than 85% of patients were non Hispanic. The mean time from first diagnosis of primary insomnia was 7.25 years and 6.56 years in the eplivanserin and the lormetazepam group, respectively. In about 80% of patients the time from first diagnosis to randomization was more than 1 year reaching 10 years in 68/283 (24.3%) patients. The patient reported sleepiness in the morning and the ability to concentrate were comparable in both treatment groups.

Safety results:

The primary safety analysis showed that eplivanserin 5 mg/day and lormetazepam 1 mg/day improved both sleepiness in the morning and ability to concentrate with no difference between groups. The discontinuation of both eplivanserin and lormetazepam was not associated with rebound insomnia as defined by a worsening versus baseline. However, the decrease in pr-WASO observed during the double-blind treatment period appeared to be maintained during the run-out period in the eplivanserin group but not in the lormetazepam group.

No meaningful withdrawal symptoms were observed after 2 weeks of discontinuation of both eplivanserin and lormetazepam.

Less than half of the patients experienced TEAEs (47.9% in eplivanserin group and 46.9% in lormetazepam group). The distribution across nervous disorders and psychiatric disorders SOCs was different between groups. More headache (13.6% versus 7.0%) and somnolence (3.6% versus 1.4%) were observed in the eplivanserin group while lower incidence in the eplivanserin group was found for depression (0.7% versus 3.5%) and anxiety (2.1% versus 4.2%). Few patients prematurely discontinued the treatment due to TEAEs, (2.9% in eplivanserin group versus 0.7% in lormetazepam group). None of the patients experienced a treatment emergent SAE. Analysis of PCSAs for laboratory, vital signs and ECG showed similar results between both groups, except a lower percentage of patients having an orthostatic hypotension SBP lower than -20mmHg in eplivanserin group compared with lormetazepam group (4.4% versus 7.0%).

Efficacy results:

Both eplivanserin and lormetazepam decreased pr-WASO with an 8 minute difference in favor of lormetazepam (95% CI:-0:02 to 16:09). The pr-NAW also decreased in both treatment groups with no difference between groups (LS mean difference from lormetazepam group = -0.09, 95% CI: -0.36 to 0.19). The increase in pr-TST was observed in both treatment groups with 20 minute differences in favor of lormetazepam (95% CI: -33:00 to -8:05). Pr-SOL remained unchanged in both treatment groups (LS mean difference from lormetazepam group = 4:39, 95% CI: -0:25 to 9:43). Both eplivanserin and lormetazepam improved Quality of Sleep and the Refreshing Quality of Sleep with no difference between groups (LS mean difference from lormetazepam group = 0.04 and 0.02, 95% CI: -0.09 to 0.16 and -0.10 to 0.15, respectively). Day time functioning as measured by the FOSQ and the SIS improved in both groups with a numerical difference in favor of eplivanserin on the FOSQ total score and 4 of the 7 SIS subscores. The responder analysis showed no meaningful difference between eplivanserin and lormetazepam groups.

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