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Brief Communication

Use of a post-sleep questionnaire-interactive voice response system (PSQ-IVRS) to evaluate the subjective sleep effects of ramelteon in adults with chronic insomnia

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ABSTRACT

Objective: Ramelteon is an MT_1/MT_2 melatonin receptor agonist approved in the US and Japan for the treatment of sleep-onset insomnia. This study evaluated the effects of ramelteon 8 mg on patient reported sleep parameters in adults with chronic insomnia in an at-home setting using a post-sleep questionnaire-interactive voice response system (PSQ-IVRS).

Methods: Adults aged 18–64 years with chronic insomnia were randomized to receive ramelteon 8 mg or placebo nightly for 3 weeks. Sleep parameters were assessed via PSQ-IVRS within 60 min of awakening each morning. Adverse effects were collected throughout the study.

Results: A total of 552 subjects (mean age 43.2 years) received treatment (274 ramelteon, 278 placebo). There was a reduction in mean sleep latency at weeks 1, 2, and 3 compared with placebo but none reached statistical significance (−4.1 min, $p = 0.088$ week 1; −2.8 min, $p = 0.258$ week 2; −4.9 min, $p = 0.060$ week 3). There were no significant differences between placebo and ramelteon in other PSQ-IVRS sleep parameters. Only headache (18 [6.5%] placebo, 18 [6.6%] ramelteon) and somnolence (5 [1.8%], 12 [4.4%] ramelteon) occurred in > 3% of subjects.

Conclusions: Use of ramelteon 8 mg in an at-home setting did not demonstrate statistically significant improvements in subjective sleep latency compared with placebo, when measured by PSQ-IVRS.

1. Introduction

Insomnia is a condition characterized by difficulty falling asleep, difficulty maintaining sleep, or nonrestorative sleep [1]. Chronic insomnia (defined as symptoms persisting for greater than 1 month) affects approximately 10% of the adult population and is associated with significant daytime impairments or distress and an overall lower quality of life [2,3].

Ramelteon is an MT_1/MT_2 melatonin receptor agonist approved in the US and Japan for the treatment of insomnia characterized by difficulty with sleep onset [4]. Ramelteon has a mechanism of action different from other prescription insomnia medications in the US. It acts through MT_1 and MT_2 melatonin receptors, which help regulate the body's normal sleep–wake cycle, and does not cause general central nervous system sedation [5,6]. In previous studies of adults with chronic insomnia, ramelteon has demonstrated the ability to significantly reduce objective latency to persistent sleep (LPS) [7–10]. Reductions in subjective sleep onset latency have been less consistent [7,9–11]. Overall, ramelteon is well tolerated with no evidence of consistent next-day residual effects, withdrawal, or potential for abuse [6–13].

The reasons for the lack of consistent subjective efficacy with ramelteon may include methodological issues (i.e., evaluations at home vs. in the lab, sleep diary vs. questionnaire, compliance with medication timing, previous use of benzodiazepine receptor agonists), inherent population differences (i.e., age, geographic location), possible subjective overemphasis of sleep difficulties that are not detected when objective measurements are performed, or a result of ramelteon's different mechanism of action (no general sedating effect). For these reasons, both objective and subjective measurements of sleep efficacy are used to provide important and complimentary information about the efficacy of sleep medications. This view is consistent with most regulatory bodies, which require both objective and subjective data for supporting the efficacy of hypnotics [14,15].

This study was designed to evaluate the effects of ramelteon 8 mg in adults with chronic insomnia in an at-home setting using a post-sleep questionnaire-interactive voice response system

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(PSQ-IVRS). The PSQ-IVRS is a sleep questionnaire that was designed to address possible methodological issues in collecting subjective data from subjects at home and provide consistency in reporting.

2. Methods

Adults aged 18–64 years with chronic insomnia [1] were recruited for this study. Eligible subjects were required to report a habitual bedtime between 10 pm and 1 am with a history of subjective sleep latency (sSL) $\geqslant$ 60 min and a total subjective sleep time (sTST) $\leqslant$ 6.5 h. All subjects were required to adhere to a sleep schedule during the study (bedtime within 30 min of habitual bedtime, remaining in bed > 6.5 h nightly). Subjects were excluded from the study if they had experienced any recent sleep schedule changes, history of significant medical or psychiatric disorder (within the past 6 months), drug or alcohol abuse (within the past 12 months), or history of primary sleep disorder other than insomnia.

Initial screening consisted of a physical exam, electrocardiogram, and medical and sleep histories. Subjects then underwent a secondary single-blind placebo screening process (day −7 to day 1). All subjects were required to complete the PSQ-IVRS survey within 60 min of awakening (consisted of filling out the PSQ on paper and then calling in the responses to the automated system). In addition, a subset of subjects (inpatient group) underwent polysomnography (PSG) screening in the sleep laboratory for two consecutive nights followed by 5 days of at-home treatment to validate the insomnia complaint. These subjects completed the PSQ-IVRS at home and in the sleep lab. All subjects were required to have a sSL of $\geqslant$ 45 min and an sTST of $\leqslant$ 6.5 h on at least three of the first five nights at home of the single-blind run-in period and the difference between the average sSL from days −7 to −5 and days −3 to −1 was required to be $\leqslant$ 20 min. A PSG-validated subset of the inpatient group, defined post hoc, was required to have a mean LPS on nights −7 to −6 > 20 min, with LPS > 15 min on each individual night.

