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Sponsor/Company: sanofi-aventis **Drug substance**: SR46349 (eplivanserin)	**Study Identifier**: NCT00913614 **Study code**: PKD10491

Title of the study:

Single dose, open label safety, tolerability, pharmacokinetic and pharmacodynamic evaluation of three different eplivanserin doses in children aged 6-17 years with insomnia of various origins.

Study center(s): National, multicenter study 10 centers

Study period:

Date first subject/patient enrolled: 11-May-2009

Date last subject/patient completed: 29-Dec-2009

The study was prematurely discontinued due to the Sponsor's decision. Further to the complete response letter issued by the FDA in September 2009, and considering the need for significant further clinical developments and market access constraints, the eplivanserin submission dossier in insomnia was withdrawn in every country where the dossier was under review.

Phase of development: 1

Objectives:

The objectives of this study were to assess the safety and tolerability of eplivanserin after administration of single ascending oral doses, to assess the pharmacokinetics (PKs) of eplivanserin and its active metabolite SR141342 after administration of single ascending oral doses and to assess the effect of single ascending oral doses of eplivanserin on global sleep parameters and sleep architecture measured via polysomnography recordings in children between 6 and 17 years of age with insomnia of various origins.

Methodology:

National, multi-center , open-label, non-randomized, non-controlled, single ascending dose, single-treatment study in two age groups 6-11 and 12-17 y.o.

Number of subjects/patients:

Planned:	42
Treated:	41
Pharmacodynamic population:	41
Pharmacokinetic population:	28
Safety population:	41

Diagnosis and criteria for inclusion:

Healthy male or female children between the ages of 6 and 17 years, inclusive (before 18th birthday) with a diagnosis of insomnia of various origins.

Complaint of childhood insomnia as defined by repeated difficulty with sleep initiation or consolidation that occurs despite adequate age appropriate time and opportunity for sleep. The existence of sleep difficulty was supported by statements from the child and/or the caregiver that sleep was not properly initiated or maintained.

Investigational product: SR46349 (eplivanserin) tablets

Dose: 0.01, 0.035, and 0.07mg/kg

Administration: oral, In the morning, around breakfast

Duration of treatment: 1 day

Duration of observation: 4 weeks

Criteria for evaluation:

Safety:

Safety assessments included all adverse events (AEs) regardless of seriousness or relationship to Investigational Product including those from the first visit planned in the Clinical Trial Protocol/Signature of the Informed Consent Form. Clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP] and temperature) and electrocardiogram (ECG) parameters (2-lead ECG was digitally recorded after at least 10 minutes in supine position, using an electrocardiographic device) were monitored during the study. In addition, growth hormone (GH) assessments were also performed.

Pharmacodynamic:

Polysomnography was performed on Day-2 after the subject had met all inclusion/exclusion criteria and 3 hours following the IP administration. All polysomnography recordings were performed in the sleep laboratory. Polysomnography included electroencephalogram, electrooculogram, and electromyogram and was conducted twice for each subject and have been started at sleep onset. Polysomnography recordings lasted at least until the subject's age-appropriate sleep duration for

- age 6 to 8 years remained in bed with recordings for at least 11 hours
- age 9 to 11 years remained in bed with recordings for at least 10 hours
- age 12 to 14 years remained in bed with recordings for at least 9 hours, and
- age ≥15 remained in bed with recordings for at least 8 hours.

If the subject was awake before the age-appropriate sleep duration, the subject should have been remained in bed until the age-appropriate sleep duration was reached.

Sleep architecture (as absolute and relative proportions): sleep stages I, II, III and IV; REM sleep stage; stage awake, and global sleep parameters: total sleep time (TST), Wake time After Sleep Onset (WASO), Number of Awakenings (NAW), and Latency to Persistent Sleep (LPS) were measured.

Statistical methods:

Safety:

The safety evaluation was based on the reported AEs, central laboratory data, vital signs and central manual reading ECG data. All the safety analyses were performed using the safety population, separately for each age group and dose level. The on-treatment period was defined as the time of eplivanserin administration up to the end of study visit.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, 12.1). Treatment emergent adverse events (TEAEs) were summarized by system-organ class and preferred term and subjects presenting TEAEs were listed.

