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Clinical Trial Synopsis TAK-375_EC302, NCT#00247390

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled Study to Determine the Long-Term Efficacy and Safety of Ramelteon in Adults With Chronic Insomnia

Name of Sponsor:

Takeda Global Research & Development Centre (Europe) Ltd.

Protocol Number:

TAK-375_EC302

Name of Active Ingredient:

ROZEREM™/TAK-375 (ramelteon)

Publication (reference): For additional information pertaining to this clinical study please refer to:

Wang-Weigand S, Mayer G, Roth-Schechter B. Long-term efficacy and safety of ramelteon 8 mg treatment in adults with chronic insomnia: results of a six-month, double-blind, placebo-controlled, polysomnography trial. Sleep Biol Rhythms 2007;5(suppl 1):A156. Abstract PO525.

Study Period:

29 July 2005 to 15 December 2006

Phase of Development:

Phase 3

OBJECTIVES

Primary:

The primary objective of this study was to evaluate the long-term efficacy of ramelteon once daily in reduction of latency to persistent sleep (LPS) compared to placebo in subjects with chronic insomnia.

Secondary:

The secondary objectives of this study were to evaluate long-term treatment effects of ramelteon in improvement of sleep latency and duration objectively and subjectively and to evaluate the long-term safety of ramelteon in the insomniac population.

Exploratory:

The exploratory objective of this study was to evaluate the quality of life, daytime function activities, and patient global impression in the insomniac population.

METHODOLOGY

This study was a multicenter, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of ramelteon over a 6-month period in adults and elderly subjects with chronic insomnia.

The test agent ramelteon was administered at a fixed dose of 8 mg. Initial subject screening included medical history (including sleep history), physical examination, laboratory tests, and an electrocardiogram (ECG) recording for each subject. Subjects who met the initial screening criteria then underwent polysomnography (PSG) screening. During 2 consecutive nights, single-blind placebo medication was taken in a sleep laboratory, and PSG recordings were carried out together with a postsleep questionnaire; the screening was continued over a 5- to 12-day outpatient period involving further single-blind medication.

Subjects who fulfilled the PSG eligibility criteria were randomly allocated to double-blind treatment. Once randomized, eligible subjects received either ramelteon 8 mg or placebo, with regular nightly dosing for a period of 6 months. During this treatment period, the subjects reported to the sleep laboratory for objective assessment of sleep parameters using PSG and subjective evaluation of treatment effects using a postsleep questionnaire on the first 2 nights of Month 1 and on the scheduled visits at the end of Months 1, 3, 5, and 6. Next-morning pharmacological residual effects were assessed using the digital symbol substitution test (DSST) and memory recall test (MRT) 45 to 60 minutes following awakening on the morning of an assessment. Patient's self-reported feelings and mood were assessed using a visual analog scale (VAS) and patient ability to concentrate and their morning alertness were evaluated using the postsleep questionnaire. On all other nights, subjects took their study medication at home as directed. On completion of the double-blind treatment, subjects reported to the sleep laboratory for PSG recordings over 2 nights while receiving single-blind placebo medication. Placebo medication was then given to subjects to take nightly over a 12-day period. The purpose of this run-out period was to evaluate possible rebound insomnia and any withdrawal effects of study medication.

Adverse events and concomitant medications were monitored throughout.

Postsleep questionnaires collected data on subjective sleep latency (sSL), subjective total sleep time (sTST), subjective number of awakenings (sNAW), subjective wake time after sleep onset (sWASO), and subjective sleep quality.

Number of Subjects:

Planned: 476 subjects.

Analyzed: Full analysis data set – 451; Safety data set – 451; Per protocol data set – 335.

Diagnosis and Main Criteria for Inclusion:

General

- Subjects were greater than or equal to 18 years of age.
- Subjects were in good health, capable of understanding the informed consent form and willing to provide signed informed consent, and who met other inclusion criteria specified in the protocol.

Study-specific

- Habitual bedtime for each subject was between 10 PM and 1 AM.
- Difficulty initiating or maintaining sleep or of nonrestorative sleep that lasted at least 3 months.
- Insomnia that caused clinically significant distress or impairment in social, occupational, or other important areas of function.
- The disturbance in sleep did not occur exclusively during the course of another sleep disorder or mental disorder.
- Difficulty sleeping was not due to the direct physiological effects of a substance or a general medical condition.

