

Efficacy and Safety of 6-Month Nightly Ramelteon Administration in Adults with Chronic Primary Insomnia

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Study Objectives: Long-duration (≥ 6 months) polysomnographic studies of insomnia medications are lacking. This study evaluated the long-term efficacy of ramelteon, a selective MT₁/MT₂ melatonin-receptor agonist used for insomnia treatment.

Design: Six-month, randomized, double-blind, placebo-controlled study.

Setting: Forty-six investigative sites in the United States, Europe, Russia, and Australia.

Participants: Four hundred fifty-one adults (age ≥ 18 years) with chronic primary insomnia.

Interventions: Ramelteon, 8 mg, or placebo 30 minutes before bedtime nightly for 6 months.

Measurements: Sleep was evaluated by polysomnography and morning questionnaires on the first 2 nights of Week 1; the last 2 nights of Months 1, 3, 5, and 6; and Nights 1 and 2 of the placebo run-out. Next-morning residual effects as well as adverse effects and vital signs were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out.

Results: Over the 6 months of treatment, ramelteon consistently re-

duced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at Week 1 and Months 1, 3, 5, and 6 (P < 0.05). Ramelteon significantly reduced subjective sleep latency relative to placebo at Week 1, Month 1, and Month 5 (P < 0.05), with reductions nearing statistical significance at Months 3 and 6 (P ≤ 0.08). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity.

Conclusions: In adults with chronic insomnia, long-term ramelteon treatment consistently reduced sleep onset, with no next-morning residual effects or rebound insomnia or withdrawal symptoms upon discontinuation.

Keywords:

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INSOMNIA IS BROADLY DEFINED AS DIFFICULTY INITIATING OR MAINTAINING SLEEP, WAKING TOO EARLY, OR NONRESTORATIVE SLEEP. IT IS ESTIMATED that up to 34% of adults in the United States^{1,2} and 37% in Europe² have some form of insomnia.

For the majority of individuals with insomnia, the symptoms are long lasting.³ Chronic insomnia (present for 30 days or more) often requires long-term treatment, typically well beyond 4 to 5 weeks.⁴ The persistent nature of insomnia poses a challenge to clinicians because most medications indicated for the treatment of insomnia are limited to short-term use. In the United States and in Europe, benzodiazepine receptor agonists (BzRAs) are the most commonly prescribed medications for the treatment of insomnia (eg, zolpidem, zolpidem MR, zaleplon, eszopiclone, and zopiclone). These medications achieve their effect through action at GABA_A receptors, which are widely distributed throughout the brain. BzRAs are considered controlled substances, and the majority (ie, zopiclone, zolpidem, zaleplon) are indicated for a maximum of 4 weeks of use.⁵⁻⁹ BzRAs have also been associated with memory and balance impairment,¹⁰ rebound insomnia, withdrawal symptoms, and abuse potential.^{11,12} Short-term studies have demonstrated

disruptions in sleep architecture (as well as increases in sleep latency) immediately after discontinuation of BzRA treatment, which makes withdrawing from these types of treatments difficult.^{13,14}

Though not indicated for insomnia, antidepressants (such as trazodone) and alternative treatments like valerian are often used to treat insomnia as well. The data regarding efficacy for treatment of sleep disorders with these agents are inconsistent, and the majority of studies are limited by sample size, lack of diagnostic criteria, and the absence of a placebo control.^{15,16}

Some newer pharmacologic agents that target melatonin receptors have been developed based on the evidence that certain melatonin receptors are involved in the control of sleep. In the 2-process model of sleep, there is a drive for sleep that accumulates during wakefulness and decreases during sleep (homeostatic process) and a 24-hour oscillatory rhythm that guides sleep and wake propensity (circadian process).¹⁷ Combined, the homeostatic and circadian processes influence the duration and timing of sleep and wakefulness. The circadian process is driven by the suprachiasmatic nucleus (SCN), which contains a number of high-affinity melatonin receptors. During the day, the SCN actively produces an arousal signal that maintains wakefulness and opposes the sleep drive. In response to darkness, the SCN works on a feedback loop, first signaling the release of melatonin (a chemical expression of darkness), which feeds back to inhibit SCN activity. In vitro studies indicate that the MT₁ receptor mediates the acute inhibition of SCN firing by melatonin¹⁸ and the MT₂ receptor is involved with the phase-shifting effects of melatonin on circadian rhythms.¹⁹⁻²¹

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However, *in vivo* studies have further complicated the issue, indicating that the MT₁ receptor may have a role in mediating phase-shifts in conjunction with the MT₂ receptor.²²

Ramelteon is the first melatonin-receptor agonist approved in the United States for the treatment of insomnia and has a mechanism of action that differs considerably from commonly used BzRAs. Ramelteon is an MT₁/MT₂ melatonin-receptor agonist with negligible affinity for either the MT₃ binding site or other neuronal receptors.²³ The actions of ramelteon on the MT₁ receptor are thought to inhibit the neuronal firing in the SCN, effectively turning off the arousal signal and allowing sleep to occur. Previous randomized, placebo-controlled studies have demonstrated the efficacy and safety of ramelteon in subjects with chronic insomnia.²⁴⁻²⁷ These trials also demonstrated that there was neither evidence of next-day residual effects nor evidence of withdrawal or rebound insomnia when ramelteon use was discontinued. Ramelteon also lacks abuse potential.²⁸

The National Institutes of Health State-of-the-Science Statement on manifestations and management of insomnia highlighted the need for long-term studies of primary insomnia.³ Not only is information about the incidence and duration of chronic insomnia scarce, but data regarding the efficacy and adverse effects with long-term pharmacologic treatment of insomnia are lacking. Lastly, no objective polysomnographic study of long duration is available. This is particularly important because a recent study demonstrated that self-reported total sleep times and sleep latencies are subjectively overestimated, even on the morning following overnight polysomnography.²⁹ Therefore, this study was designed to evaluate objective and subjective efficacy and safety of ramelteon when administered nightly for 6 months in adults with chronic insomnia.

