*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**: SR46349 (eplivanserin) | **Study Identifier**: NCT00253968<br>**Study code**: LTE6217 (GEMS) |

**Title of the study**:
Efficacy and safety of eplivanserin 5 mg/day on sleep maintenance insomnia: a 12-week multicenter, randomized, double-blind, placebo-controlled study

**Study center(s)**: International, multicenter study in 12 countries with at least 1 patient randomized in Argentina, Australia, Canada, Chile, Czech Republic, France, Germany, Mexico, The Netherlands, Spain, UK, and USA.

**Study period:**

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| Date first subject/patient enrolled: | 04-Nov-2005 |
| Date last subject/patient completed: | 10-Jan-2008 |

**Phase of development**: 3

**Objectives**:

The primary objective of this study was to assess efficacy of eplivanserin 5 mg/day in comparison to placebo after 12 weeks of treatment on sleep maintenance insomnia using the patient reported wake time after sleep onset (pr-WASO) of the patient sleep questionnaire.

The main secondary objective was to evaluate patient's daytime functioning using the Functional Outcomes of Sleep Questionnaire (FOSQ) Items 1 and 2 (concentration/memory) and Items 4 and 10 (hobby/work) with eplivanserin 5 mg/day as compared to placebo after 12 weeks of treatment.

Other secondary objectives were to evaluate residual effects (using patient's morning questionnaire) that may be associated with eplivanserin 5 mg/day as compared to placebo during the double-blind treatment period (after each night of treatment), to compare the effect on sleep following abrupt discontinuation (after 12 weeks) between eplivanserin 5 mg/day and placebo (during run-out period), to evaluate the clinical safety and tolerability of eplivanserin 5 mg/day compared to placebo after 12 weeks of treatment, and to document eplivanserin and the active metabolite SR141342 plasma concentrations.

**Methodology**:

Multicenter, randomized, double-blind, placebo-controlled study with 2 parallel groups of patients with sleep maintenance insomnia.

**Number of subjects/patients**:

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| Planned: | 948 |
| Randomized: | 967 |
| Treated: | 962 (345 receiving placebo, 617 receiving eplivanserin) |
| Efficacy population: | 962 |
| Safety population : | 962 |
| Pharmacokinetic population: | 933 |

**Diagnosis and criteria for inclusion**:

Out-patients, ≥18 years of age with diagnosis of primary insomnia according to diagnostic and statistical manual of mental disorders-fourth edition criteria (DSM-IV-TR) with predominant complaints of difficulty in initiating or maintaining sleep (nocturnal awakenings), or nonrestorative sleep for at least 1 month preceding the study visit.

Disturbances of sleep maintenance were based on patient' s information (patient has spent at least 6.5 hours and no more than 9.0 hours in bed each night over the preceding 2 weeks, patient must complain of at least 1 hour of wakefulness after sleep onset for at least 3 nights per week over the preceding month, and patient must report impact on daytime functioning associated with sleep maintenance insomnia as measured by Item 3 of insomnia severity index at screening and randomization visits) and information recorded in the patient's diary during the screening week preceding the randomization (mean pr-WASO per night ≥60 min during screening period (7 days) and no period of pr-WASO <45 min on each screening night, TST ≤7 hours and ≥3 hours on 3-worst screening nights, mean SOL per night had to be ≤30 min during the screening period).

**Investigational product**:SR46349 (eplivanserin) tablets

Dose: 5mg/day

Administration: oral, at dinner time

**Reference therapy**: Placebo tablets

Administration: oral, at dinner time

**Duration of treatment**: 12 weeks for each patient (double-blind period) + 1 week of run-in (placebo), and 2 weeks of run-out (placebo)

**Duration of observation**: 15 weeks for each patient

**Criteria for evaluation**:

**Efficacy**:

Primary endpoint
The primary endpoint was the change from baseline at Week 12 of the mean pr-WASO measured by Item 5 of the patient's sleep questionnaire.

