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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00318448
Drug substance:	zolpidem	**Study Code:**	EFC6820

Title of the study:	Efficacy, safety and tolerability of zolpidem in the treatment of children aged 6 to 17 years with ADHD-associated insomnia.
Study centers:	Multicenter (62 sites), USA and Canada
Study period: Date first patient enrolled: 02 March 2006 Date last patient completed: 10 August 2006	**Phase of development:** 3
Objectives:	The primary objective of the study was to evaluate the hypnotic efficacy of 0.25 mg/kg/day (with a maximum of 10 mg/day) of zolpidem compared with placebo in children ages 6 through 17 years (inclusive) experiencing attention-deficit/hyperactivity disorder (ADHD) associated insomnia. The secondary objectives of the study were as follows: • evaluate the clinical and biological safety of 0.25 mg/kg/day (with a maximum of 10 mg/day) of zolpidem in children with ADHD-associated insomnia; • evaluate the potential for next-day residual effects and for rebound insomnia after treatment discontinuation of zolpidem in children with ADHD-associated insomnia; • evaluate the consequences of the treatment of insomnia on behavioral and cognitive components of ADHD.
Methodology:	An international (USA and Canada) multicenter, stratified (ages 6 through 11, and 12 through 17 years) with imbalanced randomization (2:1), double-blind, placebo-controlled, and parallel groups study.
Number of patients:	Planned: 189 Randomized: 201 Treated: 201
Diagnosis and criteria for inclusion:	Male or female children 6 through 17 years of age (up to the 18th birthday), with complaints of childhood insomnia, who have been diagnosed with ADHD (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision [DSM-IV-TR] criteria).
Investigational product: Dose: Administration:	zolpidem solution 2.5 mg/mL At 0.25 mg/kg/day of body weight, with a maximum of 10 mg/day, regardless of body weight Oral solution administered 30 minutes before bedtime
Duration of treatment: 8 weeks	**Duration of observation:** A maximum of 12 weeks
Reference therapy:	Matching placebo [oral solution administered 30 minutes before bedtime]

Criteria for evaluation:	
Efficacy:	***Primary efficacy variable*** The primary efficacy variable was latency to persistent sleep (LPS) measured by polysomnography (PSG) that was to be done between Weeks 3 and 4, and if not possible between Weeks 4 and 6. ***Secondary efficacy variables*** The secondary efficacy variables were as follows: • Clinical Global Impression (CGI)-child – global improvement of insomnia; • CGI-child – global severity of insomnia; • CGI-parent/legal guardian – global improvement and severity of insomnia; • PSG sleep parameters other than LPS: wake time after sleep onset (WASO), number of awakenings after sleep onset (NAASO), and total sleep time (TST); • Actigraphic measures of sleep characteristics: (LPS and TST); • ADHD Rating Scale-IV; • School tardiness/attendance reports; • Conners' Continuous Performance Test-II (CPT-II).
Safety:	Safety was assessed through the use of reports of adverse events (AEs), clinical laboratory evaluations, vital signs [ie, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and weight], and physical examination. Other safety parameters assessed were as follows: • potential for next-day residual effects: Pediatric Daytime Sleepiness Scale (PDSS); • rebound effect: from LPS and TST, as measured by actigraphy.
Statistical methods: Efficacy:	The primary analysis was based on the change of LPS from baseline to the postbaseline PSG recorded once between Week 3 and Week 6 and considered as Week 4. Data were analyzed as observed on the intent-to-treat (ITT) population. Change from baseline in LPS was analyzed using an analysis of covariance (ANCOVA) model with treatment group and age group as fixed effects, and baseline value as the covariate. No interaction was added in the model. A 2-sided significance level of 5% was used. The model containing the interaction treatment-by-age group was explored to support the primary model. Two key secondary criteria were analyzed using a hierarchical procedure: - the *CGI-child – global improvement of insomnia* value evaluated at Visit 6 (Week 4) was analyzed (ITT population) using an analysis of variance (ANOVA) model with treatment group and age group as fixed effects - the *CGI-child – global severity of insomnia* change versus baseline evaluated at Visit 6 (Week 4) was analyzed applying the same methodology used for PSG LPS. The other secondary efficacy variables were analyzed at Visit 6 (Week 4) and at Visit 8 (Week 8) when planned, using change versus baseline and a 2 fixed factors analysis ANCOVA, if there was a planned baseline for the given parameter, otherwise using raw score and a 2 fixed-factors ANOVA as previously described.
Safety:	Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 9.0) and were classified according to treatment-emergent criteria. Normal ranges for age were used to describe potential clinical laboratory abnormalities. Analyses of the potential for next-day residual effects and rebound effects during the randomized phase and the post-treatment phase were also performed. All analyses were based on the total treated (TT) population.

