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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00530556
		Study Code:	L_8445
Generic drug name:	Zolpidem	**Date:**	17/Sep/2007

Title

Effect of Zolpidem Compared to Placebo on Insomnia and Daytime Function in Patients with Insomnia associated with Osteoarthritis.

Investigator(s), study site(s)

Multicenter seventeen (17) investigative sites enrolled subjects in this study.

Study duration and dates	First subject enrolled: March 20, 2003 Last subject completed: June 1, 2004	**Phase** IV

Objectives

Primary
The primary objective was to assess the efficacy and safety of zolpidem at doses up to 10 mg compared to placebo in subjects with insomnia associated with osteoarthritis (OA).

Secondary
Secondary objectives were to determine the effects of zolpidem at doses up to 10 mg compared to placebo on daytime functioning quality of life, and interpersonal functioning in subjects with insomnia associated with osteoarthritis

Methodology

This was a multicenter, placebo-controlled, double-blind, randomized, parallel-groups study comparing zolpidem at doses of up to 10 mg to placebo administered nightly for a period of 6 weeks. A total of 150 subjects were to be randomized to receive zolpidem or placebo in a parallel-groups design.

Following a 10 (+4)-day baseline (screening) period, subjects who met selection criteria were randomized to zolpidem or placebo in a 1:1 allocation. For subjects randomized to zolpidem, those 45 to 64 years of age received 10 mg zolpidem and those older than 64 years of age received 5 mg zolpidem.
Based on efficacy and safety assessments and discussion with the subject, the Principal Investigator could have increased the dose to 10 mg at Visit 3 (after 1 week of double-blind treatment) in subjects 65 years or older. If necessary, that dose could have been re-adjusted to 5 mg at any one of the subsequent visits.

Each subject was to participate in the study for a total period of 8 weeks, consisting of a 10 (+4)-day screening segment, followed by a 6-week, double-blind nightly treatment segment. The subjects were to have a total of 6 visits. Visits were to take place at Day –10 (Screening), Day 1 (Baseline), Week 1, Week 2, Week 4, and Week 6 (End of Study).

Number of subjects planned and analyzed

150 planned; 170 (84 placebo, 86 zolpidem) received at least 1 dose of study medication.

Diagnosis and main criteria for inclusion

Insomnia associated with osteoarthritis.

Investigational product

Zolpidem tartrate 5 mg and 10 mg capsules for oral administration nightly.

Duration of treatment

6 weeks.

Reference therapy

Matching placebo capsule (lactose) for oral administration nightly.

Criteria for evaluation

Efficacy:

The primary efficacy variable was the Patient's Global Impression of Therapy of Insomnia (PITI).

Secondary efficacy variables included the remaining items in the PITI, the Clinical Global Impression of Insomnia (CGII), sleep-related outcome measures from the Morning Questionnaire, Daytime Functioning, Life Event Questionnaire (LEQ), Pain Impact Questionnaire (PIQ), and use of pain rescue medications.

Safety:

Safety variables included all reported serious and non-serious adverse events, adverse events leading to the discontinuation of study drug, and clinically significant changes in vital signs and laboratory parameters.

Statistical procedures

The analysis of efficacy was performed on the intent-to-treat (ITT) group, consisting of all randomized subjects who had any post-treatment efficacy data, as well as on an evaluable sub-population consisting of all ITT subjects without inclusion and exclusion violations and who completed at least 28 days of treatment (per-protocol population). The process of selecting the evaluable subject population was completed prior to unblinding the study. All subjects who received study medication were included in the analysis of safety.

For nominal categorical variables, differences between the treatment groups were tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by study center. For ordinal categorical variables, differences between the treatments groups were tested using the CMH mean score test, stratified by study center. For continuous variables, differences between the treatment groups were tested using an analysis of variance (ANOVA) model with effects for treatment, center, and treatment-by-center interaction.

If the treatment-by-center interaction was not significant (=0.1), the interaction term was dropped from the ANOVA model. Throughout all statistical analyses, statistical significance was noted when $p<0.05$. All p-values were 2-sided. Missing values remained as missing; for example, no attempt was made to impute missing values and only observed values were used in data analyses and presentations. Centers were included in the ANOVA and CMH test. Centers with less than 10 subjects were pooled from the smallest to

largest to have at least 10 subjects for the ANOVA and CMH test. If aggregate was still less than 10 subjects, those centers were pooled into the smallest center with more than 10 subjects.

