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Clinical Trial Synopsis TAK-375_EC301, NCT#00237497

Title of Study:

A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Ramelteon Compared to Placebo with Zopiclone as a Reference Arm in Adults with Chronic Insomnia.

Protocol Number:

TAK-375_EC301

Name of Sponsor:

Takeda Pharmaceuticals North America, Inc.

Brand Name/Finished Product Name:

ROZEREM™/TAK-375 (ramelteon)

Publication (reference):

Hajak G, Ebrahim I, Hibberd M, Vincent S. Ramelteon, unlike zopiclone, has no effect on body sway at peak plasma levels in insomnia patients. Sleep 2007; 30(suppl):A245.

Study Period:

29 July 2005 to 02 October 2006

Phase of Development:

Phase 3

OBJECTIVES

Primary:

The primary objective of this study was to evaluate the near peak effect of ramelteon 8 mg once daily based on balance platform versus placebo with zopiclone as a reference arm in subjects with chronic insomnia with subjects' eyes open.

Secondary:

The secondary objective(s) of this study were:

- To evaluate the treatment effect of ramelteon once daily in reduction of objective and subjective latency to persistent sleep (LPS) and changes in balance platform with subjects' eyes closed compared to placebo with zopiclone as a reference arm in subjects with chronic insomnia.
- To evaluate the residual pharmacological effect, sleep architecture and withdrawal effect of ramelteon once daily compared to placebo with zopiclone as a reference arm in subjects' with chronic insomnia.
- To evaluate the safety of ramelteon in insomnic population.
- To evaluate daytime function activities.

METHODOLOGY

This was a multicenter, randomized, parallel, double-blind, double-dummy and placebo-controlled study to examine the effects of ramelteon on balance and cognitive performance at peak plasma concentration in adults diagnosed with chronic insomnia. In addition, the safety and efficacy of ramelteon compared to placebo with zopiclone as a reference arm was evaluated over 28 consecutive

nights. Ramelteon was used at a single fixed dose of 8 mg, and zopiclone was used at a single fixed dose of 7.5 mg. The study comprised 3 periods: first, an initial screening period (Day -21 to -14), where subjects were assessed for eligibility; second, a single-blind placebo and PSG screening period (Night -14 to Day -1), including a 2-night assessment in a sleep laboratory; and third, a 28-day double-blind period where subjects were randomized to 1 of 3 treatment arms (8 mg ramelteon, 7.5 mg zopiclone or placebo). The double-blind period included a 2-night PSG assessment on Nights 1 to 2 and 27 to 28 and a balance assessment on Night 14.

Number of Subjects:

Planned: 210 subjects

Analyzed: Full Analysis Set (FAS) — 275 subjects; Per Protocol Analysis Set (PPS) — 234 subjects

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects had to be:

- Men or women aged 18 to 64 years, inclusive.
- Capable of understanding and willing to comply with the protocol and had to fully understand and sign the informed consent document at screening prior to any study-related procedures being performed.

In addition, subjects had to meet the following study-specific criteria:

- Chronic insomnia as defined by:
    - A complaint of difficulty initiating or maintaining sleep or of nonrestorative sleep that lasted for at least 3 months.
    - The sleep disturbance (or associated daytime fatigue) caused clinically significant distress or impairment in social, occupational, or other important areas of functioning.
    - The disturbance did not occur exclusively during the course of narcolepsy, breathing related sleep disorder, circadian rhythm sleep disorder or a parasomnia.
    - The sleep disturbance did not occur exclusively during the course of another mental disorder (eg, major depressive disorder, generalized anxiety disorder, a delirium).
    - The disturbance was not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.
- Based on sleep history, a subjective sleep latency (sSL) ≥45 minutes.
- Based on sleep history, a subjective total sleep time (sTST) ≤6.5 hours.
- Based on sleep history, a mean LPS of ≥20 minutes on 2 consecutive screening nights with neither
- night <15 minutes.
- Based on sleep history, their habitual bedtime was between 10:00 PM and 1:00 AM.
- Able to stand with eyes closed, arms at side and feet apart at hips width for at least 1 minute with out taking a step.
- A body mass index (BMI) between 18 and 34, inclusive.
- Used pharmacological assistance to sleep 0 to 4 times per week in the last 3 months.
- Agreed to discontinue use of all pharmacological sleep aids 1 week prior to the dose of single-blind study medication and throughout the entire duration of the study.
- Women of childbearing potential were non-pregnant and non-lactating and had appropriate birth control (barrier methods, hormonal contraceptives, and/or intrauterine devices) for the entire duration of the study (women who were not of childbearing potential were

