Safety and Subjective Sleep Effects of Ramelteon Administration in Adults and Older Adults With Chronic Primary Insomnia: A 1-Year, Open-Label Study

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Objective: To evaluate the long-term safety and subjective sleep effects of ramelteon in adults with chronic insomnia.

Method: Subjects with primary insomnia (DSM-IV-TR criteria) for ≥ 3 months received ramelteon nightly for 1 year; a 3-day placebo run out followed. Subjects aged ≥ 65 years received open-label ramelteon 8 mg (N = 248); those aged 18 to 64 years received ramelteon 16 mg (N = 965). Subjects completed sleep diaries and returned to the clinic at week 1 and at months 1, 2, 3, 4, 6, 8, 10, and 12 for safety assessments and investigator-performed Clinical Global Impressions. The study was conducted from February 2003 through September 2004.

Results: There were no noteworthy changes in vital signs, physical examinations, clinical chemistry, hematology, or urinalysis values and no electrocardiogram changes to suggest adverse cardiac effects. Endocrine values remained within normal range throughout treatment. Consistent statistically significant ($p \leq .05$) decreases in free thyroxine (in adults) and free testosterone (in older men) were detected. Duration of menses increased by approximately 1 day. A total of 40.8% of subjects reported at least 1 adverse event possibly associated with ramelteon use. The adverse events reported varied considerably, the incidence of individual adverse events was low, and the frequencies of adverse events were similar at months 6 and 12. In both groups, subjective sleep latency and total sleep time improved by month 1 and was sustained during the 1-year period. At 6 months and 1 year, Clinical Global Impressions indices were improved. During placebo run out, subjective sleep latency did increase but did not return to baseline.

Conclusion: Year-long administration of ramelteon was well tolerated. Ramelteon was associated with sustained improvements in subjective sleep latency, subjective total sleep time, and Clinical Global Impressions.

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Chronic insomnia is defined as a complaint of difficulty falling asleep or maintaining sleep, or of nonrestorative sleep, lasting months to years.[1,2] The disorder is more common than is often recognized, occurring in about 10% of adults, and is more prevalent among older adults and women.[3–5]

Older benzodiazepine-receptor agonists (e.g., temazepam and triazolam), the mainstay of insomnia pharmacotherapy for many years, are associated with numerous adverse effects, including a heightened risk of psychomotor and cognitive impairment.[6–8] While newer benzodiazepine-receptor agonists (e.g., zolpidem, zolpidem modified release, zaleplon, eszopiclone) are generally regarded as safer than older benzodiazepines,[9] the foundation for this advantage is unclear. Newer agents are selective, to varying degrees, for the subset of benzodiazepine receptors (the α_1 receptor subtype) that appear to mediate hypnotic activity, and this selectivity may confer a safety advantage, although this has not been shown to be relevant in a clinical setting. Alternatively, the evident difference in the risk of adverse events may reflect the shorter average sedative half-life of newer agents, as well as the use of lower doses (relative to the minimum effective dose). Consistent with these explanations, newer benzodiazepine-receptor agonists have been linked to many of the same impairments as older agents, including those in cognition, memory, and psychomotor function.[6–8,10,11] The newer benzodiazepine-receptor agonists have also been associated with anterograde amnesia,[6–8,11] which has been linked to

activation of the α_1 receptor subtype. Newer agents have also been associated with withdrawal symptoms, such as rebound insomnia.[10,12,13] Use of both newer and older benzodiazepine-receptor agonists has been limited, particularly in chronic insomnia, by their status as controlled substances with measurable potential for abuse.[12–15]

An alternative pharmacologic approach to the treatment of insomnia is predicated on the demonstrated role of melatonin and its specific central nervous system receptors (MT_1 and MT_2) in the control of sleep and circadian rhythms.[16–18] On the basis of this physiology, melatonin receptor agonists would be expected to provide an alternate insomnia therapy without the risks associated with action at the benzodiazepine receptor. Preclinical studies of ramelteon, the first melatonin receptor agonist approved for clinical use, demonstrate that it is a selective and potent agonist at MT_1/MT_2 melatonin receptors, with negligible affinity for either the MT_3 binding site or other neuronal receptors.[19] The efficacy and safety of ramelteon have been previously reported in randomized, placebo-controlled trials employing polysomnography in subjects with chronic insomnia.[20–22] These trials also demonstrated that there was no evidence of next-day residual effects nor evidence of withdrawal or rebound insomnia on abrupt discontinuation. In addition, separate laboratory assessments indicate that ramelteon lacks abuse potential.[23]

The efficacy and safety over multiple weeks of use without evidence for tolerance suggest that ramelteon may be singularly suited for the long-term treatment of chronic insomnia. The current study was designed to assess the long-term safety and subjective effects on sleep of ramelteon treatment in individuals with chronic insomnia.

METHOD

Study Design

This was a 1-year, open-label, fixed-dose study of ramelteon for chronic insomnia treatment conducted at 123 sites in the United States from February 2003 through September 2004. Subjects received ramelteon for 48 weeks, followed by a 3-day, single-blind, placebo run-out period. The highest ramelteon doses used in previous phase 3 trials were selected for use during this trial. Because adults and older adults may have different adverse event profiles, subjects 18 to 64 years of age were assigned ramelteon 16 mg/day and subjects aged 65 years or older were assigned ramelteon 8 mg/day to evaluate the effects of exposure to ramelteon at a high dose. This study and previous studies used a 16 mg/day dose of ramelteon in adults aged 18 to 64 years (2 times the U.S. Food and Drug Administration–approved therapeutic dose) to provide a larger margin of safety. The recommended therapeutic dose for all adults (18 years and older) is 8 mg/day.

