Ramelteon (TAK-375), A Selective MT1/MT2-Receptor Agonist, Reduces Latency to Persistent Sleep in a Model of Transient Insomnia Related to a Novel Sleep Environment

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ated at 14 sleep centers in the United States. To be eligible, volunteers had to report a usual total sleep duration of 6.5 to 8.5 hours, a usual sleep latency of 30 minutes or less, and a habitual bedtime between 8:30 PM and midnight. Pregnant or nursing women were excluded. Participants were required to be within 20% of their ideal body weight and to be in good overall health, as determined by medical history, physical examination, clinical laboratory values, and 12-lead electrocardiogram.

Volunteers were excluded if they had previously slept in a sleep laboratory, had an Epworth Sleepiness Scale score > 10, had changed sleep schedules within the preceding 3 months (eg, shift work), had flown across 3 or more time zones within the preceding 7 days, had signs or symptoms of any primary sleep disorder, or had any physical or psychiatric disorder (including substance abuse) that could be associated with a sleep disturbance. Prescription medication and over-the-counter medication were discontinued 5 half-lives before administration of study medication.

The study was approved by an Institutional Review Board for each participating site, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Each participant was given written information about the study and their rights, as approved by the investigator's Institutional Review Board, and gave written consent before any study-related procedures were conducted.

Procedures

Eligible subjects were stratified into 2 groups according to reported usual sleep duration (6.5 to 7.5 or 7.5 to 8.5 hours) and then randomly assigned with double-blind procedures to 1 of 3 groups: 16 mg ramelteon, 64 mg ramelteon, or placebo. This procedure allowed the randomized groups to have approximately equal distributions of sleep duration, as a subject's habitual total sleep time (TST) could differentially impact drug response.

On the day of drug administration, subjects were instructed to (1) eat a moderate evening meal and arrive at the sleep laboratory 1.5 to 2 hours before their habitual bedtime and (2) refrain from consumption of alcohol for the preceding 48 hours and from consumption of caffeine-containing products for the preceding 6 hours. Vital signs and any changes to medical history were recorded, and specimens for clinical laboratory tests (hematology, serum chemistry, and urinalysis) were collected. Subjects were prepared for polysomnography (PSG) recordings, and drug was administered orally with water 30 minutes before scheduled bedtime. PSG recordings were performed continuously for 8 hours.

Approximately 30 minutes following PSG termination, morning toilet, and breakfast, subjects completed a postsleep questionnaire and the Digit Symbol Substitution Test (DSST). Before leaving the laboratory, physical examination, vital signs, blood and urine sample collection, 12-lead electrocardiogram, and recording of concomitant medications and adverse events were completed for safety assessment.

PSG records were scored by a single center. Interscorer reliability was maintained at 90%. The primary efficacy measure was mean latency to persistent sleep (LPS) as measured by PSG (ie, time in minutes to the first of 20 consecutive epochs of sleep). Other PSG measures included TST, wake time after sleep onset (WASO), percentage of sleep time in each sleep stage, and number of awakenings. Subjective efficacy measures collected from the post-sleep questionnaire were subjective sleep latency, subjective TST, subjective number of awakenings, and subjective sleep quality. Residual drug effects were assessed by DSST and 7-point categorical scales for level of alertness and ability to concentrate from the postsleep questionnaire.

Statistical Analyses

A sample size of at least 120 subjects in each of the 3 treatment groups was determined on the basis of 90% power to detect a 10-minute difference in LPS, with a standard deviation of 22 minutes, using 2-sided t tests with a Bonferroni correction for multiple comparisons and a significance level of .05. The estimates for differences in LPS were obtained from a similar study of the hypnotic agent zolpidem.13

Significance for most measures was determined by 2-way analysis of variance (ANOVA) with terms for center, treatment, and center-by-treatment interaction. Subsequent pairwise comparisons were performed using the Dunnett t test and least-squares means obtained from the ANOVA to assess each active-treatment arm in comparison to placebo. The 2 active-treatment arms were not directly compared. The ease of falling back to sleep was analyzed using the Cochran-Mantel-Haenszel test with effects for treatment and center.