postmenopausal for 1 year or had a history of hysterectomy and/or bilateral oophorectomy).

- Subjects were not eligible for enrollment if they met any of the following criteria:
- A known hypersensitivity to ramelteon, zopiclone or related compounds, including melatonin and melatonin related compounds.
- Participated in any other investigational study and/or taken any investigational drug within 30 days or 5 half-lives prior to the first night of single-blind study medication (whichever was longer).
- Had sleep schedule changes required by employment (eg, shift worker) within 3 months prior to the first night of single-blind study medication, or had flown across greater than 3 time zones within 7 days prior to screening.
- Participated in a weight-loss program or had substantially altered their exercise routine within 30 days prior to the first night of single-blind study medication.
- A history of, or currently had, conditions that would affect balance such as:
    - Orthostatic hypotension.
    - Dizziness.
    - Vertigo, or benign paroxysmal positional vertigo.
    - A history of seizures, sleep apnea, chronic obstructive pulmonary disease, restless leg syndrome, periodic leg movement syndrome, or fibromyalgia.
- A history of psychiatric disorder (including anxiety, depression, mental retardation, cognitive disorder, bipolar illness and schizophrenia) within the past 6 months.
- A history of drug addiction or drug abuse within the past 12 months.
- A history of alcohol abuse within the past 12 months or regularly consumed more than 14 alcoholic drinks per week or consumed any alcoholic drinks within 24 hours of all polysomnography visits.
- A current significant neurological (including cognitive and psychiatric disorders), hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological, or metabolic disease, unless currently controlled and stable with protocol-allowed medication 30 days prior to the first night of single-blind study medication.
- Used tobacco products during nightly awakenings.
- Used melatonin, or other drugs or supplements known to affect sleep/wake function within 1 week or 5 half-lives of the drug (whichever was longer) prior to the first day of single-blind study medication.
- Used any central nervous system (CNS) medication within 1 week or 5 half lives of the drug (whichever was longer) prior to the first day of single-blind study medication.
- Intended to continue taking any disallowed medication or any prescription medication, over-the counter (OTC) or herbal medication known to affect the sleep/wake function or otherwise interfere with evaluation of the study medication.
- Any clinically important abnormal finding as determined by a medical history, physical examination, electrocardiogram (ECG), or clinical laboratory tests.
- A positive urine drug screen including alcohol at screening or a positive breathalyzer test at each check-in.
- An apnea hypopnea index (per hour of sleep) >10 as seen on PSG, on the first night of the PSG screening.
- Periodic leg movement with arousal index (per hour of sleep) >10 as seen on PSG, on the first

night of PSG screening.

- Any additional condition(s) that in the investigator's opinion would (a) affect sleep/wake function, (b) prohibit the subject from completing the study, or (c) not be in the best interest of the subject.

Had lower limb prosthetics.

Test Product, Dose and Mode of Administration and Lot Number:

	Batch/Lot Number
Ramelteon 8 mg tablet, oral	Z5159041; Z5159042; Z5159045

Duration of Treatment:

For Nights -14 to -1, subjects were dosed with single-blind placebo. For Nights 1 to 28, subjects were orally administered ramelteon 8 mg tablets, zopiclone 7.5 mg encapsulated tablets or placebo tablets. All doses were taken once nightly 30 minutes before the subject's habitual bedtime.