Primary end points included adverse events as well as changes in vital signs, laboratory values, 12-lead electrocardiograms (ECGs), and results from physical examination. Clinical laboratory measures included serum chemistry, hematology, and urinalysis values as well as endocrine parameters, including thyroid stimulating hormone (TSH), triiodothyronine (T3), total thyroxine (T4), free T4, and morning cortisol, and (in men) total testosterone, free testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels. Reproductive endocrine function in women was assessed with menstrual diaries.

Subjective measures of sleep quality were obtained from subjects' daily sleep diaries (subjective sleep latency and subjective total sleep time). In addition, a clinician's assessment was obtained using the Clinical Global Impressions (CGI) scale. The CGI scale included 3 components: change of condition scored on a 7-point scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse), severity of illness scored on a 7-point scale (1 = not at all ill, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = extremely ill), and therapeutic effect scored on a 4-point scale (1 = very good, 2 = moderate, 3 = slight, and 4 = unchanged). Sleep measures collected during the 3-day, single-blind, placebo run-out period were used to assess rebound insomnia.

Subject Eligibility

Eligible subjects were men or nonpregnant, nonlactating women, at least 18 years of age, with a body mass index of 18 to 34. All subjects had a diagnosis of primary insomnia (DSM-IV-TR criteria) lasting at least 3 months and daytime complaints associated with disturbed sleep. In addition, eligible subjects had to meet severity criteria of a subjective sleep latency ≥ 45 minutes and a subjective total sleep time ≤ 6.5 hours during at least 3 nights of a 7-night lead-in period. Habitual bedtime was required to fall between 8:30 p.m. and 12:00 a.m. Participants previously enrolled in a ramelteon study were eligible if they had completed participation within 21 days of enrollment or if they could otherwise satisfy the entry criteria for the current trial. Only subjects who agreed to long-term treatment for insomnia were enrolled.

Subjects were excluded from participation if they had taken any investigational drug, other than ramelteon, within the preceding 30 days; had used any drug or supplement known to affect sleep or any central nervous system medication in the preceding week; intended to use disallowed medication during the study; had a history of drug or alcohol abuse or addiction in the preceding 12 months; or used tobacco products during nightly awakenings. Subjects also were excluded if they had sleep schedule changes required by employment within the preceding 3 months, had flown across more than 3 time zones in the preceding 7 days, had participated in a weight loss program, or had significantly altered their exercise routine in

the preceding 30 days. Several medical conditions were also grounds for exclusion, including current significant illness or disorder (unless controlled by an allowed medication); history of seizure, sleep apnea, chronic obstructive pulmonary disease, restless legs syndrome, schizophrenia, bipolar disorder, mental retardation, or cognitive disorder; or any clinically important abnormal finding from medical history, physical examination, ECG, or laboratory tests. In addition, subjects with laboratory evidence of active hepatitis A, B, or C were excluded, as were subjects with morning serum cortisol levels below 7.0 nmol/L at baseline or subjects with any other condition that warranted exclusion in the opinion of the investigator.

The institutional review board at each study site approved study procedures and informed consent forms. Each subject who chose to participate signed the informed consent form before any study-related procedures were performed. This study was conducted in accordance with the World Medical Association Declaration of Helsinki (1989), the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice, and the U.S. Food and Drug Administration Code of Federal Regulations. In accordance with the ICH Harmonised Tripartite Guideline for the extent of population exposure to assess clinical safety, this study enrolled over 600 subjects for up to 1 year of ramelteon administration to determine the frequency and timing of adverse events in an adequately sized population.

Study Procedures

At screening, a physical examination was performed, and ECG, clinical laboratory values, medical history, and sleep history were recorded. Subjects meeting enrollment criteria completed a 7-day lead-in period during which no study drugs were administered. Subjects were asked to record their medication compliance, bedtime, subjective sleep latency, and subjective total sleep time each morning in a paper sleep diary. Subjects were evaluated for continued study eligibility. Premenopausal women were asked about their menstrual history, and menstruating women were asked to complete a menstrual diary, which they maintained throughout the study. Following the 7-day lead-in period, the 48-week, open-label treatment period began. Subjects were instructed to take a single dose of ramelteon daily before bedtime and to complete their sleep diaries each morning upon waking. Follow-up clinic visits were completed at week 1 and months 1, 2, 3, 4, 6, 8, 10, and 12. At each follow-up visit, completed diaries were collected, new diaries were distributed, and adverse events were recorded. Subjects were also instructed to call and report adverse events experienced at home. Abbreviated physical examinations were performed bimonthly, and full physical examinations, including ECG, were performed at months 6 and 12.

After 48 weeks of daily ramelteon administration, subjects received single-blind, matching placebo for 3 days. After the 3-day placebo run-out period, subjects received a final assessment by physical examination, ECG, clinical laboratory tests, and measurement of hormone levels. Any adverse events experienced during the run-out phase were recorded, and daily sleep diaries and menstrual diaries were collected at the final visit.

Data Analysis

Two groups of subjects were studied: adults (18–64 years of age) receiving ramelteon 16 mg/day, and older adults (aged 65 years or older) receiving ramelteon 8 mg/day. The groups were not intended to be compared, and no control group was included in the study. Therefore, there are no statistical comparisons between groups of subjects.