METHODS

Design

This randomized, double-blind, placebo-controlled, phase III study evaluated the efficacy and safety of ramelteon, 8 mg, administered nightly for 6 months in adults in the United States, Europe, Russia, and Australia. Following an initial 1-week screening period, eligible subjects underwent a single-blind placebo run-in for 2 weeks. Thereafter, randomized subjects underwent double-blind treatment with ramelteon, 8 mg, or placebo administered 30 minutes before habitual bedtime every night for 6 months. A 2-week, single-blind, placebo run-out period followed.

Participants

Men and nonpregnant nonlactating women who were 18 years of age or older with a body mass index between 18 and 34 (inclusive) were enrolled. Subjects provided information on medical and sleep history, demographics, prior medication history, concurrent medical conditions, and current medication information. Eligible subjects were required to have chronic insomnia (difficulty initiating or maintaining sleep or non-restorative sleep lasting at least 3 months), a sleep disturbance that caused clinically significant distress or impairment, a self-reported total sleep time (sTST) of less than 6.5 hours, a self-

reported sleep latency (sSL) of at least 45 minutes per night, and a habitual bedtime between 22:00 and 01:00. Approximately 20% of enrolled subjects reported using medication to fall asleep (1-4 times/week). All sleep-related medications were discontinued at least 1 week before the start of the study. Subjects were excluded from participating if they had narcolepsy, a sleep-related breathing disorder, a circadian rhythm sleep disorder, a parasomnia, or if they had a sleep-schedule change (within 3 months), had traveled across more than 3 time zones (within 7 days), or had participated in a weight-loss program or altered their exercise routine (within 30 days). Other reasons for exclusion were a history of seizures, restless legs syndrome, periodic leg movement syndrome, fibromyalgia, a psychiatric disorder (within 6 months), or drug or alcohol abuse (within 12 months); a significant neurologic, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematologic, or metabolic disease (within 30 days); or a clinically abnormal finding as determined by medical history, physical examination, electrocardiogram, or clinical laboratory tests. Other reasons for exclusion included a known hypersensitivity to ramelteon or related compounds; any condition or use of a drug or supplement that affected the sleep-wake function (including tobacco products and central nervous system medications) and prohibited the subject from completing the study or was not in the best interest of the subject; or participation in an investigational study in the previous 30 days. Any use of concomitant medications (excluding drugs or supplements known to affect sleep or central nervous system functioning) was evaluated on a case-by-case basis throughout the study.

Following initial screening, subjects received single-blind placebo and underwent polysomnography screening on 2 consecutive nights in the sleep laboratory. Subjects were required to have a mean latency to persistent sleep (LPS) measured by polysomnography of greater than 20 minutes (neither night could have been < 15 minutes), an apnea-hypopnea index (per hour of sleep) of less than 10, and a periodic leg movements with arousal index (per hour of sleep) of less than 10. Subjects were also required to have a negative urine drug test.

The Institutional Review Board at each study site approved the study procedures and informed-consent forms. The study was conducted according to applicable Food and Drug Administration laws and regulations, the World Medical Association Declaration of Helsinki (1989), and the International Conference for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice.

Procedure

Subjects completed an initial 1-week screening period during which informed consent was obtained and medical history, physical examination, vital signs, 12-lead electrocardiograms, and clinical laboratory test data were collected. Subjects who qualified for the study based on initial screening criteria underwent polysomnography screening on the first 2 nights of the 2-week placebo run-in period, during which they received single-blind placebo 30 minutes prior to their habitual bedtime. Any excluded medications were discontinued 1 week prior to the 2-night polysomnography screening. Subjects practiced the Digit Symbol Substitution Test (DSST), immediate and delayed

memory recall tests, and the visual analog scale (VAS) for mood and feelings on the first night of polysomnography screening. Subjects were awakened after 8 hours of polysomnography recording and completed a postsleep questionnaire, the DSST, memory recall tests, the VAS for mood and feelings, and a Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ). Subjects were asked to take single-blind placebo every night for the remainder of the 2-week run-in.

Subjects meeting screening entry criteria were randomly assigned to receive ramelteon, 8 mg, or placebo nightly 30 minutes before bedtime for 6 months (168 consecutive nights). When in the sleep laboratory, sleep was monitored by PSG during the first 2 nights of Week 1 and the last 2 nights of Months 1, 3, 5, and 6. Subjects were awakened after 8 hours of polysomnography recording and asked to complete a postsleep questionnaire, the DSST, immediate and delayed memory recall tests, the VAS for mood and feelings, and the BWSQ 45 to 60 minutes after waking to evaluate subjective sleep parameters, next-day residual effects, and withdrawal symptoms. On all other nights, when at home, subjects were instructed to take their study medication nightly as directed. Safety was assessed by vital signs and clinical laboratory evaluations as well as adverse-event monitoring.