RESULTS

Overall, 375 subjects were enrolled in the study and randomly assigned to 16 mg ramelteon (n = 126), 64 mg ramelteon (n = 126), or placebo (n = 123). All assigned subjects completed the study. Demographic and baseline characteristics of subjects are shown in Table 1. There were no significant differences among the 3 treatment groups in terms of age, sex, or racial distribution; baseline Epworth Sleepiness Scale score; usual sleep duration; or characteristics of sleep history (data not shown). The PSG recordings were unavailable (ie, lost or deemed unreadable) for 5 subjects. As a consequence, the reported PSG results are derived from 370 subjects; subjective assessments include all 375 subjects.

Sleep

Mean PSG values and ANOVA results are shown in Table 2. Main condition effects for LPS and TST were significant. Paired comparisons indicated that both dosage levels of ramelteon were associated with a statistically significant decrease in mean LPS and significant increases in mean TST, and, therefore, sleep efficiency. The differences in WASO between the ramelteon groups and the placebo group were not statistically significant. The number of awakenings after persistent sleep (P = .793) and the number of awakenings lasting longer than 2 minutes (P = .853) also did not differ among treatment groups.

There were no statistically significant differences among the 3 groups for percentage of TST spent in any sleep stage.

Subjective sleep measures were evaluated using a postsleep questionnaire, and the results of the ANOVA are shown in Table 2. There was a main effect of treatment for subjective SL. Participants in the 16-mg ramelteon group reported a significantly shorter subjective SL than those in the placebo group. The mean subjective SL in the 64-mg group was similar to that seen in the 16-mg group but did not differ significantly from placebo.
There was a trend toward significance for the main effect of treatment on subjective TST. However, paired comparisons showed that subjective measures of TST did not differ significantly. Similarly, the subjective number of awakenings ($P = .441$) and the subjective ease of falling back to sleep ($P = .349$) did not differ from placebo for either ramelteon group.

### Safety Assessments

Mean DSST, subjective alertness ratings, and ability to concentrate scores are shown in Table 3. There were no statistically significant differences among the groups for mean DSST scores. The 64-mg group reported small but statistically significant declines in

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**Table 1**—Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ramelteon (16 mg)</th>
<th>Ramelteon (64 mg)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.0 ± 7.1</td>
<td>44.7 ± 6.6</td>
<td>43.9 ± 7.0</td>
<td>0.559</td>
</tr>
<tr>
<td>&lt; 50 years, n (%)</td>
<td>96 (78)</td>
<td>105 (83)</td>
<td>100 (79)</td>
<td>0.509</td>
</tr>
<tr>
<td>&gt; 50 years, n (%)</td>
<td>27 (22)</td>
<td>21 (17)</td>
<td>26 (21)</td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>76 (62)</td>
<td>82 (65)</td>
<td>71 (56)</td>
<td>0.388</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>103 (84)</td>
<td>110 (87)</td>
<td>107 (85)</td>
<td></td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>15 (12)</td>
<td>10 (8)</td>
<td>13 (10)</td>
<td></td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>5 (4)</td>
<td>6 (5)</td>
<td>6 (5)</td>
<td></td>
</tr>
<tr>
<td>Baseline ESS score, mean</td>
<td>4.5</td>
<td>5.1</td>
<td>5.1</td>
<td>0.114</td>
</tr>
<tr>
<td>Reported usual sleep duration, h</td>
<td>7.4</td>
<td>7.4</td>
<td>7.5</td>
<td>0.298</td>
</tr>
<tr>
<td>Usual sleep time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5 to 7.4 h, n (%)</td>
<td>53 (43)</td>
<td>54 (43)</td>
<td>49 (39)</td>
<td>0.737</td>
</tr>
<tr>
<td>7.5 to 8.5 h, n (%)</td>
<td>70 (57)</td>
<td>71 (57)</td>
<td>77 (61)</td>
<td></td>
</tr>
</tbody>
</table>

ESS refers to Epworth Sleepiness Scale.

*Overall P value for continuous variables from analysis of variance. Overall P value for categorical variables from Cochran-Mantel-Haenszel test for general association.