All enrolled subjects who received at least 1 dose of study medication were included in the analysis. Safety and laboratory values, as well as the assessment of rebound insomnia, were derived from observed values. Subjective efficacy parameters were analyzed using observed data from the subjects' daily sleep diaries. For each subject, sleep diary data from the 7 days preceding each scheduled visit were averaged for a weekly data point. If no measurements were available, the observation was missing. *Completers* are defined as subjects who finished 48 weeks of ramelteon treatment. Baseline is the average of all data collected before open-label treatment. Clinical laboratory values, ECG parameters, vital signs, and hormone levels were analyzed by descriptive statistics (mean [SD]) and shift tables, which allowed an assessment of the number of subjects experiencing clinically relevant changes in any given safety parameter. Normal ranges for these parameters and the criteria defining clinically relevant shifts were determined before initiation of the study. All p values are from paired t tests (postbaseline vs. baseline).

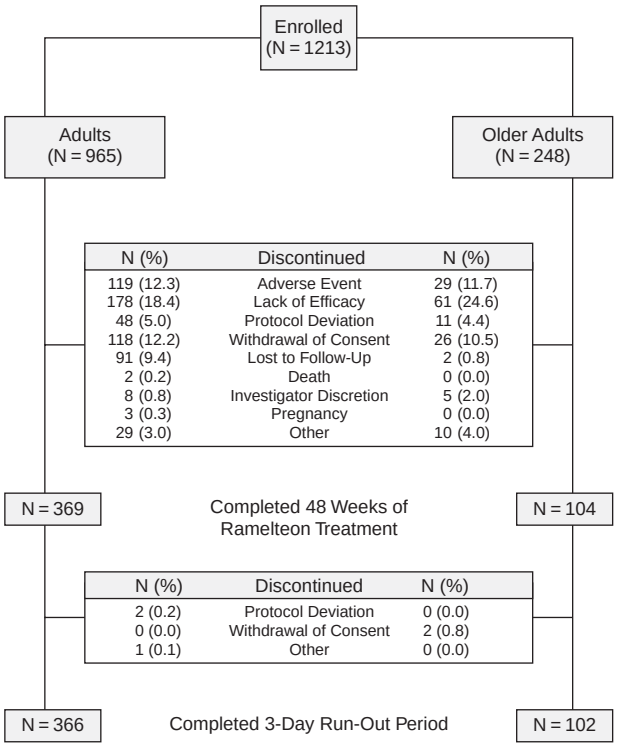
RESULTS

In total, 1213 subjects enrolled in the study; 965 were 18 to 64 years of age and were assigned to ramelteon 16 mg/day (adult group), and 248 were aged 65 years or older and assigned to ramelteon 8 mg/day (older adult group). The disposition of subjects and reasons for withdrawal are shown in Figure 1. Demographic characteristics of enrolled subjects are shown in Table 1.

Compliance and Exposure

Subjects were considered compliant if they took ramelteon before bedtime at least 3 nights per week. In the adult group, 471 (48.8%) completed at least 6 months and 370 (38.3%) completed at least 48 weeks of the study. In the older adult group, 126 (50.8%) completed at least 6

Figure 1. Disposition of Adults Receiving 16 mg of Ramelteon and Older Adults Receiving 8 mg of Ramelteon and Reasons for Withdrawal



months and 105 (42.3%) completed at least 48 weeks of the study.

Clinical Laboratory, Hematology, and Urinalysis Values

The mean serum chemistry values, mean hematology values, and mean urinalysis values remained within normal range for all analytes at all time points. Shifts in blood chemistry, hematology, and urinalysis values from low/normal to high or from high to low/normal occurred in fewer than 2% of subjects for each analyte measured. Table 2 shows the number of subjects in each group who had markedly abnormal clinical chemistry, hematology, or urinalysis values after having normal values during the baseline assessment. In general, markedly abnormal clinical chemistry values occurred in fewer than 2% of subjects who had normal values at the baseline assessment. The exceptions were blood urea nitrogen, uric acid, potassium, fasting serum glucose, hematocrit, glucose, ketones, occult blood, protein, red blood cell count, and white blood cell count, all of which had values that were markedly abnormal on at least 1 determination in > 2% of older adult subjects. Ketones, occult blood, protein, red blood cells, and white blood cells demonstrated values that were markedly abnormal on at least 1 determination in > 2% of adult subjects. Overall, there were no trends relating duration of treatment to the number of subjects with abnormal clinical laboratory, hematology, or urinalysis values.

Table 1. Demographic Characteristics of Subjects Enrolled in the Trial of Ramelteon for Chronic Insomnia[a]

Characteristic	Adult (N = 965)[b]	Older Adult (N = 248)[c]
Sex, N (%)		
Male	385 (39.9)	116 (46.8)
Female	580 (60.1)	132 (53.2)
Age, y	46.2 (11.9)	72.3 (5.6)
Race, N (%)		
White	772 (80.0)	225 (90.7)
Black	100 (10.4)	8 (3.2)
Hispanic	65 (6.7)	11 (4.4)
Asian	20 (2.1)	1 (0.4)
Native American	1 (0.1)	1 (0.4)
Other	7 (0.7)	2 (0.8)
Weight, kg	76.2 (15.7)	75.4 (14.5)
Height, cm	169.4 (9.8)	168.2 (10.0)
Body mass index, kg/m^2	26.4 (4.0)	26.5 (3.7)

[a]All values are reported as mean (SD) unless otherwise specified.
[b]Aged 18 to 64 years; ramelteon dose = 16 mg.
[c]Aged 65 years and older; ramelteon dose = 8 mg.