Summary:	A total of 201 patients were randomized to treatment. All patients were exposed at least once to study treatment (65 in the placebo group and 136 in the zolpidem group). Of these 201 patients, 23 (11.4%) withdrew from the study: 8 (12.3%) in the placebo group and 15 (11.0%) in the zolpidem group. The main reasons for discontinuation were "subject's request" in the placebo group [8 (12.3%) patients] and "adverse event" [9 (6.6%) patients] in the zolpidem group. The study population was comparably distributed between 2 age groups: 111 patients (55.2%) in the 6 through 11-years age group and 90 patients (44.8%) in the 12 through 17-years age group. As expected in a population of patients with ADHD, the majority of the study population was male (77.1%) and the sex ratio was approximately the same in both age groups. The mean ADHD duration was 6 years for the global population and the mean ADHD Rating Scale-IV total score was 29.4. A total of 92% of the population received a concomitant ADHD pharmacotherapy, mainly represented by psychoanaleptics (90%). The mean duration of insomnia was approximately 5 years for the global population. Approximately one-third of the patients had previous behavioral intervention for insomnia and approximately one-third received a previous sleep medication.
Efficacy results:	***Primary efficacy variable*** The baseline-adjusted mean change for LPS at Week 4 did not differ significantly between treatment groups (-21:16 minutes in the placebo group and -20:17 minutes in the zolpidem group). ***Secondary efficacy variables*** According to the hierarchical procedure proposed in the statistical analysis plan, and as the primary endpoint was nonsignificant, the secondary endpoints cannot be considered as significant. Hypnotic efficacy *Clinical Global Impression of the Investigator* On the CGI-child at Week 4, the mean value for improvement of insomnia was greater in the zolpidem group compared with the placebo group for the 12 through 17-years age group, but the mean values were not different between treatment groups for the 6 through 11-years age group. In addition, on the CGI-child at Week 4, the mean decreased severity of insomnia was greater in the zolpidem group compared with the placebo group for both age groups. At Week 8, on the CGI-child, the mean value for improvement of insomnia and the mean decreased severity of insomnia were greater in the zolpidem group compared with the placebo group only in the 12 through 17-years age group. On the CGI-parent/legal guardian, at Weeks 4 and 8, the mean value for improvement of insomnia and the mean decreased severity of insomnia were greater in the zolpidem group compared with the placebo group only in the 12 through 17-years age group.

