OX22-006 CSR Synopsis, 9 Nov 2007

<table>
<tr><td>Name of Sponsor/Company:
Orexo AB</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
OX22</td></tr>
<tr><td>Name of Active Ingredient:
Zolpidem</td></tr>
<tr><td colspan="3">Title of study: A double-blind, randomized, two-period crossover study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia.</td></tr>
<tr><td colspan="3">Investigator: Dr Corinne Staner (coordinating investigator)</td></tr>
<tr><td colspan="3">Study centers: France (2 centers), Belgium (3 centers) and Russia (5 centers)</td></tr>
<tr><td colspan="3">Publication (reference): NA</td></tr>
<tr><td colspan="2">Study period:
- First enrollment: 13 December 2006
- Completion date: 11 July 2007</td><td>Phase of development: II</td></tr>
<tr><td colspan="3">Objectives:
The primary objectives were:
To evaluate the hypnotic effects on sleep initiation by polysomnography (PSG) of a single dose of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia. The primary endpoint was Latency to Persistent Sleep (LPS) (to test for superiority). Secondary endpoints were Sleep Onset Latency (SOL) and Latency to Stage 1 (ST1L).
To evaluate the hypnotic effects on sleep continuity by PSG of a single dose of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia. The following PSG variables were tested for “at least as good as”: Total Sleep Time (TST), Number and duration of awakenings after sleep onset (WASO).
The secondary objectives were:
To evaluate by PSG other visually scored night sleep variables, other latency variables, sleep continuity and sleep architecture, the patient’s subjective assessment of sleep and next day residual effects of sublingual zolpidem versus oral immediate-release zolpidem (Ambien®) in patients with primary insomnia.
To assess tolerability and safety of the study treatments.</td></tr>
<tr><td colspan="3">Methodology:
This was a multi-center, double-blind, double-dummy, randomized, 2-period cross-over study.</td></tr>
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Disposition of patients:
The 73 patients were recruited across 10 centers located in France, Belgium and Russia. Patients were randomized in 8 of the 10 centers. Centers were aggregated in 4 pooled centers according to their location and to the number of patients randomized in order to study a potential center effect with a balanced number of patients in each pooled center.

	Pooled center 1	Pooled center 2	Pooled center 3	Pooled center 4	Total
No. planned:					72
No. screened:					158
No. randomized and treated:	19	19	14	21	73
Males/females:	9/10	6/13	5/9	11/10	31/42
Mean age (range):	40.9 (24-59)	45.3 (19-64)	35.8 (22-49)	41.8 (23-59)	41.3 (19-64)
No. analyzed for efficacy (per protocol set):	18	18	14	20	70
No. analyzed for safety:	19	19	14	21	73
No. completed the study:	19	18	14	21	72

Diagnosis and main criteria for inclusion:
Male and female patients between 18 and 65 years* of age who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for primary insomnia and freely gave their written informed consent to participate.
*As shown above in disposition of patients, no patient was over 64 years of age.

Test product, dose and mode of administration, batch number:
OX22 (sublingual zolpidem) was administered as single sublingual tablet of 10 mg. Packaging batch numbers: E1179 (for France and Belgium) and E1184 (for Russia). Bulk OX22 sublingual tablet batch number: RF1308A. Corresponding bulk placebo sublingual tablet batch number: RF1303PA.

Duration of treatment:
The patients received one single dose of OX22 or Ambien® and one single dose of the matching placebo of the corresponding drug on the evening of Day 1 in each treatment period, according to a randomized schedule. A 7-14 day wash-out period was included in between treatment periods. Each study treatment (OX22 and Ambien®) was administered once during the study.

Reference therapy, dose and mode of administration, batch number:
Ambien® (overencapsulated immediate-release zolpidem tablet) was administered as single oral capsule of 10 mg. Packaging batch numbers: E1179 (for France and Belgium) and E1184 (for Russia). Bulk zolpidem 10 mg oral capsule batch number: ID1416. Corresponding bulk placebo capsule batch number: ID1415.

Criteria for evaluation:
A standard PSG consists of the simultaneous recording of four electrophysiological signals i.e.:

- cerebral activity recorded via the electroencephalogram (EEG)
- ocular movement recorded via the electro-oculograms (EOG)
- muscular tone recorded via the sub chin electromyograms (EMG)
- cardiac activity recorded via the electrocardiogram (ECG)

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The PSG studies were performed in individual sound-attenuated and comfortably furnished bedrooms. Recordings of sleep were scored by sleep technicians having regular training in order to ensure an inter-expert agreement of more than 90 %. The different visual sleep parameters were derived from the visual scoring of the recordings using the Hypnos software.