Subjects who qualified were then randomized to receive nightly ramelteon 8 mg or placebo 30 min before bedtime for 21 days. Every morning they completed the PSQ-IVRS within 60 min of awakening. Subjects in the inpatient group also reported to the sleep lab on nights 1–2 and night 21 for PSG recording. The primary endpoint was mean sSL at week 3 for all subjects, with secondary endpoints including mean sSL at weeks 1 and 2, and sTST, sWASO, NAW, and quality of sleep at each week. A post hoc analysis was performed on the sleep data from the PSG-validated subset (mean sSL, mean LPS on nights 1–2 and night 21, and mean sSL after PSG recording on days 2–3 and day 22 in the lab).

A 1-week single-blind placebo run-out period followed the treatment period. Subjects continued to complete the PSQ-IVRS each morning, and rebound insomnia (defined as change from baseline in mean sSL for nights 22–28) was assessed.

Adverse events (AEs) were collected throughout the study. Physical exams, clinical laboratory tests, and electrocardiograms were performed at screening, randomization, and the final follow-up visit.

This study was conducted according to the World Medical Association Declaration of Helsinki, the ICH Harmonised Tripartite Guideline for GCP, and all applicable FDA laws and regulations. Informed consent was obtained for each subject before the start of the trial.

Statistical analyses were made using last observation carried forward data from the full analysis set (all subjects who were randomized and received at least one dose of study medication). Comparisons between ramelteon and placebo were made using *t* tests with least square (LS) means and SEs obtained from an ANCOVA model, with treatment and pooled center as factors and baseline values as a covariate.

3. Results

A total of 556 subjects were randomized, 247 (44.4%) were inpatients, and 309 (55.6%) outpatients. Of these, 552 subjects received treatment (274 ramelteon, 278 placebo) and 441 completed the study (212 ramelteon, 229 placebo). The mean age (SD) was 43.2 (12.5) years and the majority of subjects were women (357, 64.7%). A total of 176 subjects were identified in the PSG-validated subset (84 ramelteon, 92 placebo).

Overall there was a reduction in mean sSL at weeks 1, 2, and 3 compared with placebo but none of these reductions reached statistical significance (Fig. 1). There were no significant differences between placebo and ramelteon in sTST, sWASO, sNAW, or sleep quality at any timepoint.

In the PSG-validated subset, there was a statistically significant reduction in mean LPS for the ramelteon group compared with the placebo group at nights 1–2 (22.2 min vs. 42.3 min, $P < 0.001$) and night 21 (21.6 min vs. 38.9 min, $p = 0.013$). There was also a reduction in sSL for the ramelteon group compared with the placebo group that reached statistical significance at week 3 (Fig. 2).

There was no evidence of rebound insomnia detected during the placebo run-out for either the placebo or ramelteon groups. Only headache (18 [6.5%] placebo, 18 [6.6%] ramelteon) and somnolence (5 [1.8%] placebo, 12 [4.4%] ramelteon) occurred in > 3% of subjects from either group. Overall, the proportion of subjects with any treatment-related AEs was similar between groups (placebo 15.4%, ramelteon 16.5%).

4. Discussion

This study showed no significant improvements for ramelteon over placebo in subjective sleep measurements using the PSQ-IVRS in an at-home setting for adults with complaints of insomnia. However, a post hoc analysis of a subset of subjects whose sleep complaints were verified by PSG did show significant reductions in sSL at week 3. This suggests that the lack of consistent subjective efficacy with ramelteon may have more to do with the severity of the sleep disturbance of the population studied and the setting than that of data collection. In the PSG-validated subset, patient reports of difficulty falling asleep were confirmed by PSG in the sleep lab, while the majority of subjects did not have the objective verification. Previous studies have shown that patient reports of sleep latency are often overestimated and may not correlate with objective measurements [16]. It is also possible that being in the sleep lab for several days during the study reinforced medication compliance and good sleep practices that may have helped with the perception of sleep improvement.

The results of the objective sleep measurements do show significant reductions in LPS, confirming previous studies demonstrating that ramelteon improves sleep latency when measured by PSG [7–10]. Ramelteon's non-sedating mechanism of action may be a factor in the discrepancy between the objective and subjective efficacy results. A study of ramelteon 4 mg showed that prior experience with sedating sleep medications may influence the subjective experience of ramelteon. In that study, subjects with no prior hypnotic experience reported significant improvements in sSL while those with prior hypnotic experience reported no significant differences between ramelteon and placebo despite significant improvements in PSG-measured sleep latency [17].

Overall, in this study of adults with chronic insomnia, ramelteon did not demonstrate subjective improvements in sleep latency in an at-home setting, as measured by the use of the PSQ-IVRS. A post hoc analysis did demonstrate improvements in sSL for subjects with PSG-validated sleep complaints, but the use of the