Table 2. Incidence (≥ 2%) of Markedly Abnormal Clinical Chemistry, Hematology, and Urinalysis Values in Subjects With Baseline Values Within Normal Range[a]

			N (%)	
Parameter	Normal Range	Markedly Abnormal Criteria	Adult (N = 965)	Older Adult (N = 248)
Blood urea nitrogen, mmol/L	1.4–8.6	≥ 10.7	16 (1.7)	10 (4.0)
Uric acid, µmol/L	125–494[b] 125–446[c]	≥ 625[b] ≥ 506[c]	14 (1.5)	8 (3.2)
Potassium, mmol/L	3.4–5.4	≤ 3.0 or ≥ 5.8	16 (1.7)	9 (3.6)
Fasting serum glucose, mmol/L	3.9–6.7	≤ 2.8 or ≥ 10.0	17 (1.8)	8 (3.2)
Hematocrit	0.37–0.54[b] 0.34–0.48[c]	≤ 0.37[b] ≤ 0.32[c]	14 (1.5)	14 (5.6)
Glucose	Negative	≥ 1+	18 (1.9)	9 (3.6)
Ketones (qualitative)	Negative	≥ 1+	33 (3.4)	8 (3.2)
Occult blood	Negative	≥ 1+	156 (16.2)	23 (9.3)
Protein (qualitative)	Negative	≥ 1+	29 (3.0)	18 (7.3)
Red blood cells (per high-power field)	0–3[b] 0–8[c]	≥ 5	137 (14.2)	28 (11.3)
White blood cells (per high-power field)	0–5[b] 0–12[c]	≥ 20	90 (9.3)	30 (12.1)

[a]Adult ramelteon dose = 16 mg; older adult ramelteon dose = 8 mg.
[b]Men.
[c]Women.

Endocrinology

Levels of several circulating hormones were measured in order to assess potential effects of study drug on the thyroid, reproductive, and adrenal axes (Table 3). On the thyroid axis, TSH, T3, and T4 showed no consistent

Table 3. Mean Values for All Hormone Levels in Adults Receiving 16 mg of Ramelteon and in Older Adults Receiving 8 mg of Ramelteon[a,b]

Parameter	Normal Range	Baseline	Change at Month 1	Change at Month 2	Change at Month 4	Change at Month 8	Final Visit[c]
Adults							
TSH, mIU/L	0.32–5	1.862 (1.7973)	NA	–0.056 (0.0462)	0.032 (0.0464)	0.084 (0.0989)	–0.033 (0.0510)
T3, nmol/L	0.69–2.11	1.398 (0.2763)	NA	–0.003 (0.0114)	0.065 (0.0116)[d]	0.003 (0.0129)	–0.001 (0.0111)
T4, nmol/L	54–161	98.7 (20.41)	NA	0.3 (0.55)	2.5 (0.68)[d]	0.4 (0.72)	–0.6 (0.68)
Free T4, pmol/L	9–24	13.2 (1.81)	NA	–0.3 (0.06)[d]	–0.5 (0.08)[d]	–0.4 (0.08)[d]	–0.5 (0.09)[d]
Free testosterone, pg/mL	52–280	82.99 (43.356)	5.01 (1.666)[d]	4.25 (1.495)[d]	2.29 (2.024)	3.37 (1.792)	3.44 (1.970)
FSH, IU/L	1–15	5.95 (5.123)	NA	NA	0.33 (0.093)[d]	NA	–0.03 (0.101)
Morning cortisol, nmol/L	138–718	391.1 (169.04)	–16.2 (5.07)[d]	–17.6 (5.61)[d]	–8.3 (6.68)	–23.4 (6.91)[d]	–41.4 (5.87)[d]
Older adults							
TSH, mIU/L	0.32–5	2.032 (1.2772)	NA	0.095 (0.0833)	0.145 (0.0848)	0.108 (0.1785)	0.170 (0.0862)[d]
T3, nmol/L	0.69–2.11	1.294 (0.2148)	NA	–0.046 (0.0206)[d]	–0.024 (0.0210)	–0.086 (0.0233)[d]	–0.034 (0.0186)
T4, nmol/L	54–161	97.5 (19.42)	NA	1.0 (0.99)	2.3 (1.24)	1.5 (1.30)	0.3 (1.14)
Free T4, pmol/L	9–24	13.2 (2.02)	NA	–0.2 (0.12)	–0.3 (0.15)[d]	–0.3 (0.15)[d]	–0.3 (0.15)
Free testosterone, pg/mL	52–280	57.47 (22.121)	–10.63 (3.025)[d]	–7.28 (2.758)[d]	–8.07 (3.689)[d]	–8.20 (3.286)[d]	–8.39 (3.286)[d]
FSH, IU/L	1–15	13.10 (12.469)	NA	NA	0.57 (0.175)[d]	NA	0.10 (0.171)
Morning cortisol, nmol/L	138–718	375.2 (127.21)	–24.4 (9.40)[d]	–30.5 (10.13)[d]	–4.6 (12.24)	–14.1 (12.45)	–25.0 (9.89)[d]

[a]All data are least squares mean (SE) with the exception of baseline data, which are presented as mean (SD).
[b]NA indicates that data were not evaluated at this time point.
[c]Final visit data consist of results taken at the end of the study (for completers) or at study discontinuation.
[d]$p \leq .05$ vs. baseline.
Abbreviations: FSH = follicle-stimulating hormone, T3 = triiodothyronine, T4 = total thyroxine, TSH = thyroid stimulating hormone.

