CLINICAL STUDY RESULTS.ORG STUDY 190-028

Title of Study: "The Safety and Efficacy of Eszopiclone in Subjects with Mild to Moderate Obstructive Sleep Apnea Syndrome"	
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Study Center: Sleep Medicine Institute, Inc., Atlanta, GA; Tri-State Sleep Disorders Center, Cincinnati, OH	
Study Period: 07 August 2003 – 06 January 2004	**Clinical Phase:** Phase II
Primary Objective: To evaluate the hypnotic efficacy of eszopiclone in subjects with mild to moderate obstructive sleep apnea syndrome compared to placebo. **Secondary Objective:** To evaluate the safety of eszopiclone in subjects with mild to moderate obstructive sleep apnea syndrome compared to placebo.	
Methodology: A randomized, double-blind, placebo-controlled, crossover efficacy and safety study in subjects with obstructive sleep apnea syndrome.	
No. of Subjects: Randomized: 22; Completed: 21 (95.5%); Discontinued: 1 (4.5%)	
Diagnosis and Main Criteria for Inclusion: Male or female subjects between the ages of 35 and 64 years, inclusive, with an Apnea-Hypopnea Index (AHI) ≥10 and ≤40 episodes per hour.	
Test Product: Eszopiclone [(S)-zopiclone] tablets. **Reference Product:** Placebo tablets. **Dosage:** Eszopiclone 3.0 mg. **Mode of Administration:** Oral. **Meal Relationship:** Dosing occurred at least two hours after dinner.	
Duration of Treatment: On two separate occasions separated by a 5-7 day washout period, a bed-time dose of double-blind study medication was administered for two consecutive days.	
Criteria for Evaluation **Efficacy:** Sleep apnea and efficacy endpoints were based on polysomnography (PSG) readings. The primary sleep apnea measure was the apnea and hypopnea index (AHI), determined by the total number of apnea and hypopnea episodes divided by total sleep time in hours; the mean of the AHI scores from the two consecutive nights in the sleep laboratory was used to define the primary study endpoint. The secondary endpoints were divided into sleep apnea endpoints and sleep efficacy endpoints. The secondary sleep apnea endpoints were: mean duration of apnea and hypopnea episodes, arterial low oxygen saturation during apnea and hypopnea episodes, number of arousals, apnea index, hypopnea index, respiratory arousals index, spontaneous arousals index, mean duration of apnea episodes, mean duration of hypopnea episodes, longest duration of apnea episodes, longest duration of hypopnea episodes, longest duration of apnea and hypopnea episodes, lowest oxygen saturation during apnea episodes, lowest oxygen saturation during hypopnea episodes, mean oxygen saturation during apnea episodes, mean oxygen saturation during hypopnea episodes, and mean oxygen saturation during apnea and hypopnea episodes. The secondary sleep efficacy endpoints were: latency to persistent sleep (LPS), sleep efficiency, wake time after sleep onset (WASO), number of awakenings, wake time before persistent sleep, movement during sleep, wake time during sleep, wake time after sleep, latency to each stage of sleep, total sleep time in each sleep stage, percent of total sleep time in each sleep stage, cumulative wake time, wake time during each hour of the night, wake time during each quarter of the night and wake time during the last third of the night. **Safety:** The safety variables were: adverse events, clinical laboratory assessments, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), physical examinations, 12-lead ECG readings, and brief neurological examinations.	

STATISTICAL METHODS

General: All statistical procedures were performed using SAS Version 8.2 or higher. All statistical tests were two-sided and were conducted at the 5% significance level, unless otherwise specified. Continuous variables were summarized using descriptive statistics, including number of subjects, mean, least squares (LS) mean, median, standard deviation (SD), minimum, and maximum. Summaries of categorical variables included counts of subjects and percentages. All summaries were presented by treatment group, unless otherwise specified. For summary purposes, baseline was defined as the last available value prior to the first dose of double-blind study medication, unless otherwise specified.