Subjects received single-blind placebo during a 2-week washout period to evaluate rebound effects. Sleep was monitored by polysomnography in the sleep laboratory on the first 2 nights of the washout period. Subjects were instructed to take placebo medication at home nightly for the remaining 12-day period.

Sleep-Related Measures

The prospectively defined primary efficacy endpoint was LPS measured by polysomnography, and TST was a secondary polysomnography efficacy variable. Analysis of sleep architecture included total time spent in each sleep stage (Stage 1, Stage 2, Stage 3/4, and rapid eye movement [REM]) and latency to REM. Self-reported efficacy was assessed by a postsleep questionnaire the morning after polysomnography recordings in the sleep laboratory, which evaluated mean sSL, mean sTST, mean subjective number of awakenings, mean subjective wake time after sleep onset, and mean sleep quality (evaluated on a 7-point Likert scale on which 1 = excellent and 7 = extremely poor). The postsleep questionnaire was also used to evaluate morning level of alertness and ability to concentrate, using the same 7-point Likert scale.

Next-Morning Residual Measures

For the DSST,³⁰ subjects were given a set of symbols with corresponding single-digit numbers and were asked to make as many symbol-for-digit substitutions as possible, working from left to right without skipping any boxes within a 90-second period. The number of correct substitutions in the 90-second period was recorded.

Memory recall tests were used to assess effects on memory. Approximately 45 to 60 minutes after waking, subjects were read a list of words. Immediately afterward, subjects were given 2 minutes to record as many words as they remembered (Immediate Recall). Subjects waited another 25 minutes and were

again given 2 minutes to recall as many words as possible from the list (Delayed Recall).

The VAS for mood and VAS for feeling were used to assess next-day residual effects.³¹⁻³³ The VAS for mood consisted of 12 items: drowsy, slowed down, sleepy, sedated, tired, worn out, listless, fatigued, exhausted, sluggish, weary, and bushed. The VAS for feelings included 8 items: calm/anxious, energetic/fatigued, thinking slowed down/thinking speeded up, peaceful/tense, normal/spacey, at ease/nervous, relaxed/excited, and normal/easily irritated. For each item, subjects graded their subjective states using a scale of 0 (a little) to 100 (a lot).

Treatment-Discontinuation Measures

LPS was measured by polysomnography on the first 2 nights of Month 7 (the placebo run-out period) to evaluate rebound insomnia. Rebound was defined as mean LPS during placebo run-out that was equal to or worse than mean LPS at baseline.

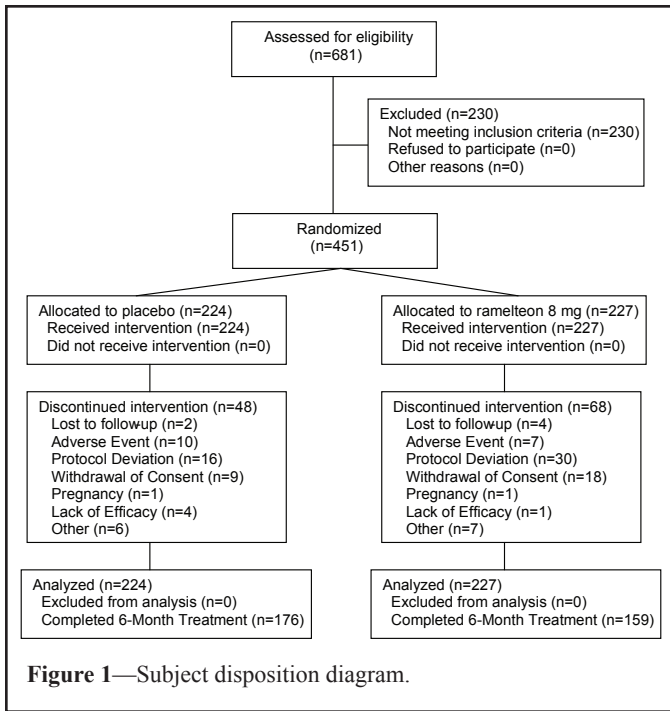
The Tyrer BWSQ was used to assess withdrawal effects after the treatment period.³⁴ Subjects were presented with 20 possible symptoms and were asked to rate each symptom on a 3-point scale with 0 equal to no experience; 1, moderate experience; and 2, severe experience.

Safety Assessments

The incidence of adverse events, including severity (mild, moderate, or severe) and the relationship to study drug, were recorded at each polysomnography visit. Vital-sign assessment and clinical laboratory tests were also obtained the morning following polysomnography recordings. Follow-up clinical laboratory tests, a physical exam, and adverse event monitoring were conducted 7 days after the final treatment.