statistically significant changes in either group. Isolated statistically significant changes were observed on measures of T3 and T4, which increased at month 4 in adults; on measures of T3, which decreased at months 2 and 8 in older adults; and on measures of TSH, which increased at the final visit in older adults. Statistically significant decreases ($p \leq .05$) in free T4 from baseline were observed at each time point in the adult group (–0.3 pmol/L at month 2, –0.5 pmol/L at month 4, –0.4 pmol/L at month 8, and –0.5 pmol/L at the final visit). Conversely, statistically significant increases in free T4 were only detected at months 2 and 8 in the older adult group. On the reproductive axis, total testosterone, FSH, and LH, which were recorded in men only, showed no statistically significant differences at any time point except a significant increase in FSH in adult men and older adult men at month 4. Free testosterone values were statistically significantly elevated in adult men at months 1 and 2. These values returned to normal by month 4. Conversely, in older men, free testosterone values were significantly lower than baseline values at each posttreatment visit (–10.63 pg/mL at month 1, –7.28 pg/mL at month 2, –8.07 pg/mL at month 4, –8.20 pg/mL at month 8, and –8.39 pg/mL at the final visit). Morning cortisol values decreased significantly in adults at months 1, 2, 8, and the final visit and in older adults at months 1, 2, and the final visit.

For each endocrine parameter, fewer than 3% of subjects who had normal values at baseline exhibited hormone levels that were abnormal (shifts above or below the normal range) except for TSH, total testosterone, free testosterone, and morning cortisol. Abnormal TSH levels were more common among patients in the older adult group. This observation is explained in part by the fact that 36 patients (14.5%) in the older group were using thyroid medications at the start of the study. Total testosterone values that fell below 150 ng/dL were reported as endocrine adverse events (see below).

Subjects with morning cortisol values below a sex-specific lower limit of normal had the occurrence recorded as an adverse event (N = 44) and received further evaluation. Ten subjects (3 in the older adult group [all male], 7 in the adult group [1 male, 6 female]) experienced cortisol levels below 3.0 nmol/L on at least 1 occasion and had adrenal function reassessed using an adrenocorticotropic hormone stimulation test. Eight subjects had normal results, and 2 had abnormal results (1 adult male, 1 older adult male) from the adrenocorticotropic hormone stimulation test. The adult male subject was discontinued from the study and found to have persistent low blood cortisol at follow-up. The older adult male, also discontinued from the study, had normal values at follow-up. In both cases, cortisol levels were not considered related to study drug.

There were significant increases from baseline (4.9 days) in self-reported duration of menses at the first (6.1 days), sixth (5.7 days), and twelfth (5.6 days) menstrual cycles ($p \leq .05$, each). The intensity of menstrual flow remained normal for at least 80% of women at the first, sixth, and twelfth menstrual cycles.

Vital Signs and ECG

Mean changes from baseline to each subject's final visit showed no statistically significant changes in weight, heart rate, or diastolic blood pressure in either group. Very small changes in oral temperature, respiration rate, and systolic blood pressure were observed intermittently

Table 4. Treatment-Emergent Adverse Events Occurring in ≥ 5% of All Patients

Variable[a]	Adults	Older Adults	Total
Patients Taking Ramelteon[b] for 6 Months			
N	471	126	597
Any adverse event	380 (80.7)	105 (83.3)	485 (81.2)
Nasopharyngitis	67 (14.2)	13 (10.3)	80 (13.4)
Headache NOS	63 (13.4)	2 (1.6)	65 (10.9)
Upper respiratory tract infection NOS	45 (9.6)	10 (7.9)	55 (9.2)
Somnolence	36 (7.6)	11 (8.7)	47 (7.9)
Sinusitis NOS	32 (6.8)	2 (1.6)	34 (5.7)
Influenza	26 (5.5)	4 (3.2)	30 (5.0)
Patients Taking Ramelteon[b] for 1 Year			
N	370	105	475
Any adverse event	300 (81.1)	89 (84.8)	389 (81.9)
Nasopharyngitis	55 (14.9)	11 (10.5)	66 (13.9)
Headache NOS	50 (13.5)	2 (1.9)	52 (10.9)
Upper respiratory tract infection NOS	41 (11.1)	8 (7.6)	49 (10.3)
Somnolence	30 (8.1)	10 (9.5)	40 (8.4)
Sinusitis NOS	29 (7.8)	2 (1.9)	31 (6.5)
Diarrhea NOS	19 (5.1)	6 (5.7)	25 (5.3)
Influenza	21 (5.7)	3 (2.9)	24 (5.1)

[a]Values are presented as N (%) except where noted otherwise.
[b]Adult ramelteon dose = 16 mg; older adult ramelteon dose = 8 mg.
Abbreviation: NOS = not otherwise specified.

throughout the study; however, these differences had no identifiable pattern of change, and the mean values remained within normal range.

Adverse Events

Of the 1213 subjects enrolled in the study, 847 (69.8%) reported at least 1 adverse event between the time of first administration of ramelteon and 14 days after the last dose. A total of 495 subjects (40.8%) reported adverse events that were deemed by the investigator to be possibly, probably, or definitely related to administration of ramelteon. There was no difference in adverse event incidence between the 2 age groups. The percentage of subjects reporting adverse events in each category as mild (30.7%), moderate (54.2%), or severe (15.1%) and the distributions of severities were similar between the 2 age groups. One hundred forty-eight subjects (12.2%) discontinued because of adverse events (Figure 1).

The most common adverse events, occurring in at least 5% of subjects, are shown in Table 4. The overall incidence of adverse events was similar at 6 months and 1 year.