- sTST less than 6.5 hours per night, and sSL greater than or equal to 45 minutes.
- Mean latency of greater than 20 minutes on 2 consecutive screening nights - with neither night less than 15 minutes

Any subject who meets any of the following criteria was excluded from entering the study:

- Known hypersensitivity to ramelteon or related compounds.
- Participation in any other investigational study and/or taken any investigational drug within 30 days or 5 half-lives prior to the first dose of single-blind study medication, whichever is longer.
- Sleep schedule changes required by employment (eg, shift worker) within 3 months prior to the administration of single-blind study medication.
- Having flown across greater than 3 time zones within 7 days prior to or during screening.
- Participation in a weight loss program or substantial alteration of exercise routine within 30 days prior to the administration of single-blind study medication.
- History of seizures, sleep apnea, restless leg syndrome, periodic leg movement syndrome (PLMS), chronic obstructive pulmonary disease, or fibromyalgia,
- The subject has a history of psychiatric disorder (including anxiety, depression, mental retardation, cognitive disorder, bipolar illness, and schizophrenia) within the past 6 months.
- History of alcohol abuse within the past 12 months, as defined in the *Diagnostic & Statistical Manual of Mental Disorders, 4th Edition Revised* (*DSM-IV-TR*), or regular consumption of more than 14 alcoholic drinks per week, or consumed any alcoholic drinks within 24 hours of any PSG visits.
- History of drug abuse within the past 12 months, as defined in *DSM-IV-TR*.
- Significant hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematologic, neurological, or metabolic disease, unless currently controlled and stable with protocol-allowed medication, within 30 days prior to the first night of single-blind study medication.
- Apnea hypopnea index (per hour of sleep) >10 as seen on the first PSG screening night (Screening Visit 2).
- PLMS with arousal index (per hour of sleep) >10 as seen on the first PSG screening night (Screening Visit 2).
- Positive urine drug screen at Screening Visit 1 or any of the PSG assessment visits.
- Positive breathalyzer test on any of the PSG assessment visits.
- Use of tobacco products (including nicotine gum and patch) or any other products that may interfere with the sleep wake cycle during nightly awakenings.
- Use of any central nervous system medication or other drugs or supplements known to affect sleep/wake function within 1 week (or 5 half-lives of the drug, whichever is longer) prior to the administration of single-blind study medication.
- Intention to continue taking any disallowed medication or any prescription medication or over-the-counter (OTC) medication that is 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, ECG, or clinical laboratory tests, as determined by the investigator.
- 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) indicate that continuation in the study would not be in the best interests of the subject.
- History of hepatitis B or hepatitis C.

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

	Batch/Lot Number
Ramelteon 8 mg tablet, oral administration	Z5159042, Z5159043
Placebo tablet, oral administration	Z5157051, Z5157055, Z5157064

Duration of Treatment:

The total duration of this study was approximately 200 days (7 months), including Screening and single-blind placebo run-in/out periods. Eligible subjects were randomized to receive 1 bedtime dose of either ramelteon 8 mg or matching placebo for 6 months.

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

None

Criteria for Evaluation:

Efficacy:

The primary efficacy variable for this study was the mean LPS of 2-night PSG at Month 3 and then Month 6.

Secondary efficacy variables were as follows:

- Mean total sleep time (TST) from PSG, on 2 nights over the 6 months (first 2 nights of Week 1, last 2 nights of Months 1, 3, 5, and 6) of the double-blind treatment.
- Mean sSL and sTST (by postsleep questionnaires) on 2 nights over the 6 months (the morning after the first 2 nights of Week 1, last 2 nights of Months 1, 3, 5, and 6) of double-blind treatment. sNAW, sWASO, and sleep quality were measured using postsleep questionnaires over a 6-month period (the morning after the first 2 nights of Week 1, last 2 nights of Months 1, 3, 5, and 6 of the double-blind treatment).
- Sleep architecture variables include percentage of TST in rapid eye movement (REM) sleep, stage 1, 2 and 3/4 non-rapid eye movement (NREM) sleep and latency to REM as determined by PSG.
- The Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire (BWSQ) was used to assess effects of withdrawal from study medication after completion of the double-blind treatment period.
- Next-morning pharmacological residual effects were assessed objectively using the DSST and MRT scores as well as subjectively using VAS for mood and feeling and postsleep questionnaire for subject-reported level of alertness and ability to concentrate. Assessments were made on the morning after the first 2 nights of Week 1 and last 2 nights of Months 1, 3, 5, and 6.

Exploratory variables were as follows:

- Quality of life using the SF-12 questionnaire.
- Patient treatment effects using Patient Global Impressions (PGI).
- Daytime functioning using the daytime function questionnaire.
- Patient health state using the health assessment questionnaire (EQ-5D).

Safety:

Safety variables included adverse events, clinical laboratory test results, vital signs, ECGs, and physical examination.