†P value was calculated using all 5 race categories (White, Black, Hispanic, Asian, other)

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**Table 2**—Statistical Results from Polysomnography and Subjective Efficacy Parameters

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 123</th>
<th>Ramelteon (16 mg) n = 124</th>
<th>Ramelteon (64 mg) n = 123</th>
<th>Overall P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to persistent sleep, min</td>
<td>24.6 ± 21.9</td>
<td>14.1 ± 15.1</td>
<td>15.5 ± 15.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>411.3 ± 41.7</td>
<td>425.4 ± 37.6</td>
<td>422.4 ± 34.8</td>
<td>.008</td>
</tr>
<tr>
<td>Wake time after sleep onset, min</td>
<td>42.1 ± 33.3</td>
<td>37.4 ± 28.1</td>
<td>39.5 ± 25.7</td>
<td>.436</td>
</tr>
<tr>
<td>Mean number of awakenings</td>
<td>6.7 ± 3.69</td>
<td>6.8 ± 4.01</td>
<td>7.0 ± 3.98</td>
<td>.793</td>
</tr>
<tr>
<td>TST in stage 1 sleep, %</td>
<td>12.6 ± 6.2</td>
<td>11.7 ± 5.5</td>
<td>12.8 ± 6.1</td>
<td>.282</td>
</tr>
<tr>
<td>TST in stage 2 sleep, %</td>
<td>58.0 ± 8.9</td>
<td>59.3 ± 9.2</td>
<td>58.9 ± 8.2</td>
<td>.426</td>
</tr>
<tr>
<td>TST in stage 3/4 sleep, %</td>
<td>9.8 ± 9.1</td>
<td>8.7 ± 9.0</td>
<td>8.2 ± 7.5</td>
<td>.280</td>
</tr>
<tr>
<td>TST in REM sleep, %</td>
<td>19.6 ± 5.7</td>
<td>20.3 ± 6.3</td>
<td>20.0 ± 6.0</td>
<td>.648</td>
</tr>
<tr>
<td>Subjective sleep latency, min</td>
<td>31.2 ± 26.8</td>
<td>22.2 ± 24.1</td>
<td>25.4 ± 28.3</td>
<td>.022</td>
</tr>
<tr>
<td>Subjective total sleep time, min</td>
<td>410.6 ± 56.0</td>
<td>427.8 ± 57.4</td>
<td>419.9 ± 56.7</td>
<td>.060</td>
</tr>
<tr>
<td>Subjective sleep quality‡</td>
<td>3.3 ± 1.0</td>
<td>3.1 ± 1.2</td>
<td>3.5 ± 1.1</td>
<td>.012</td>
</tr>
<tr>
<td>Subjective number of awakenings</td>
<td>3.2 ± 2.20</td>
<td>3.1 ± 1.97</td>
<td>3.5 ± 2.74</td>
<td>.441</td>
</tr>
<tr>
<td>Subjective ease of falling back to sleep§, % responding yes</td>
<td>23.2%</td>
<td>22.2%</td>
<td>30.4%</td>
<td>.349</td>
</tr>
</tbody>
</table>

Results are presented as mean ± SD. TST refers to total sleep time; REM, rapid eye movement.

*Significance of overall treatment effect vs placebo was assessed by 2-way analysis of variance.

†Pairwise comparison with placebo by the Dunnett t test (from analysis of variance). Pairwise comparison P values are provided when the overall treatment P value is significant.

‡Rating scale: 1 = excellent, 7 = extremely poor

§Ease of falling back to sleep was measured by the answer to the question “Did you have difficulty falling back to sleep? Yes or No.” Data are presented as percentage of subjects responding yes.
subjective levels of alertness and ability to concentrate, as compared to the placebo group. The 16-mg group was not significantly different from the placebo group on any of these measures.

No serious adverse events were reported or observed. Overall, 63 subjects reported at least 1 adverse event (n = 21 for placebo; n = 20 for 16 mg; n = 22 for 64 mg). No adverse events were dose related. The most common adverse event was headache; other adverse events reported in more than 2% of subjects in any treatment group were fatigue, somnolence, nausea, and dizziness (Table 4). There were no consistent or clinically important differences in vital signs, clinical laboratory values, or electrocardiographic findings between the 2 treatment groups. No subject discontinued the study because of an adverse event, abnormal laboratory test, vital sign measurement, electrocardiographic finding, or physical examination finding.