In total, 38 subjects (3.1%) experienced a serious adverse event between the time of first drug administration and 14 days after administration of their last dose. These events were distributed across 38 classifications, with most classifications including only 1 event. The only classifications with more than 1 event were chest pain (1 subject in each age group), cholelithiasis (1 subject in each age group), uterine fibroids (3 subjects in the adult group), and benign prostatic hyperplasia (2 subjects in the older adult group). Of the serious adverse events reported, 3 were felt to be possibly treatment related: cerebrovascular accident, syncope, and prolactinoma. Two subjects in the 18- to 64-year age group died during the study, both as a result of automobile accidents. Neither of the 2 automobile-related deaths occurred while the subjects were operating a motor vehicle. Both events were deemed unrelated to study drug by the study investigator.

Of the 248 older adults receiving ramelteon 8 mg/day, 1 subject was diagnosed with bladder cancer and 1 with colon cancer. Of the 965 adults receiving ramelteon 16 mg/day, 1 subject developed a prolactinoma, 1 developed a brain neoplasm, and 3 developed uterine fibroids. Only the prolactinoma was deemed possibly related to study drug by the clinical investigator; all others were deemed unrelated to study drug.

Subjective Measures of Sleep

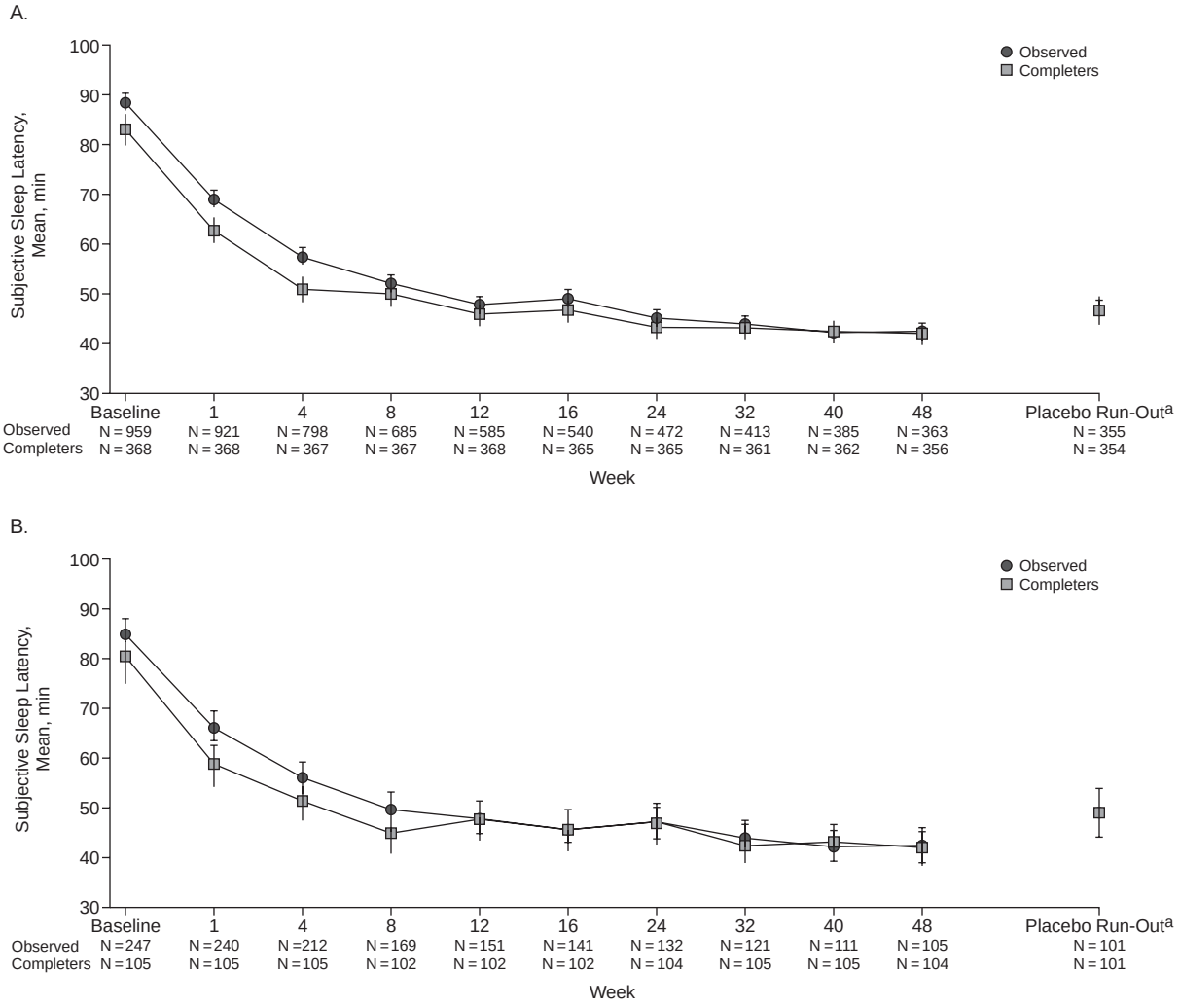
Figures 2 and 3 show mean observed values (all subjects with data available) and completer values (subjects who completed 48 weeks of treatment) for subjective sleep latency and subjective total sleep time over 48 weeks. Both adult and older adult subjects reported statistically significant reductions in subjective sleep latency and increases in subjective total sleep time at week 1. Subjects in both groups continued to report significant reductions from baseline in subjective sleep latency and subjective total sleep time at each follow-up visit (months 1 through 12).