Statistical Methods:

The full analysis set (FAS) comprised all subjects who had been randomized and had taken at least 1 dose of double-blind study medication.

The primary efficacy variable was mean LPS of 2-night PSG. The primary analysis was based on this variable at Month 3 and then Month 6 of the double-blind treatment period using last observation carried forward (LOCF) data for the FAS population. The 2 treatment groups were compared using an analysis of covariance (ANCOVA) model with treatment group as a factor and the baseline LPS as a covariate. The treatment comparison for the Month 6 data was to be contingent if ramelteon 8 mg was statistically significant over placebo at the 0.05 significance level for the Month 3 data. Probability values, point estimates, and 2-sided 95% confidence intervals for the treatment differences were calculated. Type III sum of squares was used to generate the ANCOVA results. Mean LPS was also analyzed using the ANCOVA model described above at Week 1 (Nights 1-2) and end of Months 1 (Nights 22-23) and 5 (Nights 134-135) for the FAS, mean LPS was categorized into either ≤30 minutes or >30 minutes.

Analyses performed on secondary efficacy variables were conducted using both the FAS and the per protocol analysis set (PPS) populations. An ANCOVA model similar to the one used for the primary efficacy variable was applied to the following efficacy variables:

- TST at Week 1 (Nights 1 to 2) and end of Months 1 (Nights 22 to 23), 3 (Nights 78 to 79), 5 (Nights 134 to 135) and 6 (Nights 162 to 163) for the FAS population using LOCF and observed data.
- Subjective variables assessed via the postsleep questionnaire, namely, sSL, sTST, number of awakenings (NAW), wake time after sleep onset (WASO), sleep quality, restorative nature of sleep, level of alertness and ability to concentrate at Week 1 (Nights 1 to 2) and end of Months 1 (Nights 22 to 23), 3 (Nights 78 to 79), 5 (Nights 134 to 135), and 6 (Nights 162 to 163) for the FAS population using LOCF and observed data.

Where applicable, analyses were performed on the FAS population using observed data for the placebo Run-Out Visit.

The analyses at Month 3 and Month 6 are considered as primary. The analyses at all other visit are considered as supportive. Within the ANCOVA model, treatment was fitted as a factor and the baseline value for the parameter of interest fitted as a covariate. Probability values, point estimates, and 2-sided 95% confidence intervals (CIs) for the treatment differences are presented. Type 3 sum of squares are used to generate the ANCOVA results. The region effect and the treatment-by-region interaction were explored for the primary efficacy variable at Month 3 and Month 6 using ANCOVA models similar to the one described above.

Analyses performed on the special safety variables were conducted using the FAS population. Special safety variables include residual pharmacological effect variables, sleep architecture variables, rebound insomnia, and withdrawal effects of treatment assessed using the Tyrer BWSQ data. An ANCOVA model similar to the one used for the primary efficacy variable was applied to the following variables: DSST score, MRT, VAS for feelings, VAS for mood was to be calculated for the FAS population using observed data at Week 1 and end of Months 1, 3 5 and 6. LPS was used to assess rebound insomnia. Change from Baseline in LPS for each day of the single-blind placebo run-out period was to be analyzed. Assessments performed on each day during the single-blind placebo run-out period were analyzed separately. Rebound insomnia was analyzed using the same statistical methods as described for the primary efficacy variable for the FAS population using observed data. Withdrawal effects were assessed with analysis of change in total score from the Tyrer BWSQ assessment during the single-blind placebo run-out period. The change in total score on each day of the single-blind placebo run-out period (Day 1 and Day 2 off treatment, respectively) from the average of scores obtained on Day 163 and Day 164 during Month 6 was analyzed. Withdrawal effects were analyzed using the same statistical methods described for the primary efficacy variables, with the Month 6 score as the covariate for the FAS population using observed data.

SUMMARY OF RESULTS

Subject Disposition:

Overall, 451 subjects were randomized to treatment, 224 to placebo and 227 to ramelteon 8 mg. A total of 48 placebo-treated subjects (21.4%) and 68 ramelteon-treated subjects (30.0%) discontinued double-blind treatment prematurely. The most common reasons for premature discontinuation were major protocol deviation (10.2%), withdrawal of consent (6.0%), and adverse event (3.8%). Lack of efficacy accounted for 1.8% of discontinuations in the placebo treatment group compared with 0.4% in the ramelteon treatment group.

One subject was randomized to placebo but received ramelteon. This subject was included as a ramelteon-treated subject in the safety analysis set, and as a placebo-treated subject in the full analysis set. Thus the number of ramelteon–treated subjects in efficacy analyses is 227 and in safety analyses is 228.