Main secondary endpoint
The main secondary endpoint was the change from baseline at Week 12 of the mean of the FOSQ Items 1 and 2 (concentration/memory) and mean of Items 4 and 10 (hobby/work).

Other secondary endpoints
Other secondary endpoints were:

- from daily assessments from patient's morning questionnaire, the change from baseline at Week 6 and Week 12 of the following parameters: patient reported WASO (pr-WASO) at Week 6 only, patient reported number of nocturnal awakenings (pr-NAW), measured by Item 4 of the Patient's sleep questionnaire, patient reported total sleep time (pr-TST), measured by Item 6 of the Patient's sleep questionnaire, patient reported sleep onset latency (pr-SOL), measured by Item 3 of the Patient's sleep questionnaire, and patient reported sleep quality and refreshing sleep quality, measured by Items 8 and 9 of the Patient's sleep questionnaire.
- from assessments made at each visit, the change from baseline at Week 6 and Week 12 of the following parameters: subscore for each domains and total score of the FOSQ, total score for anxiety and for depression of the hospital anxiety and depression scale (HADS), and mean of Items 1 and 2 and mean of Items 4 and 10 of the FOSQ at Week 6 only
- Patient global impression (PGI) scale rated by the patient at Week 6 and Week 12.

**Safety**:

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

**Pharmacokinetics:**

The pharmacokinetic samples were collected before dosing on Days 14, 63, and 84 to describe eplivanserin and its active metabolite SR141342 concentrations in plasma in the targeted population.

**Statistical methods**:

**Efficacy**:

Primary endpoint

*Main analysis*

As primary analysis, the comparison of the pr-WASO (change from baseline) between eplivanserin versus placebo was performed at Week 12 on intent-to-treat (ITT) population with a mixed-effect model with repeated measures (MMRM) approach, assuming a missing at random mechanism. This model ran using statistical analysis software (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, and treatment-by-visit interaction, as well as the centered baseline mean pr-WASO (ie, baseline mean WASO after centered baseline individual values on the grand mean baseline) as continuous fixed covariate.

This model provided the baseline adjusted least-squares mean (LS-mean) estimates at Week 12 by treatment group, as well as the difference of these estimates (eplivanserin versus placebo) with the corresponding standard error, degrees of freedom, Student's t-test statistics, and associated 95% confidence interval (CI).

*Supportive analysis*

To assess the sensitivity of the primary analysis, supportive analyses of covariance (ANCOVA) were performed based on "Last observation carried forward (LOCF)" and "Observed cases (OC)".

Main secondary endpoints

The main secondary variables were analyzed using the same model (MMRM on ITT population) as for the primary analysis.

Other secondary endpoints

The mean change from baseline to Week 6 and to Week 12 of other patient's morning sleep questionnaire variables (pr-WASO at Week 6 only, pr-TST, pr-NAW, pr-SOL, pr-quality and refreshing sleep quality), the change from baseline of the total score for anxiety and for depression of the HADS**,** and the mean of the FOSQ Items 1 and 2 (concentration/memory) and Items 4 and 10 (hobby/work) at 6 weeks only, and total scores for the domains of the FOSQ (general productivity, activity level, vigilance, intimacy and sexual relationships, social outcome, and total score) were analyzed using the same model as for the primary and main secondary analyses (MMRM).

For PGI scale, the percentage for each category was described by group at each evaluation under double-blind period (by visit using OC strategy and at last available assessment). Analyses were performed using Chi square test to compare the percentage of favorable responses at the end of the double-blind treatment (for each of the 4 questions) versus unfavorable ones.

**Safety**:

All safety analyses were performed on all treated population.

Adverse events

Adverse events were coded using the medical dictionary for regulatory activities (MedDRA, version 10.1). Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that 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, but worsened in intensity or become serious during the period defined above were considered as TEAE. If the date of onset was missing, the event was considered as treatment emergent.