Results from the 3 dimensions of the CGI scale were consistent with sleep assessments. For both the adult and older adult groups, baseline severity of illness was rated as 3.9 on a scale of 1 (normal) to 7 (most extremely ill). By month 12, the severity of illness rating had decreased to 2.6 among adults and 2.7 among the older adults. Change of condition, also rated on a scale of 1 (very much improved) to 7 (very much worse), was "much improved" in adults (2.3) and older adults (2.4) at month 6; this improvement was sustained for both groups through month 12 (2.2 and 2.4, respectively). Therapeutic effect, rated on a scale of 1 (very good) to 4 (unchanged or worse), was rated as "moderate" at month 6 and month 12 (at both time points: adult, 2.0; older adult, 2.2).

Discontinuation Effects

Mean subjective sleep latency and subjective total sleep time (completers) after the 3-day run-out period are shown in Figures 2 and 3. At the last visit following ramelteon discontinuation, a statistically significant increase in subjective sleep latency (adults: 6.3 minutes, $p = .0023$; older adults: 10.9 minutes, $p = .0021$) and a statistically significant decline in subjective total sleep time (adults: –9.6 minutes, $p = .0020$; older adults: –16.8 minutes, $p = .0017$) was observed. The mean values observed during the run-out period did not exceed baseline values.

Figure 2. Subjective Sleep Latency in Adults Receiving 16 mg of Ramelteon Daily (A) and in Older Adults Receiving 8 mg of Ramelteon Daily (B)

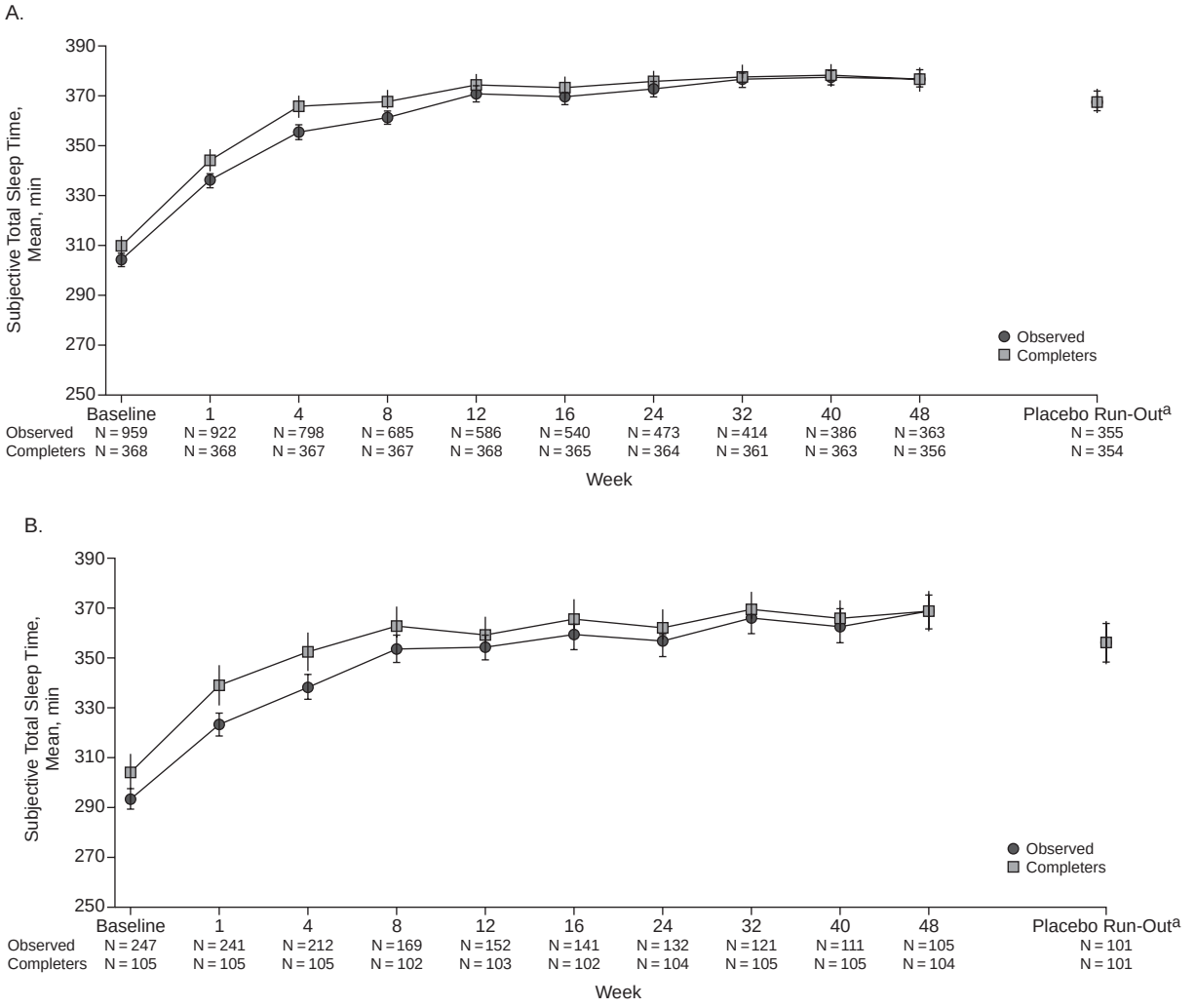


[a]Placebo run-out data point is an average of subjective sleep latency during the 3 days of placebo administration.