Statistical Analysis

All statistical analyses were performed using SAS[®] version 8.2 (SAS, Inc., Cary, NC). Descriptive statistics were used to summarize continuous variables. Frequency counts and percentages were calculated for categorical data. All statistical analyses were 2 sided and performed at the 5% significance level. All subjects who were randomly assigned and who received at least 1 dose of study medication were included in each analysis. The primary efficacy variable was the mean LPS from 2 consecutive nights of polysomnography at Month 3 and then Month 6. All polysomnography variables were scored by a central reader. The ramelteon and placebo groups were compared using an analysis of covariance (ANCOVA) model with treatment group as a factor and the baseline LPS as a covariate. Treatment comparison at Month 6 was contingent on statistical significance over placebo at the 0.05 significance level for the Month-3 data. Baseline polysomnography variables were defined as the average of nonmissing observations from the single-blind placebo lead-in period. P values for comparisons were obtained using t tests from the ANCOVA model of the overall treatment comparison. All secondary efficacy endpoints were analyzed in the same manner as the primary endpoint, with the parameter of interest as a covariate. All primary and secondary variables were based on last observation carried forward. Anal-



yses of exploratory variables (ie, rebound insomnia, BWSQ) and safety variables were based on observed data only.

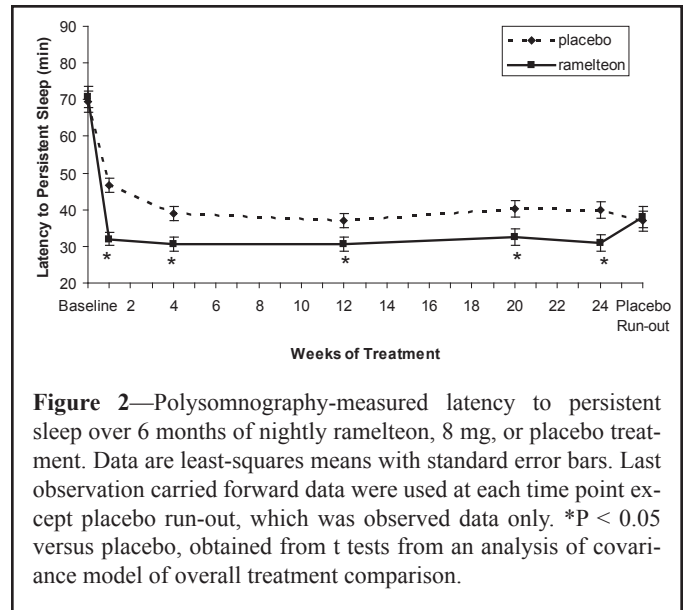
RESULTS

Disposition and Baseline Characteristics

A total of 451 subjects met entry criteria and were randomly assigned to receive ramelteon, 8 mg, (n = 227) or placebo (n = 224). Of these subjects, 335 (74.3%) completed double-blind treatment: 159 (70.0%) in the ramelteon group and 176 (78.6%) in the placebo group (Figure 1). Subject demographics were similar between groups. Overall, the majority of subjects were women (63.2%), and 85.4% were Caucasian, 13.3% were black or African American, 1.6% were Asian, and 0.2% were American Indian or Alaskan Native. The average age of the participants was 46.2 years (14.80 SD, range: 18 to 79 years). On average, subjects reported that it usually took 83.1 minutes (36.94 SD) to fall asleep, and they slept 4.9 hours (0.88 SD). The majority (96.7%) reported that their lack of sleep was associated with a decreased ability to function.

Polysomnographic Sleep Measures

Mean baseline LPS and TST were similar in the ramelteon, 8 mg, (70.75 and 329.28 minutes, respectively) and placebo groups (69.53 and 329.72 minutes, respectively). Significantly greater reductions of LPS were observed with ramelteon compared with placebo throughout treatment (Week 1 and Months 1, 3, 5, and 6; $P < 0.05$ each) (Figure 2). Similarly, a consistently greater change from baseline was observed in the ramelteon group (ranged from 54%-56%) compared with the placebo group (ranged from 30%-47%). A significantly greater increase of TST was observed with ramelteon compared with placebo at Week 1 (ramelteon: 381.1 minutes, placebo: 365.7 minutes; $P < 0.001$) but not at any other time point (Table 1).



Sleep Architecture

There were no statistically significant changes in percentage of time spent in Stage 1 or REM sleep with ramelteon versus placebo except for a small but statistically significant change in Stage 1 at the placebo run-out (Table 2). There was a small but statistically significant increase in percentage of time spent in Stage 2 sleep with ramelteon compared with placebo at each time point (Week 1, Month 1, 3, 5, and 6) and a small but statistically significant decrease in the percentage of time spent in Stage 3/4 sleep with ramelteon compared with placebo at each time point (Week 1, Month 1, 3, 5, and 6).

Self-Reported Sleep Measures

Mean baseline sSL and sTST was similar in the ramelteon, 8 mg, (79.76 and 303.77 minutes, respectively) and placebo groups (78.53 and 303.14 minutes). Significantly greater reductions in sSL were observed with ramelteon compared with placebo at Week 1 and Months 1 and 5 ($P < 0.05$ each) (Figure 3). Reductions in sSL were also observed at Months 3 and 6, though they did not reach statistical significance ($P < 0.08$). There were consistently greater improvements from baseline in the ramelteon group (ranged from 35%-40%) compared with the placebo group (ranged from 18%-30%) throughout the entire treatment period. There were no statistically significant differences between ramelteon and placebo at any time point on the following measures: sTST, subjective number of awakenings, and sleep quality (Table 1). No significant differences in subjective wake time after sleep onset was observed between ramelteon and placebo at any time point except Month 6 (ramelteon: 90.89 minutes, placebo: 79.54 minutes; $P = 0.036$) (Table 1).