Reference Therapy, Dose and Mode of Administration, Batch Number:

	Batch/Lot Number
Zopiclone 7.5 mg capsule, oral	86 and 114
Placebo capsule, oral	J2023; M028775; J2870; J3019
Placebo tablet, oral	Z5157051; Z5157055; Z5157072; Z5157073

Criteria for Evaluation:

The primary endpoint for this study was the calculated area of center of pressure (COP) in cm^2 recorded on the AccuSway® balance platform during Night 14 with eyes open.

The secondary endpoints for this study were the calculated area of COP with eyes closed during Night 14, latency to persistent sleep, sSL, sTST, subjective wake time after sleep after onset of sleep (sWASO), subjective number of awakenings (sNAW), subjective quality of sleep, restorative nature of sleep, morning alertness, and morning ability to concentrate.

The tertiary endpoints were collected on the daytime function questionnaire. These were morning alertness, ability to concentrate and start time and length of nap x, for x = 1, 2, 3 and 4.

Statistical Methods:

The primary analysis variable was the calculated area of COP recorded on the balance platform with subject's eyes open. The primary analysis was based on the change from predose to 1.5 to 2 hours postdose during Night 14 for the FAS population.

The FAS population comprised subjects who had been randomized and had taken at least 1 dose of double-blind medication. They were analyzed according to the treatment group to which they were randomized. Analyses for a given variable only included subjects with measurements for that variable.

The safety population comprised subjects who had been randomized and taken at least 1 dose of double-blind medication. Subjects were analyzed according to the study medication they received.

The PPS population comprised subjects who had been randomized, had taken at least 1 dose of study medication, and excluded subjects identified as major protocol violators.

The FAS population was considered the primary analysis population for all endpoints. The PPS population was used as a secondary analysis population for the primary variable and also for COP with eyes closed, latency to persistent sleep and sTST. The safety analysis population was used to analyze all safety endpoints.

The treatment groups were compared using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and predose values of the calculated area of COP on Night 14 as a covariate. Pairwise comparisons between the 2 active treatment groups and placebo were performed in a step-wise procedure.

The pairwise comparison between zopiclone 7.5 mg and placebo was tested first at the 5% significance level. If zopiclone 7.5 mg was statistically significant over placebo, then the comparison between ramelteon 8 mg and placebo was performed and tested in the same manner at the 5% significance level. Probability values, point estimates, and 2-sided 95% confidence intervals (CI) for the treatment differences in the change from predose were presented. Type III sum of squares was used to generate the ANCOVA results.

Analyses of secondary endpoints were performed on last observation carried forward (LOCF) data.

In addition, analyses were performed using observed data use to support the LOCF data.

The change from predose to 1.5 to 2 hours postdose in the calculated area of COP during Night 14 with

subjects eyes closed was analyzed in the same manner as the primary analysis.

In addition, the proportion of subjects unable to stand on the balance platform during Night 14 was analyzed as a categorical variable in a similar manner as for quantitative demographic and baseline endpoints. Pairwise comparisons between the 2 active treatment groups and placebo were also performed using a Chi-Squared test. For all other secondary analysis endpoints, the pairwise comparisons between the ramelteon 8 mg and placebo treatment groups and between zopiclone 7.5 mg and placebo treatment groups were compared using ANCOVA with treatment group as a factor and baseline value as a covariate. Probability values, point estimates, and 2-sided 95% CIs for the treatment differences were presented.

Analyses of tertiary endpoints were listed using observed data for the FAS population. In addition, the total nap time was summarized descriptively.

SUMMARY OF RESULTS

Subject Disposition:

A total of 275 subjects (mean age of 42.4 years), including 104 male and 171 female subjects, were randomized in the study from the 635 subjects who were screened. Two hundred and forty nine (249) subjects completed the study. There were 26 discontinuations (due to major protocol deviations [13], withdrawal of consent [5], adverse events [4], lack of efficacy [2] and other [2]).