All p-values were reported to four decimal points with p-values less than 0.0001 reported as <0.0001. Wherever an analysis of variance (ANOVA) model was described, SAS PROC MIXED was used to evaluate the data.

The analysis populations were defined as follows:

Intent-to-Treat (ITT) Population - all subjects who received at least one dose of double-blind study medication. The ITT Population was used for the analysis of all safety endpoints.

Completer Population - all ITT subjects who completed both treatment periods. The analyses of sleep apnea measures and efficacy endpoints were performed on the Completer Population.

The Single Blind Placebo (SBP) Population - all subjects who received single-blind placebo but did not receive double-blind study medication. Data from this population were presented in data listings only.

Efficacy: All sleep apnea and efficacy parameters were analyzed using the Completer Population. For each measure, the mean of the observations from the two consecutive nights in the sleep laboratory was used to define the endpoint. If only one value was available, then it was used as the endpoint. If neither observation was available, then the endpoint was treated as missing.

Baseline was defined as the mean observation of the two consecutive nights during the single-blind placebo.

In addition, for all sleep apnea and efficacy measures, Night 1 and Night 2 results were also analyzed using the same method as for the primary analysis. Night 1 represented the Night 1 results at Visits 3 and 4, and Night 2 represented the Night 2 results at Visits 3 and 4.

Statistical Methods

Safety: All analyses of safety variables utilized the ITT Population. All adverse events were coded using the COSTART dictionary (Version 5.0, 1995). Treatment-emergent adverse events were defined as 1) adverse events that occurred or worsened (increased in severity and/or frequency) on or after the first dose of study medication, 2) adverse events with a missing start date and a stop date on or after the first dose of study medication, or 3) adverse events with both a missing start and stop date. Adverse events that occurred within 14 days after treatment discontinuation were considered treatment-emergent AEs. Each treatment-emergent AE was assigned to a treatment (placebo, eszopiclone 3 mg) if the event began or worsened upon or after the start of the treatment but prior to the first administration of the next treatment.

The following treatment-emergent AE summaries were produced and presented by treatment and by COSTART body system and preferred term:

- All Adverse Events (including number of events and subject incidence)
- Adverse Events by Severity (mild, moderate, or severe)
- Adverse Events by Relationship to Treatment (not related, unknown, possible, probable, or definite)
- Single-blind adverse events (adverse events that occurred during the single-blind placebo treatment period)

The following conventions were followed in summarizing adverse events:

- For subject incidence summaries, each subject was counted only once within each body system and within each preferred term. If a subject reported more than one adverse event within a preferred term and/or a body system, the adverse event with the highest known severity within each body system and each preferred term was included in the summaries by severity.
- For summaries by relationship to study medication, adverse events were reported by the strongest relationship within each body system and within each preferred term (adverse events with unknown relationship were considered “more related” than events not related to study drug).

A listing of serious adverse events (SAEs), as well as a listing of adverse events for discontinued subjects, was presented.

RESULTS

EFFICACY (Night 1/Night 2 Average results are presented unless otherwise indicated):

Primary Sleep Apnea Endpoint: the mean total AHI was similar on eszopiclone 3 mg and on placebo treatment (90% C.I. for mean difference = -1.7,1.9).

Secondary Sleep Apnea Endpoints:

- There were no significant difference in the hypopnea index between eszopiclone 3 mg and placebo treatment at Night 1/Night 2 Average (90% C.I. for mean difference -2.9, 1.0). There was a nearly significant difference (90% C.I. for mean difference of -0.1, 2.2) in the apnea index between eszopiclone 3 mg (3.9 episodes/hour) and placebo (2.8 episodes/hour) at Night 1/Night 2 Average.
- Eszopiclone 3 mg significantly reduced the spontaneous arousal index compared with placebo (13.6 vs. 11.4, respectively; 90% C.I. for mean difference = –3.7, -0.7). There was no significant difference in respiratory arousals between the eszopiclone 3 mg and placebo groups but there was a trend towards a significant decrease in total arousals with eszopiclone (22.9 vs. 21.0 for placebo, 90% C.I. for mean difference = –3.7, 0.0).
- There were no significant differences in the average or longest duration of apnea and hypopnea episodes between the eszopiclone 3 mg and placebo groups.
- There was a nearly significant difference (90% C.I. of –1.3, 0.0) in the average oxygen saturation during hypopnea episodes between placebo (90.3%) and eszopiclone 3 mg (89.6%). There were no significant differences in any other oxygen saturation parameter between the eszopiclone 3 mg and placebo treatment groups.

Sleep Efficacy Endpoints:

- There was no statistically significant difference in LPS between the eszopiclone 3 mg and placebo groups for the Night 1/Night 2 Average ($p = 0.4493$). The largest treatment difference was seen at Night 1 (11.0 min in the placebo group and 6.4 min in the eszopiclone 3 mg group, $p = 0.0559$).
- Eszopiclone 3 mg significantly increased sleep efficiency for the Night 1/ Night 2 Average as compared with placebo (88.3% v. 85.0%, $p = 0.0075$). Eszopiclone 3 mg also significantly increased sleep efficiency at Night 1 compared with placebo (88.5% v. 83.4%, $p = 0.0058$).
- Eszopiclone 3 mg significantly decreased objective WASO compared with placebo for the Night 1/ Night 2 Average (41.3% v. 54.6%, $p = 0.0125$). Eszopiclone 3 mg also significantly decreased WASO at Night 1 compared with placebo (41.1% v. 59.9%, $p = 0.0090$).
- There was no significant difference between eszopiclone and placebo treatment in the objective number of awakenings or any objective wake time parameter at any time point during the study period.
- At post-dose hours 2 through 8, there was significantly less cumulative wake time with eszopiclone 3 mg relative to placebo (each test $p < 0.05$).
- Eszopiclone 3 mg significantly reduced wake time during hours 2,3, and 4 compared with placebo (each test $p < 0.05$).
- Eszopiclone 3 mg significantly reduced the objective wake time for the Night 1/ Night 2 Average during the first and second quarters of the night as compared to placebo ($p < 0.05$).
- There was no significant difference in objective wake time during the last third of the night between eszopiclone and placebo treatments for the Night 1/ Night 2 Average.
- There was no significant difference in duration of apnea and hypopnea episodes or lowest oxygen saturation during apnea and hypopnea episodes between eszopiclone and placebo treatments for the Night 1/Night 2 Average.

SAFETY:

- There were no deaths.
- There were no SAEs or AEs leading to discontinuation in either treatment group.
- There was a higher rate of overall AEs reported during eszopiclone treatment (47.6%) than during placebo treatment (31.8%).
- There were no severe AEs.
- There were more AEs potentially related to eszopiclone treatment (38.1%) than to placebo treatment (9.1%). There were three adverse events (14.3%) of unpleasant taste (with or without dry mouth) that were considered definitely related to eszopiclone treatment.
- There were very few AEs related to drug class effects (<5% in either treatment group).
- Mean hematology and serum chemistry parameter results were similar between both treatments and time points.
- There were no clinically significant laboratory abnormalities reported during placebo or eszopiclone treatment.
- Mean changes from baseline in heart rate, diastolic and systolic blood pressure, respiration rate, temperature, and weight were small and similar between placebo and eszopiclone treatment periods.
- There were no clinically significant vital sign abnormalities reported with either placebo or eszopiclone treatment.
- There were no subjects with abnormal clinically significant ECG results with either placebo or eszopiclone treatment.
- No QT_{C-B} value exceeded 500 msec during any treatment period at any time point during the study. Only two subjects had QT_{C-B} values > 450 msec at baseline and these values remained > 450 msec during double-blind placebo and eszopiclone treatment.
- All subjects passed the neurological tests at every visit.