Measures of Next-Day Residual Effects

There were no statistically significant differences between ramelteon and placebo at any time point on measures of morning level of alertness and ability to concentrate, the DSST, or immediate and delayed memory recall (Table 3). With the ex-

Table 1—Polysomnography and Self-Reported Sleep Measures Over 6 Months of Treatment

	Baseline	Week 1	Month 1	Month 3	Month 5	Month 6	Placebo Run-out
PSG-Recorded Sleep Measures							
TST, minutes							
Placebo	329.72 (3.957)	365.73 (3.073)	373.79 (3.049)	379.31 (3.134)	379.07 (3.357)	380.11 (3.255)	383.00 (3.957)
Ramelteon	329.28 (3.931)	381.08 (3.059) ^a	380.01 (3.028)	382.46 (3.113)	380.81 (3.335)	381.39 (3.233)	372.87 (4.148)
Self-Reported Sleep Measures							
sTST, minutes							
Placebo	303.14 (4.393)	330.24 (3.673)	340.33 (4.040)	344.90 (4.160)	347.34 (4.412)	349.49 (4.346)	359.31 (4.475)
Ramelteon	303.77 (4.374)	337.00 (3.665)	342.24 (4.040)	352.30 (4.160)	351.56 (4.402)	345.39 (4.336)	352.79 (4.698)
sNAW							
Placebo	3.83 (0.164)	3.51 (0.140)	3.30 (0.115)	3.42 (0.139)	3.17 (0.137)	3.20 (0.154)	3.41 (0.284)
Ramelteon	3.73 (0.163)	3.59 (0.140)	3.58 (0.115)	3.24 (0.139)	3.25 (0.137)	3.32 (0.154)	2.88 (0.299)
sWASO, minutes							
Placebo	105.21 (4.595)	91.33 (3.510)	84.88 (3.718)	80.72 (3.544)	79.51 (3.874)	79.54 (3.822)	72.36 (3.661)
Ramelteon	101.42 (4.574)	94.22 (3.494)	90.82 (3.710)	83.47 (3.536)	84.68 (3.856)	90.89 (3.796) ^a	78.32 (3.854)
Sleep quality ^b							
Placebo	4.61 (0.066)	4.33 (0.061)	4.17 (0.066)	4.06 (0.067)	4.07 (0.069)	4.01 (0.065)	3.87 (0.071)
Ramelteon	4.72 (0.066)	4.21 (0.061)	4.18 (0.066)	4.04 (0.067)	3.94 (0.069)	4.01 (0.065)	3.86 (0.075)

Data are reported as least-square means (SE). The number of subjects was 224 in the Placebo group and 227 in the Ramelteon group. The number for each time point may be slightly less in either group due to available data.

Abbreviations: PSG, polysomnography; TST, total sleep time; sTST, subjective total sleep time; sNAW, subjective number of awakenings; sWASO, subjective wake time after sleep onset.

^aP < 0.05 vs placebo (obtained using t-tests from the analysis of covariance model of the overall treatment comparison).

^bEvaluated on a 7-point Likert scale on which 1 = excellent and 7 = extremely poor.

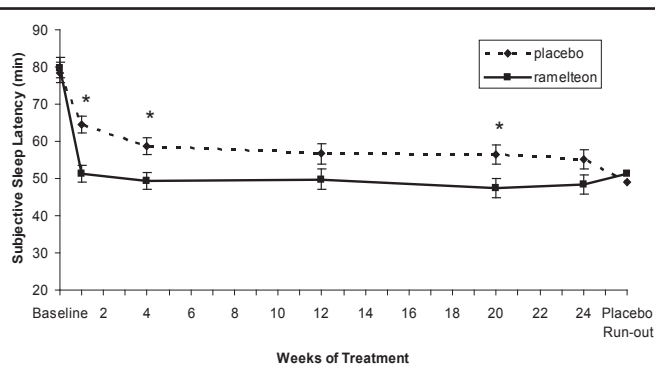


Figure 3—Subjective sleep latency measured over 6 months of nightly ramelteon, 8 mg, or placebo treatment. Data are least-squares means with standard error bars. Last observation carried forward data were used at each time point except placebo run-out, which was observed data only. *P < 0.05 versus placebo, obtained from t tests from an analysis of covariance model of overall treatment comparison.

ception of sporadic significant differences on individual items of the VAS, no consistent statistically significant differences were observed on the various VAS assessments for mood and feeling throughout the 6-month treatment.

Measure of Rebound Insomnia

No rebound insomnia (defined as mean LPS during placebo run-out that was equal to or worse than mean LPS at baseline) was observed during the single-blind, placebo run-out period (Figure 2). LPS did not return to baseline levels in either group. There was no significant difference between ramelteon and placebo in LPS.

Measures of Withdrawal

Baseline BWSQ scores (assessed at the end of Month 6) were similar between groups (ramelteon: 1.8; placebo: 1.4). There was no statistically significant difference between ramelteon and placebo in BWSQ scores on placebo run-out Day 2 (P = 0.711) or Day 3 (P = 0.679).