No important differences were observed between treatments for most of the demographic characteristics recorded at baseline. The prevalence of most concurrent medical conditions and concomitant medications was also similar among the treatment groups. The use of agents acting on the renin-angiotensin system, cardiac therapy, sex hormones and modulators of the genital system and thyroid therapy was slightly more common in the placebo and zopiclone groups compared to the ramelteon group. The use of analgesic agents was slightly more common in the ramelteon group than the placebo and zopiclone groups.

Efficacy Results:

The therapeutic effect observed in clinical trials of a drug cannot be directly compared to the effects found in clinical trials of other drugs and may not reflect the therapeutic effects observed in practice. In addition, therapeutic effects observed in a single clinical trial may not reflect the overall therapeutic effects observed in all clinical trials of a drug.

The primary endpoint in this study was COP with subjects' eyes open, which is a validated measure of balance and stability, at approximately 1.5 hours post-dose on Night 14 of double-blind treatment. The ramelteon treatment group did not show a statistically significant difference from the placebo group (P=0.532), indicating no effect on the subjects' balance. As expected from the reference arm, the zopiclone treatment significantly increased COP compared to the placebo group (log-transformed LS mean increased by 0.783cm; P<0.001), thus significantly worsening subjects' balance in the middle of the night. One subject was unable to perform the test following dosing with zopiclone. Subgroup analyses by age, gender and BMI showed similar results to the main analysis. Subgroup analysis by race showed similar trends for the 'White' group, whereas the other race subgroups were too small for interpretation.

The secondary endpoint results of the FAS LOCF in this study include the following:

- Ramelteon showed no statistically significant difference from placebo in the COP assessment with eyes closed. As expected, zopiclone treatment statistically worsened the subjects' balance compared to the placebo group. Two subjects were unable to perform the test following dosing with zopiclone. Subgroup analyses by age, gender and BMI showed similar results to the main analysis. Subgroup analysis by race showed similar trends for the 'White' group, whereas the other race subgroups were too small for interpretation.
- Over the 4-week treatment period, large reductions in LPS were observed in all 3 treatment groups. Compared to placebo, LPS in the ramelteon and zopiclone groups was reduced at

Nights 1 to 2 and Nights 27 to 28, with a statistically significant difference from placebo in the ramelteon group at Nights 1 to 2 (p=0.031). A categorical analysis compaing subjects with post baseline LPS ≤ 30 or > 30 minutes showed a significant difference from placebo at Nights 1 to 2 for both ramelteon and zopiclone.

- Ramelteon showed a 52% reduction in LPS from baseline at Nights 1 to 2 and a 55% reduction at Nights 27 to 28; thus clearly demonstrating a maintenance of treatment effect. Zopiclone showed a lower reduction to baseline values (44% and 38% at Nights 1 to 2 and 27 to 28 respectively). A reduction of 38% and 52% at Nights 1 to 2 and 27 to 28 was observed in the placebo group.
- Similar to the LPS results, over the 4-week treatment period, large reductions in sSL were observed in all 3 treatment groups. Compared to placebo, sSL in the ramelteon and zopiclone groups was reduced at Nights 1 to 2 and Nights 27 to 28, with a statistically significant difference at Nights 1 to 2.
- Ramelteon showed a 32% reduction in sSL from baseline at Nights 1 to 2 and a 33% reduction at Nights 27 to 28; thus clearly demonstrating a maintenance of treatment effect. Zopiclone showed a lower reduction to baseline values (42% and 48% at Nights 1 to 2 and 27 to 28 respectively). A reduction of 22% and 43% at Nights 1 to 2 and 27 to 28 was observed in the placebo group.
- Over the 4-week treatment period, all other subjective sleep endpoints (sTST, sWASO, sNAW, sleep quality and restorative nature of sleep) showed improvement in all 3 treatment groups. In the ramelteon treatment group, there was no statistically significant difference in these endpoints from placebo at Nights 1 to 2 and 27 to 28 for these subjective measures. However, the zopiclone treatment group showed statistically significant improvements from the placebo group during both time periods.
- For all sleep endpoints, objective and subjective, unusually large changes from baseline were observed in the placebo group over the 4-week treatment period which may have impacted the overall statistical outcome of the treatment comparisons.