**DISCUSSION**

Preclinical data have shown ramelteon to be a selective melatonin-receptor agonist with a high affinity for MT1 and MT2 receptors and a low affinity for MT3 receptors. In addition, ramelteon shows no measurable affinity for any of a large number of other ligand binding sites, including GABA, benzodiazepine, dopamine, and opiate receptors. The availability of a pharmacologic treatment for insomnia that acts at the MT1/MT2 receptor rather than the benzodiazepine receptors will diversify the overall therapeutic approach to insomnia.

In the current study, ramelteon, 16 or 64 mg, administered 30 minutes before habitual bedtime reduced LPS in a model of transient insomnia related to sleeping in a novel environment. Both ramelteon doses were associated with increases in TST, primarily due to reduced wakefulness before sleep onset. Neither ramelteon dose altered sleep architecture. Both ramelteon doses were well tolerated in this single-dose model.

The results obtained in this study have several interesting aspects that differentiate ramelteon from the benzodiazepine-receptor agonists traditionally used for the management of insomnia. First, there appears to be a flat dose-response curve. Despite a 4-fold difference in dose, there was only a 1.5-minute difference between 16 and 64 mg of ramelteon on the primary endpoint LPS. The difference in TST between the doses was only 3 minutes. A 4-fold difference with benzodiazepine-receptor agonist dose, in the therapeutic range, would typically show a much larger difference on a variety of sleep parameters in addition to an increase in side effects. The only dose effects seen were the increased difficulty concentrating and alertness seen with the 64-mg but not the 16-mg dose. This general lack of a dose-response curve with ramelteon needs to be confirmed with other doses. If confirmed, it suggests a sleep on-off switch type of therapeutic response that may need only 1 dose. No serious adverse events were reported or observed. Overall, 63 subjects reported at least 1 adverse event (n = 21 for placebo; n = 20 for 16 mg; n = 22 for 64 mg). No adverse events were dose related. The most common adverse event was headache; other adverse events reported in more than 2% of subjects in any treatment group were fatigue, somnolence, nausea, and dizziness (Table 4). There were no consistent or clinically important differences in vital signs, clinical laboratory values, or electrocardiographic findings between the 2 treatment groups. No subject discontinued the study because of an adverse event, abnormal laboratory test, vital sign measurement, electrocardiographic finding, or physical examination finding.

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out to determine the efficacy of ramelteon as well as the dose-
response effects in subjects with chronic insomnia. Finally, while
the DSST did not show any residual effects, decreased morning
ability to concentrate and level of alertness was found in the 64-
mg group. This is surprising given the short half-life of ramelteon
as well as the fact that hypnotic activity as evidenced by
WASOnset as well as number of awakenings was not evident
with either dose. Thus, while it is likely that residual effects do
not occur with ramelteon even at the highest doses, this conclu-
sion needs to be validated with additional studies. The absence
of significant adverse events and clinically significant alterations in
vital signs and clinical laboratory values (in addition to the low
abuse potential [based on preclinical data] associated with
ramelteon MT1/MT2-receptor activity7,15) support further investi-
gation of ramelteon. No significant residual effects of 16 mg and
64 mg of ramelteon on DSST, in comparison to placebo, were
observed. The lack of a significant effect on DSST is consistent
with the 1.3-hour half-life of ramelteon (16-mg dose) and the 2.6-
hour half-life of its active metabolite M-II,9 although the absence
of an active control condition limits the strength of our conclu-
sions about residual effects on the DSST.

In conclusion, the results of the current study demonstrate a
significant reduction in LPS and increase in TST with ramelteon
treatment, without alteration of sleep architecture or significant
side effects, in a model of transient insomnia related to sleeping
in a novel environment. The mechanism of ramelteon (selective
MT1/MT2 agonism) may offer a novel way to treat insomnia.

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