Summary: Efficacy results (cont'd):	*Other PSG sleep parameters* Total sleep time, WASO, and NAASO were divided by time-in-bed (TIB) to obtain, respectively, sleep efficiency, %WASO and %NAASO to take into account TIB that may differ according to age. The baseline-adjusted mean change for sleep efficiency, %WASO and %NAASO did not differ significantly for both treatment groups, at Week 4, in the ITT population: • sleep efficiency least squares (LS) mean = 1.66% in the zolpidem group versus 1.16% in the placebo group; • %WASO LS mean = 0.63% in the zolpidem group versus 1.29% in the placebo group; • %NAASO LS mean = 0.13% in the zolpidem group versus -0.21% in the placebo group. *Actigraphic measures of sleep parameters* The baseline-adjusted mean change for LPS and TST did not differ significantly for the treatment groups at Week 4, in the ITT population: • LPS: LS mean = -13:12 minutes in the zolpidem group versus -14:46 minutes in the placebo group; • TST: LS mean = 0:26 minutes in the zolpidem group versus -2:20 minutes in the placebo group. <u>Effect on behavioral component of ADHD</u> *ADHD Rating Scale-IV* The baseline-adjusted mean change for the ADHD Rating Scale-IV total score did not differ significantly for both treatment groups at Weeks 4 and 8, in the ITT population. *School tardiness/attendance reports* Only incomplete data were obtained due to the summer vacation period, and the descriptive statistics of these data were not informative. <u>Effect on cognitive component of ADHD</u> *Conners' Continuous Performance Test II (CPT-II)* The mean change from baseline did not differ significantly for both treatment groups, at Weeks 4 and 8 regarding the number of omission errors and the number of commission errors, in the ITT population. Mean change from baseline for the average reaction time was increased in the zolpidem group compared with the placebo group at Week 4 (41.72 ms versus 1.35 ms, respectively) and at Week 8 (40.06 ms versus 13.78 ms, respectively) but the variability of the results was notably increased at Week 8 compared with Week 4, in the ITT population.
Safety results:	A total of 201 patients were exposed to investigational product (IP). Median IP exposure was 56 days for both treatment groups**.** A total of 111 patients were exposed to zolpidem for at least 8 weeks.

Summary: Safety results (cont'd):	A total of 201 treated patients were evaluated for the occurrence of treatment-emergent adverse events (TEAEs). The incidence of patients with at least 1 TEAE was greater in the zolpidem group (62.5%) when compared with the placebo group (47.7%). There were no deaths during the study. One patient (in the placebo group) experienced at least 1 serious adverse event (SAE) that was recorded as treatment-emergent. Investigational product was permanently discontinued due to TEAEs for 9 (6.6%) patients in the zolpidem group versus 0 in the placebo group. The most frequent system-organ classes (SOCs) involved (≥10% in the zolpidem group and higher than in the placebo group) were "Nervous system disorders" and "Psychiatric disorders." The most frequent TEAEs (≥5%) in the zolpidem group were dizziness (23.5% versus 1.5% in the placebo group), headache (12.5% versus 9.2%), and hallucinations (7.4% versus 0). The SOC "Psychiatric disorders" was the main contributor to permanent IP discontinuation (3.7%), and the main AE leading to permanent IP discontinuation was "hallucination". No relevant changes of laboratory parameters were noted. No relevant changes of vital signs parameters were noted. ***Other safety parameters*** Next-day residual effects *Pediatric Daytime Sleepiness Scale (PDSS) total score* The decrease in PDSS baseline-adjusted mean change at end-of-treatment (EOT) was greater in the zolpidem group compared with the placebo group, but the difference between treatment groups was not statistically significant, in the TT population. Rebound effect Rebound effect was measured on actigraphy sleep characteristics after treatment discontinuation. *Latency to persistent sleep (LPS)* A worsening from baseline for LPS was observed in both treatment groups, greater in the zolpidem group than in the placebo group on Night 1 [LS mean change from baseline 31:55 minutes versus 16:05 minutes, respectively] and greater in the placebo group than the zolpidem group on Night 2 (11:18 minutes versus 6:26 minutes, respectively), but the difference between treatment groups at either timepoint was not significant. *Total sleep time (TST)* A slight worsening from baseline for TST was observed for placebo and zolpidem treatment groups on Night 1 (LS mean change from baseline -13:19 minutes versus -11.21 minutes, respectively) but no longer on Night 2 (15:44 minutes versus 7.08 minutes, respectively). Treatment groups were not significantly different at either timepoint.

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