Two kinds of sleep parameters were derived from the visual analysis of sleep:

- Sleep continuity parameters comprised both sleep initiation and sleep maintenance variables. Sleep initiation indicated how easy the patient fell asleep and the time needed to reach stable persistent sleep. Sleep maintenance included general parameters that roughly indicated how sleep was maintained after sleep onset (total sleep time, sleep efficiency, and wake after sleep onset) as well as more subtle indicators of maintenance disturbances such as sleep fragmentation indices and intrasleep arousal, wake and awakenings.
- Sleep architecture parameters comprised stages distribution variables documenting duration and proportion of the different sleep stages and sleep profile variables that provided an outline on the time course of the different sleep stages during the recording period.

The **primary pharmacodynamic endpoints** consisted of sleep parameters measured by PSG in order to assess both the hypnotic effects on sleep initiation and the hypnotic effects on sleep continuity (maintenance) of OX22 versus Ambien®.

The primary sleep initiation endpoint was:

- Latency to Persistent Sleep (LPS)

The secondary sleep initiation endpoints were:

- Sleep Onset Latency (SOL)
- Latency to Stage 1 (ST1L)

The sleep continuity (maintenance) endpoints were:

- Total Sleep Time (TST)
- Number and duration of awakenings after sleep onset (WASO)

The following **secondary pharmacodynamic endpoints** were assessed:

- Other visually scored night sleep variables, such as sleep continuity (maintenance), sleep architecture and sleep profile variables (from PSG measurements)
- Subjective assessment of sleep: Leeds Sleep Evaluation Questionnaire (LSEQ). The LSEQ was used to monitor subjectively perceived changes in sleep.
- Next day residual effects: Bond and Lader Visual Analogue Scale (VAS), Digit Symbol Substitution Test (DSST) and Leeds psychomotor tests.
- The Bond and Lader VAS assessed subjective feelings such as alertness, contentedness and calmness. DSST assessed the capacity for attention and concentration, and required information processing (sensorial information recognizing). The Leeds psychomotor test was a computerized system that allowed assessment of attention abilities and vigilance. It was divided into two parts; Critical Flicker Fusion Test (CFFT) and Multiple Choice Reaction Time (MCRT).

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The following **safety variables** were assessed:

- Adverse events
- ECG
- Vital signs
- Laboratory results (biochemistry, hematology and urinalysis)
- Physical examinations

Statistical methods:

Pharmacodynamic analyses:

PSG variables for the two treatments were compared in a two-period crossover analysis using an ANOVA model with study center, sequence, patient, period and treatment as class variables. Differences between treatments were estimated and tested within the statistical model. Exploratory analyses of the secondary variables were carried out and tabulated by treatment as numbers (n), means, standard deviations and min- and max-values. All evaluable patients (per protocol set) were included in the pharmacodynamic analyses.

Safety analyses:

Safety was assessed for all randomized patients who had taken at least one dose of study medication (all patients in this study). Vital signs, ECG, laboratory results and physical examination were tabulated by parameters, investigational medicinal product (IMP) and time for all patients. Adverse events were coded and classified according to their preferred term and then tabulated according to their intensity and their relationship to the study treatments.

Study procedures:

The screening visit was divided into one initial day, followed by two consecutive screening nights. The patients first came to the clinic for a screening day (S1) that took place within 21 days before start of the first assessment period. Patients eligible after evaluation on Day S1 then returned to center for performing two consecutive screening nights (S2 to S3 and S3 to S4). The screening nights were used to ascertain if the patients met the PSG inclusion criteria of the study.

For eligible patients, the screening visit was followed by two assessment periods of three days and two nights each. There was a wash-out period of 7 to 14 days between the two assessment periods. The patients were admitted fasting to the study center on Day -1 (the day before administration of the study product) of each period for a habituation night from Day -1 to Day 1. Inclusion and exclusion criteria were re-checked on Day -1. In the evening of Day 1, using the double-dummy method, patients were administered a single dose of OX22 or Ambien® and the placebo to the corresponding treatment. The order in which patients received OX22 and Ambien® was randomized. The PSG recordings were initiated immediately after product administration. No food was allowed from 3 h before product administration to the end of the PSG recording period (in the morning of Day 2). The patients remained at the study center until the afternoon of Day 2. The investigator authorized them to leave the center after a review of the safety results.

The end of study visit (one day) took place between 7 and 14 days after the end of the second assessment period.

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SUMMARY – CONCLUSIONS

Pharmacodynamic results:

The results showed that, compared to Ambien®, OX22 significantly shortened the three endpoints that related to sleep initiation, i.e. latency to persistent sleep ($p = 0.001$), sleep onset latency ($p < 0.01$) and latency to stage 1 ($p < 0.01$). For the two other endpoints of the primary objectives (wake after sleep onset and total sleep time), OX22 was at least as good as Ambien® in total sleep time, although the non-inferiority limit was not achieved for the duration of wake after sleep onset.