Safety

The overall incidence of adverse events was similar in the ramelteon (51.8%) and placebo groups (50.7%). The most frequently occurring adverse events are shown in Table 4. A total of 18 (10 in placebo group, 8 in ramelteon group) subjects discontinued treatment due to an adverse event. Seven subjects reported a total of 9 serious adverse events (2 in placebo group, 5 in ramelteon group) during the 6 months of this study; only leukopenia was considered to be possibly treatment related. A 64-year-old woman in the ramelteon group was diagnosed with leukopenia on Day 78 of treatment and was withdrawn from the study on Day 79. Blood levels were back to normal by Day 84, and no other clinical abnormalities were detected. The adverse event was considered to be possibly treatment related due to the appearance of symptoms during treatment and the resolution of symptoms upon drug discontinuation. No deaths were reported during this study. No clinically significant changes in vital signs or physical exams were reported.

DISCUSSION

To date, other than this study, no long-term (≥ 6 months), polysomnographic, placebo-controlled studies of medications

Table 2—Sleep Architecture

	Baseline	Week 1	Month 1	Month 3	Month 5	Month 6	Placebo Run-out
Stage 1, % TST							
Placebo	11.51 (0.364)	10.61 (0.234)	10.44 (0.257)	9.97 (0.241)	10.01 (0.226)	10.07 (0.273)	10.09 (0.258)
Ramelteon	11.33 (0.362)	10.60 (0.233)	10.05 (0.255)	10.19 (0.239)	10.13 (0.224)	9.96 (0.271)	9.32 (0.271) ^a
Stage 2, % TST							
Placebo	59.56 (0.770)	57.78 (0.402)	57.34 (0.410)	57.68 (0.436)	58.10 (0.450)	57.89 (0.475)	57.84 (0.532)
Ramelteon	57.09 (0.764)	59.93 (0.400) ^a	59.01 (0.407) ^a	59.55 (0.433) ^a	60.17 (0.447) ^a	60.31 (0.472) ^a	58.59 (0.557)
Stage 3/4, % TST							
Placebo	10.37 (0.697)	12.72 (0.339)	12.68 (0.353)	12.27 (0.362)	11.94 (0.358)	12.37 (0.378)	12.38 (0.455)
Ramelteon	12.89 (0.692)	9.76 (0.337) ^a	10.81 (0.351) ^a	10.45 (0.360) ^a	10.05 (0.356) ^a	10.45 (0.376) ^a	11.77 (0.477)
REM, % TST							
Placebo	18.56 (0.390)	18.92 (0.290)	19.61 (0.293)	20.10 (0.315)	19.96 (0.316)	19.67 (0.323)	19.76 (0.335)
Ramelteon	18.69 (0.387)	19.69 (0.289)	20.07 (0.291)	19.78 (0.313)	19.65 (0.314)	19.27 (0.321)	20.23 (0.352)
Latency to REM, min							
Placebo	80.50 (2.766)	82.19 (2.595)	79.41 (2.339)	79.97 (2.640)	80.69 (2.846)	79.10 (2.705)	78.70 (2.738)
Ramelteon	79.61 (2.747)	74.73 (2.584) ^a	71.49 (2.323) ^a	73.16 (2.622)	74.25 (2.827)	75.00 (2.687)	76.69 (2.870)

Data are reported as LS Mean (SE). The number of subjects was 224 in the Placebo group and 227 in the Ramelteon group. The number for each time point may be slightly less in either group due to available data.

Abbreviations: TST, total sleep time; REM, rapid eye movement.

^aP < 0.05 vs placebo (obtained using t-tests from the analysis of covariance model of the overall treatment comparison).

indicated for insomnia have been reported in adults with primary insomnia. A few long-term studies of BzRAs have evaluated subjective efficacy, but no objective parameters were measured.³⁵⁻³⁷ This lack of long-term, objective sleep studies is significant because subjective outcome measures have been shown to be unreliable relative to polysomnographic measures.²⁹

On polysomnographic recordings, ramelteon reduced LPS from 70.75 minutes at baseline to 32.02 minutes at Week 1. Reductions of this magnitude were consistently observed at each subsequent visit over a period of 6 months, which implies sustained efficacy with no evidence of tolerance. The differences in LPS relative to placebo in the present study are comparable to those found with other sleep aids. The LPS mean difference from placebo was approximately 15 minutes at Week 1 and 9 minutes at Month 6. In a recent meta-analysis, the mean difference from placebo on polysomnographically recorded LPS with traditional BzRAs (eg, triazolam, temazepam, nitrazepam) was 10 minutes and with newer BzRAs (eg, zopiclone, zolpidem, eszopiclone, zaleplon) was 12.8 minutes.³⁸

Clinical significance is difficult to determine in sleep studies, especially when the objectively measured differences from placebo are in the 10- to 15-minute range. Two indicators of clinically meaningful effect are either a 50% or greater improvement in the primary symptom or, specifically for insomnia studies, a reduction in LPS to at or near 30 minutes.³⁹ In this study, the mean percentage change in LPS from baseline for subjects in the ramelteon group was greater than 50% for all time points, whereas the mean percentage change for subjects in the placebo group was consistently less than 50% improvement (Figure 2). Additionally, the mean LPS for subjects in the ramelteon group were at or near 30 minutes for all time points (Figure 1). This suggests that the reductions in LPS for ramelteon subjects in this study may be considered clinically meaningful based on current recommendations for assessing clinically significant effects.