The primary efficacy endpoint of the study was the percentage of subjects responding that the study medication "Helped me get a better night's sleep" on the PITI. The percentage of subjects having a primary endpoint and its exact binomial 95% confidence interval were computed for each visit and the last visit by each treatment. The endpoint analysis (i.e., the last non-missing value for each subject) was the primary analysis.

Secondary endpoints were as follows:
- The percentage of subjects responding favourably to Items 1, 2, 3 and 5 of the PITI
- The mean change from baseline in the subject's perceived total sleep time, length of time spent falling asleep, number of times they woke up, and duration of being awake during the night (Morning Questionnaire)
- The mean change from baseline in quality of sleep and morning energy (Morning Questionnaire)
- The mean change from baseline in the subject's sleep-related daytime functioning (Evening Questionnaire)
- The mean change from baseline in severity of illness on the CGII
- The mean scores in therapeutic effect and side effects on the CGII
- The percentage of subjects responding favourably to the Patient's Global Impression of Therapy - Daytime Functioning (PGITF)
- The mean change from baseline of the total score in the LEQ
- The mean amount of pain rescue medication taken
- The mean change from baseline of the scores in the PIQ

Extent of exposure, concomitant medications, and change from baseline in vital signs were summarized. Adverse events were summarized by body system, frequency, and intensity.

Clinical laboratory tests, including clinical chemistry and hematology, and mean changes from baseline for each vital sign parameter were summarized by treatment group using descriptive statistics (mean, standard deviation (SD), minimum, median, and maximum). Details of clinically significant abnormalities were listed for all subjects showing such abnormalities.

Summary

Efficacy Results:

A statistically significantly greater proportion of subjects who received zolpidem (10 mg or 5 mg based on age) nightly for 6 weeks responded favourably that study medication "Helped me get a better night's sleep" on the PITI compared to subjects who received placebo nightly for 6 weeks. At the Endpoint Visit, 83.3% of subjects in the zolpidem group and 50.0% of subjects in the placebo group responded favourably to PITI item 4 (p=0.001), a difference of 33%. Statistically significant differences favouring zolpidem were also observed when the primary endpoint was analyzed by age (45 to 64 years and > 64 years).

Overall, statistically significant differences favouring zolpidem were observed for other PITI items such as "medication helped me sleep" (p=0.001), "medication lengthened the time slept" (p=0.001), "medication strength was just right" (p=0.001) and in change from baseline at most study visits in the majority of sleep-related outcomes from the morning and evening questionnaires (=0.045).

Other secondary objectives of this trial were to determine the effects of zolpidem at doses up to 10 mg compared to placebo on daytime functioning, quality of life, and interpersonal functioning in subjects with insomnia associated with OA. Statistically significantly better outcomes were observed with zolpidem compared to placebo at nearly every visit for CGII results in mean change from baseline in severity of illness and mean scores in therapeutic effect. No statistically significant treatment effect was noted for mean scores in side effects on the CGII.

Statistically significantly greater percentages of the zolpidem treatment group reported that "study medication improved daytime functioning" and "helped me have a better day" compared to the placebo group (=0.006).

No statistically significant treatment differences were observed for mean change from baseline in total score in the LEQ or in PIQ scores.

Ten subjects (3 placebo, 7 zolpidem) used pain rescue medication during the study.

Safety Results:
The percentages of subjects in the placebo and zolpidem treatment groups who experienced at least 1 treatment-emergent adverse event were 38.1% (32/84) and 45.3% (39/86), respectively. The most common (=2.5%) treatment-emergent adverse events were somnolence (3.6%) in the placebo group and dizziness (5.8%), somnolence (4.7%), nausea (3.5%), and nasopharyngitis (3.5%) in the zolpidem treatment group. The majority of treatment-emergent adverse events were mild or moderate in severity.
A notably higher percentage of zolpidem subjects experienced dizziness compared to placebo subjects (5.8% vs. 0%).

One placebo subject (myocardial infarction) and 1 zolpidem subject (angina and chest pain) experienced serious adverse events during the study; none of the serious adverse events were considered to be related to study drug by the investigator.

Seventeen (17) subjects (8 placebo, 9 zolpidem) prematurely discontinued study drug due to at least 1 adverse event. The majority of these events were considered related to study drug by the investigator. The most common adverse events leading to premature discontinuation were anxiety (2 subjects) in the placebo group and dizziness (3 subjects) and somnolence (2 subjects) in the zolpidem treatment group.

Changes from baseline in laboratory parameters and vital signs were unremarkable and did not suggest any-treatment related trends.

Date of the report: 23 September 2005