Other sleep continuity and sleep architecture parameters such as sleep efficiency index, total time awake, time spent in stage 2 and time spent in non REM sleep were significantly ($p < 0.05$) improved with OX22 compared to Ambien®. Regarding sleep profile parameters, compared to Ambien®, OX22 in the first 2-h recording interval significantly ($p < 0.001$) decreased time spent awake or drowsy and significantly ($p < 0.05$) increased time spent in stage 2. These effects either disappeared or were not more significant in the three following 2-h intervals of the recording period.

No significant differences in subjective sleep parameters could be observed although results on the "getting to sleep" subscale pointed in the same direction as the sleep initiation parameters (latency to stage 1, sleep onset latency and latency to persistent sleep), i.e. that the ease with which the patients fell asleep was found more improved with OX22.

Results of the next day residual effects indicated that there were no differences between OX22 and Ambien®.

Safety results:

This two-period cross-over study showed that single administrations of OX22 and Ambien® were well tolerated. During the study, 31 adverse events were reported in 24 patients. The majority of the adverse events (23) were of mild intensity and 7 of the adverse events were of moderate intensity. There were no severe adverse events reported. Ten (10) adverse events were considered related to OX22 and 12 adverse events were considered related to Ambien®. The most frequent treatment related adverse event observed was somnolence, which was expected with zolpidem. Two SAEs were reported in one patient (pregnancy and miscarriage), one of which occurred before administration of the first treatment. The patient discontinued the study after the first dose (Ambien®) due to the SAEs. Both SAEs were considered unrelated to study treatment.

No clinically relevant changes in vital signs, ECG, laboratory tests or physical examination were reported.

Overview of adverse events by treatment, system organ class and preferred term

System organ class Preferred term	Ambien® (n=73) nae (n, %)	OX22 (n=72) nae (n, %)
Nervous system disorders	**6 (6, 8.2%)**	**5 (4, 5.6%)**
Somnolence	2 (2, 2.7%)	3 (3, 4.2%)
Dizziness	2 (2, 2.7%)	1 (1, 1.4%)
Headache	---	1 (1, 1.4%)
Hypersomnia	1 (1, 1.4%)	---
Migraine	1 (1, 1.4%)	---
Gastrointestinal disorders	**6 (6, 8.2%)**	**2 (2, 2.8%)**
Dysgeusia	2 (2, 2.7%)	2 (2, 2.8%)
Nausea	4 (4, 5.5%)	---
Respiratory, thoracic and mediastinal disorders	**3 (2, 2.7%)**	---
Bronchitis acute	1 (1, 1.4%)	---
Respiratory disorder	1 (1, 1.4%)	---
Rhinitis allergic	1 (1, 1.4%)	---
Infections and infestations	**1 (1, 1.4%)**	**1 (1, 1.4%)**
Influenza	1 (1, 1.4%)	1 (1, 1.4%)
Pregnancy, puerperium and perinatal conditions	**1 (1, 1.4%)**	---
Abortion spontaneous	1 (1, 1.4%)	---
Pregnancy	---	---
Cardiac disorders	---	**1 (1, 1.4%)**
Sinus bradycardia	---	1 (1, 1.4%)
General disorders and administration site conditions	**1 (1, 1.4%)**	---
Asthenia	1 (1, 1.4%)	---
Metabolism and nutrition disorders	---	**1 (1, 1.4%)**
Iron deficiency anemia	---	1 (1, 1.4%)
Musculoskeletal and connective tissue disorders	---	**1 (1, 1.4%)**
Hypotonia	---	1 (1, 1.4%)
Psychiatric disorders	---	**1 (1, 1.4%)**
Nightmare	---	1 (1, 1.4%)
Skin and subcutaneous disorders	---	**1 (1, 1.4%)**
Erythema	---	1 (1, 1.4%)

nae = number of experienced adverse events within the category, n = number of patients having experienced at least one event

Conclusions:

The present study demonstrates that OX22 is superior to Ambien® in terms of shortening sleep initiation parameters including the sleep initiation endpoints latency to persistent sleep, sleep onset latency and latency to stage 1. OX22 was found to be at least as good as Ambien® in the sleep continuity (maintenance) endpoint of total sleep time. Regarding the secondary objectives, the present results indicate that, overall, OX22 did not significantly differ from Ambien®. The differences that were observed in favor of OX22 relate to its faster sleep inducing effect. No significant differences in subjective sleep parameters could be observed although results on the "getting to sleep" subscale pointed in the same direction as the sleep initiation parameters (latency to

stage 1, sleep onset latency and latency to persistent sleep), i.e. that the ease with which the patients fell asleep was found more improved with OX22. Results of the assessments of next day residual effects indicate that there were no significant differences between OX22 and Ambien®.

In summary, the present study shows that OX22 is superior to Ambien® in terms of sleep inducing properties and that the two drugs do not significantly differ in sleep continuity (maintenance) properties. Moreover there were no between drug differences in terms of safety assessments (adverse events, laboratory tests, physical examinations, vital signs, and ECGs).

Date of final report: *9 November 2007*