Self-reported sleep latency showed results similar to polysomnographic recordings, with a statistically significant reduction of sSL at Weeks 1 and 4. Thereafter, the ramelteon treatment effect remained remarkably constant, although not all time points reached statistical significance when compared with placebo. No differences between ramelteon and placebo were observed on other subjective sleep parameters. It is noteworthy that this study was powered for polysomnography-derived sleep measures, (ie, it was not powered to detect differences on subjective measures of sleep). Generally, sSL does not show the same magnitude of improvement as do polysomnographic measures.^{40,41} The discrepancy between the polysomnography outcomes and those on self-reported measures may also be the result of sleep-time misperception.^{29,42} A number of studies have demonstrated that subjects tend to underestimate their total sleep time and overestimate their time to sleep onset.^{29,42,43}

Overall, various sleep parameters improved considerably from baseline with ramelteon, although improvements from baseline were also observed in the placebo group. In this study, sleep latency decreased from baseline by approximately 30 minutes in the placebo group and 40 minutes in the ramelteon group at the 6-month visit. These improvements with placebo are comparable to those found in other sleep studies. In a placebo-controlled study of the BzRA eszopiclone in individuals with chronic insomnia, the placebo group showed a 30-minute decrease in sSL from baseline at 6 months.³⁵ Similarly, studies of medications not indicated for the treatment of insomnia, the antidepressant trazodone⁴⁴ and the herbal supplement valerian,⁴⁵ have reported improvements in sleep under the placebo condition. An improvement on sleep parameters in placebo groups is common in sleep studies⁴⁶ and may be due to a combination of the general placebo effect and improved sleep hygiene resulting from study participation.⁴⁷ However, it should be noted that subjects in the ramelteon group demonstrated significant improvements in sleep latency over and above placebo at all time points.

Table 3—Next-Day Residual Measures

	Baseline	Week 1	Month 1	Month 3	Month 5	Month 6	Placebo Run-out
Morning alertness							
Placebo	4.09	3.88	3.90	3.75	3.80	3.70	3.67
Ramelteon	4.12	4.00	3.86	3.79	3.79	3.78	3.67
Ability to concentrate							
Placebo	4.10	3.89	3.96	3.79	3.85	3.75	3.67
Ramelteon	4.15	3.95	3.83	3.73	3.77	3.79	3.67
DSST							
Placebo	36.00	38.31	40.51	38.36	40.27	41.72	41.49
Ramelteon	35.27	38.08	40.48	39.29	40.77	41.53	42.27
Immediate memory recall							
Placebo	6.78	8.13	7.60	8.98	8.81	8.46	8.43
Ramelteon	6.89	8.11	7.50	9.12	8.67	8.36	8.09
Delayed memory recall							
Placebo	4.87	6.44	6.30	7.79	7.45	7.42	6.95
Ramelteon	5.04	6.41	6.32	7.92	7.46	7.24	6.52
VAS for feelings – energetic/fatigued							
Placebo	47.99	42.53	41.77	40.72	39.08	39.22	38.14
Ramelteon	47.83	44.67	42.66	39.45	40.93	43.26 ^a	42.22 ^a
VAS for mood - drowsy							
Placebo	36.06	31.11	30.22	29.61	30.62	28.65	27.76
Ramelteon	35.22	34.46 ^a	31.96	29.69	30.24	30.69	28.86
VAS for mood – slowed down							
Placebo	34.43	30.12	28.87	29.11	29.28	28.11	26.25
Ramelteon	33.85	33.27 ^a	30.87	28.78	29.88	30.41	28.42
VAS for mood - sleepy							
Placebo	37.86	33.17	31.78	30.41	31.23	30.12	28.62
Ramelteon	37.68	36.42 ^a	33.08	31.12	31.58	31.94	29.48
VAS for feelings – thinking slowed down/speeded up							
Placebo	39.08	39.91	38.88	39.25	39.28	40.90	40.79
Ramelteon	39.31	38.39	40.59	40.58	39.46	37.34 ^a	37.94

Data are reported as least-square mean. The number of subjects was 224 in the Placebo group and 227 in the Ramelteon group. The number for each time point may be slightly less in either group due to available data. DSST refers to Digit Symbol Substitution Test.

Subjective morning alertness and ability to concentrate are evaluated on a 7-point scale in which 1 = excellent and 7 = extremely poor. Visual analog scale (VAS) for Feelings: 0 = energetic, 100 = fatigued; VAS for Mood: 0 = a little, 100 = a lot;

^aP < 0.05 vs placebo (obtained using t-tests from the analysis of covariance model of the overall treatment comparison).

At Week 1, TST measured by polysomnography was significantly increased in the ramelteon group compared with the placebo group; however, no significant differences were detected at any other time points. When sleep time was examined by sleep stage, subjects in the ramelteon group spent a greater percentage of TST in Stage 2 sleep and a lower percentage of TST in Stage 3/4 sleep. The changes in Stage 2 and 3/4 sleep are consistent with previous studies of ramelteon, although these changes are not likely to be clinically meaningful given the small magnitude of the change.^{25-27,48}

No next-day effects were observed on measures of psychomotor function, immediate and delayed memory recall, level of alertness, and ability to concentrate over 6 months of treatment. The VAS for mood and feeling were similar between the ramelteon and placebo groups as well. The overall lack of next-day impairment with ramelteon is consistent with previous placebo-controlled studies of up to 35 days of ramelteon treatment in adults with chronic insomnia.²⁴⁻²⁷ These findings are in contrast to some studies of BzRAs, which achieve their effect through action at the $\alpha 1$ subunit of the GABA_A receptor. Action at this subunit has been associated with retrograde amnesia.⁴⁹⁻⁵¹

Table 4—Incidence of Adverse Events Occurring in more than 3% of Subjects

Adverse Event	Placebo (n = 223)	Ramelteon (n = 228)
Headache	18 (8.1)	18 (7.9)
Upper respiratory tract infection	6 (2.7)	11 (4.8)
Nasopharyngitis	11 (4.9)	10 (4.4)
Urinary tract infection	9 (4.0)	9 (3.9)
Dizziness	5 (2.2)	7 (3.1)
Nausea	8 (3.6)	7 (3.1)

Data are presented as number (%).