The values used as baselines were screening values for laboratory parameters and the Day-2 values for vital signs and ECG parameters. For laboratory parameters with laboratory ranges, an on-treatment analysis was performed, using all post-baseline assessments done during the on-treatment period including rechecked values. Counts of subjects with abnormalities (out-of-normal laboratory range values) were provided in summary tables showing shifts from normal and abnormal baselines to post baseline abnormalities. For heart rate, blood pressures and ECG parameters, raw data and changes from baseline were summarized in descriptive statistics for each parameter of interest and time point.

Pharmacokinetics:

Plasma concentrations of eplivanserin and metabolite SR141342 were determined by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method with a lower limit of quantification of 0.05 ng/mL for both analytes. Pharmacokinetic

parameters were calculated by non-compartmental methods using nominal sampling times. The following PK parameters were calculated for following oral administration of 0.01 and 0.035 mg/kg/day eplivanserin in children 6 to11 and 12 to17 years of age: C_{max}, AUC_{last}, AUC, AUC_{0-24}, t_{max}, $R_{ac, pred}$.

Pharmacodynamics:

Individual listing for pharmacodynamic data was provided.

Summary:

Disposition and baseline Demographics:

In both age groups, the majority of subjects were male except the 12 to 17 years old subjects who received eplivanserin 0.07 mg/kg. In the 12-17 years old group more than two third of the subjects were caucasian. In the 6 to 11 years old group, two third of the subjects who received eplivanserin 0.035 mg/kg and 0.07 mg/kg were black while the majority of subjects who received eplivanserin 0.01 mg/kg were caucasians (71.4%). Subjects' age was comparable at baseline in each age group regardless of treatment dose received. In the 6 to 11 years old group, the major reason for insomnia was attention deficit hyperactivity disorder (ADHD). While in the 12 to 17 years old group the major reasons for insomnia were primary insomnia and ADHD.

Safety results:

Adverse events in subjects 6 to 11 years of age

Three subjects in the 0.01 mg/kg group, 1 subject in the 0.035 mg/kg group and 3 subjects in the 0.07 mg/kg group had at least 1 TEAEs. None were severe. None of the subjects experienced serious TEAEs. The most common TEAEs were somnolence and lethargy

Adverse events in subjects 12 to 17 years of age

Two subjects in 0.01 mg/kg group, 4 subjects in the 0.035 mg/kg group and 3 subjects in the 0.07 mg/kg group had at least 1 TEAEs. None were severe. None of the subjects experienced serious TEAEs.

Pharmacokinetics:

At 0.035 mg/kg all subjects were exposed to eplivanserin and metabolite SR141342 with measurable plasma concentrations observed up to at least 24 h post-dose. A 3.5 fold increase in dose (0.01 mg/kg to 0.035 mg/kg) gave an approximately 4 to 5-fold increase in systemic exposure (AUC_{0-24} and C_{max}) to eplivanserin and SR141342. The predicted steady-state accumulation ratios (AUC/AUC_{0-24}) following a single oral 0.035 mg/kg dose were approximately 2-fold for eplivanserin and 5 to 11-fold for SR141342. Overall, the pharmacokinetic parameters observed in children in both age groups (6 to 11 years and 12 to 17 years) were consistent with those observed in adults (based on pharmacokinetic parameters observed in various studies in adults at doses from 1 to 5 mg).

Efficacy results:

Safety results:

Laboratory parameters, vital signs and ECG parameters

With respect to laboratory parameters, few subjects had out of range values during the treatment. The most commonly reported abnormal values were high chloride values and total cholesterol values. Few patients reported abnormal values related to red or white blood cells. None were reported as TEAEs.

Heart rate, SBP and DBP at supine position as well as body weight, BMI and BSA showed no major changes compared to baseline values.

Pharmacokinetic results:

Individual listings are provided in Appendix 14.2.5

Pharmacodynamic results:

Individual listings are provided in Appendix 14.2.6.

Issue date: 30-Apr-2010