For summaries of all TEAEs, counts were provided by-treatment group for each preferred term within each system organ class concerned. Percentage was calculated with the number of patients from the all treated population in each group. Serious AEs 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 signs parameters were provided by treatment group and according to normal and abnormal baseline values for laboratory parameters.

For quantitative safety parameters, descriptive statistics were used to summarize results and changes from baseline values by treatment group and by visit and at last on treatment value. Summaries were presented using patients having at least both a baseline and a postbaseline evaluation.

Next day residual effects

The next day residual effects assessed through the changes from baseline at Week 6 and 12 of the 2 items of the sleep morning questionnaire (sleepiness in the morning and ability to concentrate in the morning) were analyzed using the same model (MMRM) as for the primary analysis.

Rebound insomnia

Rebound insomnia was assessed by calculating the weekly mean change from baseline of the pr-WASO and pr-TST during the 1st and the 2nd week of the run-out period and the total duration of the run-out period. The change from baseline was analyzed with ANCOVA with baseline as covariate.

Withdrawal effects

The withdrawal effects variables include the change from end of treatment of each individual symptom and total score at mid-point (Run-out Week 1) and the end of the run-out period (Run-out Week 2). The change from the end of study treatment to each week of the run-out period was analyzed with ANCOVA with the end of treatment value as covariate.

**Pharmacokinetics**:

Eplivanserin and its active metabolite SR141342 plasma concentrations obtained from eplivanserin-treated group were classified as "$C_{trough}$ and $C_{12H}$" if time interval between sampling and last dose was 18 to 24h and 10 to 14h, respectively. The occurrence of steady state was assessed graphically for both compounds by plotting $C_{trough}$ collected on Days 14, 63, and 84 in all eplivanserin-treated patients. The average trough concentrations ($C_{trough, av}$) in case of steady state achievement were calculated for each patient and summarized by standard descriptive statistics as well as $C_{trough}$ and $C_{12H}$. In addition, $C_{trough, av}$ descriptive statistics were provided by age category (<65 and ≥65 years) and gender for each age category.

**Summary**:

**Disposition and baseline Characteristics**:

A total of 967 patients in 12 countries were randomized (620 patients in the eplivanserin group and 347 patients in the placebo group). Among the randomized patients, 5 patients (3 in the eplivanserin group and 2 in the placebo group) did not receive any of the study treatment. Hence, 962 patients received the study treatment (345 patients received placebo and 617 patients received eplivanserin), which consisted the all treated population and the ITT population of the study.

Premature discontinuation of the study treatment was observed in 21.8% of the 620 randomized patients in the eplivanserin group and 26.2% of the 347 randomized patients in the placebo group.

All treated patients in both treatment groups were similar in their demographic and patient characteristics at baseline. Overall mean age at baseline was 51.2 years and about 18% of the total treated patients were elderly (aged ≥65 years). The overall percentage of female patients (57.0%) was slightly higher than male patients (43.0%).

Insomnia characteristics at baseline were comparable between treatment groups with one-third of the all treated population diagnosed with insomnia for more than 10 years before randomization and one-third were diagnosed between 1 to 5 years before randomization. The severity of insomnia at baseline was similar in both treatment groups.

At baseline, the overall mean wake time after sleep onset was about 1.7 hours and the mean of total sleep time was about 5.7 hours in both treatment groups. More than one-third of the all treated patients had taken previous medications affecting sleep before the conduct of the study (ie, analgesics, hypnotics and sedatives, antihistamines for systemic use, and anxiolytics).

**Efficacy results**:

Primary endpoint

The patients' reported wake time after sleep onset (pr-WASO) at Week 12 decreased from baseline (improved) by 54:20±1:40 min:sec in the eplivanserin group and by 42:48±2:15 min:sec in the placebo group. The difference between the 2 treatment groups was significant (LS mean difference from placebo of -11:32±2:49 min:sec, p<0.0001).