Many commonly prescribed sleep medications (eg, BzRAs, trazodone) are also associated with psychomotor and cognitive impairment.^{49,51-54}

Ramelteon was well tolerated with an adverse-event profile similar to that of placebo, which is consistent with previous clinical studies. For instance, 2 long-term safety studies extensively evaluated the effects of ramelteon on numerous safety

variables and found no clinically meaningful changes on a range of variables, including vital signs, findings on physical exam, clinical chemistry, hematology, urinalysis, and electrocardiogram trends.^{55,56} It is notable that this study also had a relatively low dropout rate, which may speak to tolerability associated with the use of ramelteon. Previous efficacy and safety studies with ramelteon have had low dropout rates, very similar to those of placebo.^{25,26}

When subjects discontinued using ramelteon after 6 months of treatment, no rebound insomnia and no withdrawal effects were observed. However, there was no continuation of treatment effect upon discontinuation of ramelteon, and LPS and sSL were similar to those of placebo during the run-out period. These findings are in line with other clinical trials of ramelteon.^{24,26,27,57} In a study of substance abusers given ramelteon or the benzodiazepine triazolam, ramelteon did not demonstrate any potential for abuse liability, unlike triazolam.²⁸ In contrast, BzRAs are controlled substances with the potential for abuse.^{5,58-60} For instance, in a 4-week study of zaleplon and zolpidem in adults with chronic insomnia, significant rebound and withdrawal effects were observed in the zolpidem group.⁶¹

A limitation of this study is that no subjective measures were recorded in the at-home setting, and the inclusion and exclusion criteria were quite strict. Together, these factors may limit the external validity of this study, although this limitation is true of all well-controlled clinical trials. Another limitation is that few assessments of daytime function or quality of life were done in this study. Impairment in daytime functioning is a common complaint in patients with insomnia (as reflected in the large percentage of subjects in this study reporting a decreased ability to function) and should be taken into account when treating the disease. However, this study focused primarily on the objective sleep-latency effects, and a more comprehensive analysis of improvements in daytime function is needed. Although sleep onset was consistently improved in the present study, a potential limitation of these data is that efficacy was only evaluated across 2 nights in the sleep laboratory, and, thus, no conclusion about the sustainability of these results in the at-home setting can be made from this study. Also, there was no active control group, such as a BzRA group or a melatonin group. Future studies using a head-to-head design will be particularly important when evaluating differences on measures of tolerance, rebound, and withdrawal. The ability to measure withdrawal was somewhat limited by the standard measure that is available (BWSQ). The BWSQ is validated based on a 1-week assessment and is intended to measure symptoms associated with the use of benzodiazepines. It has not been validated using a shorter assessment period or with an insomnia medication with a mechanism of action similar to that of ramelteon.

The mechanism of action of ramelteon is unlike that of any of the traditional sleep medications in which the hypnotic effect is mediated through the GABA_A receptor. Ramelteon acts as an agonist at the MT₁/MT₂ melatonin receptors, which are not involved in general central nervous system sedation but, instead, influence the body's sleep-wake cycle. Activation of the MT₁ and MT₂ receptors in the SCN may both precipitate the acute hypnotic effects of ramelteon as well as shift the endogenous melatonin phase. Previous studies have shown that ramelteon is capable of inducing a significant phase advance.^{62,63} Mela-

tonin studies have shown that the optimal timing for exogenous melatonin to cause a phase advance (based on the melatonin response curve) is during the afternoon or early evening.^{64,65} Based on these data, all of the phase-shift studies of ramelteon have administered medication in the afternoon. In addition, these studies have been in healthy adults with no evidence of sleep disorders. There have been no studies of the phase-shifting effects of ramelteon when given at bedtime in adults with insomnia. The effects of ramelteon in insomnia have been on time to sleep onset without determining the melatonin phase of the subjects. Although it is possible that the sleep-promoting effects of ramelteon are partly a result of phase shifts mediated by the MT₂ receptor, it is also possible that sleep promotion is a result of the acute hypnotic effects of ramelteon via activation of the MT₁ receptor. At the current time, there have not been enough studies of both the phase-shifting and sleep-promoting effects of ramelteon in adults with insomnia to establish the exact mechanisms responsible for its effects. It is possible that both pathways play a role in reducing the time to sleep onset.

In conclusion, in adults with chronic primary insomnia, long-term treatment with ramelteon, 8 mg, significantly reduced sleep onset at all measured time points over 6 months of nightly administration. There were no significant next-day residual effects and no rebound insomnia or withdrawal symptoms upon discontinuation. Ramelteon was well tolerated, with a low incidence of adverse events that was similar to that of placebo.

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