No differences were observed between treatments for most of the demographic characteristics recorded at Baseline. The 2 treatment groups were very similar in terms of age, gender balance, race, and baseline sleep characteristics.

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.

Primary Efficacy Results:

The primary endpoint in this study was the mean LPS of 2-night PSG assessment at Month 3 and then Month 6. The following results were observed in the FAS LOCF population. Beginning with the first 2 nights of week 1 and over the entire double-blind treatment period of 6 months, with assessments of the last 2 nights of Months 1, 3, 5, and 6, the ramelteon treatment group showed a statistically significant difference in LPS from the placebo group ($p<0.05$), indicating a significant and persistent shortening of sleep onset by ramelteon.

Summary of LPS Mean Sleep Latency Results by Treatment (Minutes) Difference Between Ramelteon 8 mg and Placebo

	Placebo (n=224)		Ramelteon 8 mg (n=227)				
	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean Difference (SE)	95% CI	P-value(a)
Baseline	222	69.53 (2.82)	225	70.75 (2.8)	–	–	–
Week 1	222	46.70 (1.89)	224	32.02 (1.88)	-14.68 (2.67)	(-19.92, -9.44)	<0.001
End Month 1	222	38.88 (1.96)	225	30.64 (1.94)	-8.24 (2.76)	(-13.66, -2.82)	0.003
End Month 3	222	37.05 (1.96)	225	30.68 (1.94)	-6.37 (2.76)	(-11.79, -0.96)	0.021
End Month 5	222	40.24 (2.31)	225	32.63 (2.23)	-7.60 (3.26)	(-14.01, -1.20)	0.020
End Month 6	222	39.82 (2.18)	225	30.93 (2.16)	-8.89 (3.07)	(-14.93, -2.86)	0.004

(a) P-values obtained using t-tests from ANCOVA model of the overall treatment comparison.

Secondary Efficacy Results:

The following results were observed in the FAS LOCF population:

- sSL was evaluated at the same time points as LPS. Beginning with the first 2 nights of Week 1 and over the treatment period of 6 months, with assessments at the last 2 nights of Months 1, 3, 5, and 6, the ramelteon treatment group showed a statistically significant difference from the placebo group ($P<0.05$) at Week 1, and Months 1 and 5. Differences at Months 3 and 6 were above the level of statistical significance ($P=0.072$ and $P=0.073$, respectively).
- The increase in mean TST from PSG was statistically significant for ramelteon at Nights 1 to 2 ($P<0.001$), indicating a significant increase in sleep duration. For the remainder of treatment, the ramelteon group showed numerically longer TST without attaining statistically significant differences.
- The differences sTST and sleep quality recorded on postsleep questionnaires were not statistically significant.
- There was no rebound insomnia: no significant difference was observed in LPS first 2 days when subjects were off the active treatment during single-blind placebo run-out period (on Nights 1 to 2 of Month 7) between ramelteon and placebo treatment and there was no reversal of treatment effect compared with Baseline.
- Similarly, results obtained with the Tyrer BWSQ showed no difference between ramelteon and placebo groups on the first 2 days when subjects were off the active treatment during single-blind placebo run-out period (on Nights 1 to 2 of Month 7). Together, these results indicate no withdrawal effects with ramelteon.
- There were no objective next-morning residual effects based on DSST and MRT immediate/delayed recall scores. There were no subjective morning residual effects based on ratings of morning alertness and ability to concentrate.
- There was no clinically relevant difference between ramelteon and placebo for the overall rating of VAS for feelings and mood.

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.

The incidence of adverse events was similar between treatments. The majority of reported events (>95%) were mild or moderate in intensity. The most common adverse events were headache, reported by 7.9% of ramelteon-treated subjects and 8.1% of placebo-treated subjects; upper respiratory tract infection, reported by 4.8% of ramelteon-treated subjects and 2.7% of placebo-treated subjects; and nasopharyngitis, reported by 4.4% of ramelteon-treated subjects and 4.9% of placebo-treated subjects. There were a total of 50 subjects (22.4%) with adverse events on placebo vs 54 subjects (23.7%) with adverse events on ramelteon that were deemed at least possibly related by the investigator. No deaths were reported. Two placebo-treated subjects and 5 ramelteon-treated subjects experienced serious adverse events. One serious adverse event of leukopenia was deemed possibly related to ramelteon. Ten placebo-treated subjects (4.5%) and 7 ramelteon-treated subjects (3.1%) withdrew from the study due to adverse events. Compared with placebo, no rebound insomnia and no withdrawal effects were observed.

Date of Synopsis:

08 August 2008