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Sponsor/company:	sanofi-aventis	ClinicalTrials.gov Identifier:	NCT00283790
		Study Code:	PM_L_0289
Generic drug name:	Zolpidem	Date:	11/Feb/2009

Title of the study: Investigation of psychomotor and cognitive residual effects after single oral doses of zolpidem tartrate extended-release 12.5 mg and eszopiclone 3 mg compared to placebo in healthy young volunteers, using flurazepam 30 mg as an external comparator (PM_L_0289)

Investigator(s): Gary Zammit, PhD, Clinilabs, 1090 Amsterdam Ave., New York, NY 10025

Study center(s): One

Publications (reference): None

Study period:

Date first subject enrolled: 23/Jan/2006

Date last subject completed: 07/Apr/2006

Phase of development: IV

Objectives:

Primary: To assess the residual psychomotor and cognitive effects 8.5 hours after a single nighttime dose of zolpidem tartrate extended-release 12.5 mg and eszopiclone 3 mg respectively, in comparison to placebo in healthy young subjects.

Secondary: The evaluation of subjective sleep efficacy measures from the Morning Sleep Questionnaire, Sleep Treatment Questionnaire, Leeds Sleep Evaluation Questionnaire (LSEQ), Bond & Lader (B&L) Visual Analog Scale. In addition, to assess the residual psychomotor and cognitive effects 8.5 hours after a single nighttime oral dose of flurazepam 30 mg in study subjects when used as an external comparator.

Methodology: This was a single center, randomized, double-blind, placebo controlled 3-way cross-over study evaluating a single nighttime dose of each study drug. Each treatment group received treatment A (placebo), B (12.5 mg zolpidem tartrate extended-release as tablets), and C (3 mg eszopiclone as tablets). Non-randomized dosing with the external comparator (treatment D: 30 mg flurazepam as capsules) was conducted at the end of the randomized sequence.

Number of subjects/patients: Planned: 60 (in order to attain 36—6 per sequence—assuming 40% dropout rate)

Randomized: 42

Treated: 42

Evaluated:

Efficacy/pharmacodynamic: 30

Safety: 42

Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion: Healthy men and women between 18 and 45 years of age with a usual bedtime between 21:00 and 01:00, a body mass index between 18 and 32 kg/m^2, normal findings in the medical history and physical examination, normal laboratory values and vital signs. Women were to have a negative urine pregnancy test and use a medically acceptable form of contraception during the entire study period.

Investigational product: Zolpidem tartrate extended-release

Dose: 12.5 mg

Administration: tablets

Duration of treatment: One night Duration of observation: One day

Reference therapy: Placebo

Dose: placebo

Administration: p.o. tablets

Reference therapy: Eszopiclone

Dose: 3 mg

Administration: p.o. tablets

Reference therapy: Flurazepam

Dose: 30mg

Administration: p.o. capsules

Criteria for evaluation:

Efficacy/pharmacodynamic:

Primary measure - Psychometric testing was administered beginning at 8.5 hours post-dose. Subjects performed the Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Immediate and Delayed Recall of Supraspan Word Lists (IRC and DRC), Compensatory Tracking Task (CTT), and Digit Symbol Substitution Test (DSST) tests.

Secondary measures: Sleep measures from Morning Sleep Questionnaire, Leeds Sleep Evaluation Questionnaire (LSEQ), and Bond & Lader (B&L) Visual Analog Scale

Safety: Safety was assessed on the basis of reported adverse events, physical examinations, vital signs, and laboratory tests.

Pharmacokinetics: Not applicable

Pharmacokinetic sampling times and bioanalytical methods: Not applicable

Statistical methods: Four analysis populations were used: 1) safety evaluable subjects who took at least one dose of study medication, 2) an intent-to-treat population who had at least one baseline measure and completed all three periods of randomized treatment, 3) a completers population who also completed the fourth and final non-randomized period and 4) a per-protocol population who completed all four treatment periods and did not have any protocol violations.

For the primary endpoint, a mixed model analysis of covariance (ANCOVA) was employed to analyze change from baseline to end of period in Critical Flicker Fusion test. The ANCOVA model included terms for treatment, sequence, period, random effect of subject within sequence, and baseline values. The two contrasts corresponding to the two pairwise comparisons, zolpidem tartrate extended-release v. placebo and eszopiclone v. placebo were tested at α=0.025 and estimated using LS means differences with associated 95% confidence intervals. This study was not designed as a safety study, so only descriptive statistics were provided for safety parameters.

Summary:

Efficacy/pharmacodynamic results: Zolpidem tartrate extended-release 12.5 mg was associated with statistically significant performance decrements from baseline on 3 psychomotor/cognitive assessments (CFF, CTT and delayed word recall accuracy) compared to placebo while eszopiclone 3 mg was associated with decrements from baseline on 4 measures (CRT accuracy, immediate word recall accuracy, delayed word recall accuracy and delayed word recall errors) compared to placebo. Zolpidem tartrate extended-release significantly improved 6 subjective assessments of sleep relative to placebo – 2 measures indicating improvement in sleep onset, 3 indicating sleep maintenance improvements and 1 reflecting improvement in quality of sleep. Eszopiclone improved 5 of the same measures (2 onset, 2 maintenance, 1 quality of sleep). The active comparator flurazepam 30 mg was associated with performance decrements on 4 psychomotor/cognitive assessments.

Safety results: This study was not designed as safety study. The percentage of patients with at least one treatment-emergent adverse event was highest in the eszopiclone treatment group (26.8%), and slightly lower at 23.1%, 22.0% and 17.5% of patients in the flurazepam, placebo and zolpidem tartrate extended release groups, respectively. No serious AEs or overdoses occurred. One woman discovered that she was pregnant after undergoing baseline testing and receiving a single dose of eszopiclone, and subsequently discontinued from the study. One other subject discontinued study participation due to an AE (upper respiratory infection) 7 days after with a treatment visit at which she received a single dose of eszopiclone. No clinically relevant changes were observed for laboratory and vital signs parameters.

Pharmacokinetic results: Not applicable

Date of report: 21-Jan-2009