Main secondary endpoints

The analysis of the change from baseline at Week 12 of the mean of the FOSQ Items 1 and 2 (concentration/memory) did not reach the statistical significance level at 5% (LS mean difference from placebo of 0.03, 95% CI: -0.06 to 0.12). As this was a hierarchical step down procedure, further conclusions cannot be made on the significance of the other secondary variable, mean of the FOSQ Items 4 and 10 (hobby/work) (LS mean difference from placebo of 0.06, 95% CI: -0.03 to 0.15).

Other secondary endpoints

*Patient's daily morning questionnaire*

The MMRM analyses of the change from baseline of the patients' daily morning questionnaire parameters showed the following:

- the wake time after sleep onset (pr-WASO) at Week 6 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -13:06 min:sec, 95% CI: -18:19 to -7:53)
- the total sleep time (pr-TST) at Week 6 and Week 12 increased more in the eplivanserin group compared to the placebo group (LS mean difference from placebo of 11:05 min:sec, 95% CI: 4:03 to 18:06 at Week 6 and 10:56 min:sec, 95% CI: 3:06 to 18:45] at Week 12)
- the number of nocturnal awakenings (pr-NAW) at Week 6 and Week 12 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of –0.39, 95% CI: -0.52 to -0.26 at Week 6 and –0.33, 95% CI: -0.48 to -0.19 at Week 12)
- the sleep quality scores at Week 6 and Week 12 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -0.11, 95% CI: -0.18 to -0.03 at Week 6 and -0.10, 95% CI: -0.19 to -0.02 at Week 12)
- the sleep refreshing quality scores at Week 6 and Week 12 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -0.11, 95% CI: -0.18 to -0.03 at Week 6 and -0.09, 95% CI: -0.18 to -0.01 at Week 12)
- there was no difference between the treatment groups in the pr-SOL at Week 6 and Week 12.

*Functional Outcomes of Sleep Questionnaire (FOSQ)*

A slight improvement (less difficulty) in the FOSQ vigilance score at Week 6 and Week 12 was observed more frequent in the eplivanserin group than in the placebo group. However, no apparent improvements were observed in both treatment groups in the other FOSQ parameters.

*Hospital anxiety and depression scale*

There was no difference between the treatment groups in the depression scores of the HADS at Week 6 and Week 12 and in the anxiety score at Week 6, but a slight decrease from baseline in the anxiety score at Week 12 was observed in the eplivanserin group compared to the placebo group (LS mean difference from placebo of -0.48, 95% CI: -0.93 to -0.03).

*Patient global impression*

With the exception of the PGI Item 2-sleep induction, the percentage of patients with favorable responses in the PGI items was higher in the eplivanserin group than the placebo group:

- Item 1, aid to sleep: treatment has helped in 62.1% of patients in the eplivanserin group versus 50.2% in the placebo group at Week 6 and respectively in 64.8% versus 52.7% at Week 12
- Item 3, sleep duration: treatment has lengthened sleep duration in 60.0% of patients in the eplivanserin group versus 48.3% in the placebo group at Week 6 and respectively in 61.1% versus 48.8% at Week 12
- Item 4, medication strength: treatment was considered just right in 48.8% of patients in the eplivanserin group versus 41.3% at Week 6 and respectively in 53.9% versus 43.3% at Week 12.

**Safety results**:

The mean duration of exposure to the study drug was comparable between eplivanserin and placebo groups (74.3 and 71.8 days, respectively). More than half of the treated patients in each group (54.0% in the eplivanserin group and 61.4% in the placebo group) were exposed to the study drug between 9 to 12 weeks.

The percentage of patients who experienced at least 1 TEAE was similar in both treatment groups (54.8% and 49.6% in the eplivanserin and placebo groups, respectively).