DISCUSSION

There were no meaningful differences in clinical laboratory values, vital signs, and body weight in this long-term, open-label study of older adults taking ramelteon 8 mg/day and adults taking ramelteon 16 mg/day. With either dose of ramelteon, average clinical chemistry, hematology, and urinalysis values were comparable at 6 months and 12 months and remained within normal range during the 48-week treatment period. Post hoc analyses demonstrated changes in vital signs (i.e., oral temperature, respiration rate, and systolic blood pressure) and ECG parameters. These analyses showed small, clinically insignificant changes with no consistent pattern of effect on each measure. Such effects may have been expected in light of the considerable power of this large study. Similarly, measures of thyroid function showed isolated, statistically significant changes from baseline over the course of 48 weeks of treatment with ramelteon in both groups. With the exception of T4, the differences returned to normal by the final visit. The incidence of abnormal T4, free T4, and T3 levels was low (< 3% of subjects). In the absence of coherent changes among the thyroid measures, isolated changes in 1 parameter are of limited clinical significance. More importantly, an open-label study of this kind needs to be considered in light of data from a placebo-controlled trial, which showed no evidence of ramelteon having an effect on thyroid function.[24] Free testosterone values were elevated in adult men in the early months of the study. These values returned to normal by month 4. Conversely, in older men, free testosterone values at each posttreatment visit were significantly lower

Figure 3. Subjective Total Sleep Time in Adults Receiving 16 mg of Ramelteon Daily (A) and in Older Adults Receiving 8 mg of Ramelteon Daily (B)



[a]Placebo run-out data point is an average of subjective total sleep time during the 3 days of placebo administration.

than baseline values. It is unlikely that this effect was dose dependent for 2 reasons: (1) the adult group was receiving twice the dosage as the older adult group, and (2) a placebo-controlled, double-blind study of endocrine effects during 6 months of ramelteon exposure shows no evidence of a drug-dependent effect on testosterone.[24] However, the double-blind, placebo-controlled study did not include older adult men, so it is possible that the effect of ramelteon on free testosterone is an age-dependent effect. Because the mean free testosterone level of older adult men (57.47 pg/mL) enrolled in the current study was relatively low at baseline (normal range: 52–280 pg/mL), it is also possible that the observed decreases in the free testosterone would have occurred even in the absence of study drug. However, without a placebo group, the latter possibility could not be assessed.

Statistically significant decreases in cortisol were observed in adults at each posttreatment visit and in older adults in the early months of the study and at final visit. The clinical significance of these cortisol changes is likely to be limited. Although morning cortisol levels had decreased to levels warranting further evaluation in 10 of 1213 subjects, adrenocorticotropic hormone stimulation tests were normal in all but 2 subjects. In a placebo-controlled endocrine study, there was no evidence of a drug-dependent effect on cortisol after 6 months of ramelteon treatment.[24]

The majority of women reported no change in the intensity of their menstrual flow, but the duration of menses significantly increased by approximately 1 day during the 48 weeks of ramelteon treatment. No clinical signs or symptoms associated with these changes were reported,

although in the absence of a complete endocrine characterization of menses, which was not measured in women during this trial, the mechanisms of these changes are unknown. A study designed to evaluate the effects of ramelteon on hormonal changes in women would be necessary to further evaluate this result. A separate placebo-controlled study indicated that there may be isolated changes in prolactin, but no changes in ovulation were observed, suggesting that the changes are not clinically significant.[24]

Although it was not possible to assess the relative incidence of adverse events without a placebo control group, the data from the current study are consistent with previous reports,[20–22,25] which suggest that ramelteon has a low incidence of adverse events. The most common adverse events in this study were respiratory infections, headache, and somnolence, which are consistent with data from previous placebo-controlled trials of ramelteon.[20–22,25] Importantly, long-term use of the drug was not associated with significant increases in the incidence of adverse events.

Numerous studies have consistently demonstrated that ramelteon is well tolerated, with the most common adverse events being headache and somnolence. Ramelteon has not been shown to cause any dose-related effects and has not shown consistent clinically meaningful, next-day residual pharmacologic effects. Ramelteon has been administered at doses up to 160 mg/day in abuse liability studies, with no safety or tolerability concerns.[23]

In this long-term, open-label study of older adults taking ramelteon 8 mg/day and adults taking ramelteon 16 mg/day, ramelteon was associated with statistically significant improvements in subjective sleep latency and subjective total sleep time relative to baseline that were manifest at the initial assessment (week 1) and sustained over 48 weeks of treatment. These results are consistent with previously reported double-blind studies of the safety and efficacy of ramelteon for up to 6 months in adults[20,26] and older adults[21,25] with chronic insomnia. However, in the absence of a placebo control group, the ability to interpret the effects of ramelteon on sleep from this study is limited. The improvements in sleep latency may result from improved sleep behaviors required for the study and cannot be solely attributed to ramelteon.

Discontinuation of ramelteon resulted in a modest reversal of subjective sleep latency (6.3-minute increase from month 12 in older adults and 10.9-minute increase from month 12 in older adults). However, subjective sleep latency after discontinuation (46.6 minutes for adults and 49.2 minutes for older adults) did not revert back to baseline levels (88.8 minutes for adults and 85.1 minutes for older adults). This suggests that, unlike other sleep medications,[27–30] ramelteon may not exhibit rebound insomnia (traditionally defined as a return to baseline levels of sleep impairment), although the lack of a placebo control in this study prevents any definitive conclusions from being drawn.

CONCLUSION

The MT_1/MT_2 melatonin receptor agonist ramelteon was administered for up to 1 year to adult and older adult subjects with chronic primary insomnia. The safety profile of ramelteon during long-term use was comparable to that observed in randomized, controlled trials of ramelteon for up to 35 days. Subjective measures of sleep suggest that ramelteon may be associated with improved sleep characteristics within the first week of treatment that are sustained during long-term use.

Drug names: eszopiclone (Lunesta), ramelteon (Rozerem), temazepam (Restoril and others), triazolam (Halcion and others), zaleplon (Sonata and others), zolpidem (Ambien and others).

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