The following special Safety Results were observed in the FAS LOCF population:

- In the ramelteon group, no difference from placebo was detected for the DSST and MRT endpoints at 1.5 to 2 hours post dose, whereas a significant reduction in mean score was observed in the zopiclone group for both DSST and MRT, indicating drug-related psychomotor and memory impairment at the approximate peak plasma concentration
- Ramelteon had no effect on any measure of sleep architecture at any timepoint when compared to placebo. In contrast, zopiclone had a statistically significant effect on all measures of sleep architecture. Zopiclone significantly decreased the amount of time in NREM 1 (Nights 1 to 2), increased the amount of time in NREM 2 (both time points), decreased the amount of time in NREM 3/4 (Nights 27 to 28), and decreased the total percentage of REM sleep (both time points). Zopiclone also significantly increased latency to REM at Nights 1 to 2 (about 27 minutes, P<0.001) and Nights 27 to 28 (about 21 minutes, p<0.001).
- Morning alertness and ability to concentrate from the postsleep questionnaire were reduced (improved) in all 3 treatment groups as a function of time. Changes in morning alertness were statistically significant compared with placebo in both the ramelteon and zopiclone treatment groups at Nights 27 to 28; however, no significant difference was observed for either treatment at either timepoint for morning ability to concentrate.

Tertiary Endpoint Results

- The mean total nap time increased from baseline for placebo and ramelteon, whereas no change was observed in the zopiclone group.

Safety Results:

Adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice. In addition, the rates observed in a single clinical trial may not reflect the overall rates observed in all clinical trials of a drug.

A total of 105 (38.2%) subjects experienced non-serious adverse events during the study: 31 (33.0%) subjects who received placebo, 32 (36.4%) subjects who received ramelteon, and 42 (45.2%) subjects who received zopiclone.

The most common adverse events were nausea, fatigue, dysgeusia, headache and somnolence. Nausea and dysgeusia were almost exclusively experienced by subjects in the zopiclone group and somnolence was almost exclusively experienced by subjects in the zopiclone and ramelteon groups; fatigue was more common in the ramelteon group. The incidence of headache was similar between all treatment groups.

The most common drug-related adverse events mirrored the most common adverse events. The majority of subjects experienced adverse events that were mild or moderate in intensity. Five subjects reported severe adverse events, 2 in the ramelteon group and 3 in the zopiclone group. No severe adverse events were experienced by subjects in the placebo group.

Two (2.3%) subjects in the ramelteon group reported SAEs during the study. One of these SAEs, schizophrenia (paranoid type) was considered possibly related to study drug. The other SAE, alcohol withdrawal effect, was judged by the investigator to be not related to study drug. No SAEs were reported in either the placebo group or in the zopiclone group. There were no deaths reported in any treatment group during the study.

A total of 6 subjects discontinued treatment due to adverse events: 2 (2.3%) subjects in the ramelteon group and 4 (4.3%) subjects in the zopiclone group.

There were 28 subjects with positive urinary drug screen results: 8 (8.5%) subjects, placebo; 8 (9.1%) subjects, ramelteon; and 12 (12.9%) subjects, zopiclone. All subjects with positive urinary drug screen results were protocol violators.

There were no relevant differences in mean vital signs between treatment groups and no relevant mean changes from baseline either between or within treatment groups. There were only a small number of subjects with clinically significant abnormal changes from baseline for blood pressure and pulse rate. All ECGs were normal and there were no relevant differences between treatment groups.

There was a similar number of subjects with abnormalities or changes to the physical examination from baseline or markedly abnormal laboratory results across all treatment groups.

The zopiclone group had more subjects with non-serious adverse events, clinically significant lab abnormalities and discontinuations than either the placebo or ramelteon groups. Two unexpected SAEs were reported in the ramelteon group with only 1 possibly related. The safety profile for zopiclone and ramelteon were consistent their labeled information.

Date of Synopsis: 18 August 2008