There was no clear-cut difference between treatment groups in the most frequently reported TEAEs by system organ class with more than 10% approximately in each group. The most frequent TEAEs in the eplivanserin group were infections and infestations, nervous system disorders, gastrointestinal disorders, and musculoskeletal and connective tissue disorders. These TEAEs were also the most frequent in the placebo group.

The most frequently reported TEAEs by preferred term with an incidence of ≥1% in eplivanserin-treated patients (and at least 1% higher than placebo group) were dizziness, upper respiratory tract infection, dry mouth, anxiety, depression, gastroenteritis, diverticulitis, urinary tract infection, pharyngolaryngeal pain, and vertigo. In the placebo group, the most frequently reported TEAEs with an incidence of ≥1% (and at least 1% higher than the eplivanserin group) were somnolence and toothache. Most of the TEAEs observed in both treatment groups were of mild to moderate severity and were resolved at the last assessment.

Diverticulitis was observed in 8 (1.3%) patients in the eplivanserin group, of whom 1 patient had a serious episode. No patient prematurely discontinued the study treatment due to diverticulitis and all of the cases were resolved.

Gender effect analysis showed comparable percentage of patients with at least 1 TEAE between female and male patients in both treatment groups (eplivanserin group: female 55.8%; male 53.4% and placebo group: female 52.3%; male 46.1%).

In the eplivanserin group, a higher percentage of patients with at least 1 TEAE was ≥65 years of age compared to <65 years of age whereas the percentage was similar in the placebo group; eplivanserin group: ≥65 years, 64.9% of the 111 patients; <65 years, 52.6% of the 506 patients and placebo group: ≥65 years, 48.3% of the 58 patients; <65 years, 49.8% of the 287 patients.

There was 1 patient in the eplivanserin group who died due to pneumonia (bilateral post obstructive pneumonia), which was unrelated to the study drug according to the Investigator.

The overall incidence of serious adverse events (SAEs) was low and similar in both treatment groups (1.9% and 2.0% in the eplivanserin and placebo groups, respectively). All of the reported serious TEAEs were observed each in 1 patient only.

The percentage of patients who discontinued the study treatment due to AE was similar in both treatment groups (5.7% and 5.2% in the eplivanserin and placebo groups, respectively).

Analyses of PCSA for laboratory, vital signs, and ECG showed similar results between the two treatment groups. A 68 year-old male patient in the eplivanserin group experienced PCSA in QTcB and QTcF >500 ms reported as TEAE of mild severity (QTcB 509 ms, QTcF 519 ms on Day 92; baseline QTcB 366 ms and QTcF 364 ms). The patient recovered with QTcB and QTcF values returned to normal at the last visit/assessment (QTcB 402 ms and QTcF 408 ms on Day 147).

A tendency for weight decrease from baseline was observed in eplivanserin-treated patients as opposed to weight increase from baseline (ie, ≥5% kg) that was observed more in the placebo group.

There was no evidence of next day residual effect or rebound insomnia observed in the eplivanserin-treated patients.

A slight increase in the total score of the Physician Withdrawal Checklist was observed in the eplivanserin group 2 weeks after the end of treatment, but the increase was not considered meaningful as it would correspond to less than 1 symptom of mild severity.

**Pharmacokinetics**:

Mean eplivanserin and SR141342 $C_{trough}$ values were consistent with exposures previously reported in healthy subjects regardless of age. The <65 and ≥65 years age groups are unbalanced. However, as previously observed in Phase 1 studies, higher (18 to 45%) plasma concentrations of both eplivanserin and SR141342 were observed in patients older than 65 years as compared to patients below 65 years. Slightly higher eplivanserin (19%) plasma concentrations were observed in female patients as compared to male patients in the ≥65 years age group but remained similar in the <65 years age group. Across the age, higher SR141342 (28 to 41%) plasma concentrations were observed in female patients as compared to male patients.

**Issue date:** 12-May-2010