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Research paper

# Efficacy and safety of sublingual ramelteon as an adjunctive therapy in the maintenance treatment of bipolar I disorder in adults: A phase 3, randomized controlled trial☆

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ABSTRACT

*Background:* The optimal long-term management strategy for bipolar I disorder patients is not yet established. Evidence supports the rationale for circadian rhythm regulation to prevent mood episode relapse in bipolar patients. This study evaluated the efficacy and safety of a new sublingual formulation of the melatonin receptor agonist ramelteon (ramelteon SL) as adjunctive therapy in the maintenance treatment of bipolar I patients.

*Methods:* In a double-blinded trial in the United States and Latin America, adult bipolar I disorder patients stable for ≥ 8 weeks before baseline and with a mood episode 8 weeks to 9 months before screening, were randomized to once-daily ramelteon SL 0.1 mg (n = 164), 0.4 mg (n = 160), or 0.8 mg (n = 154), or placebo (n = 164), in addition to their existing treatment. The primary endpoint was time from randomization to relapse of symptoms. The prespecified futility criterion in a planned, unblinded, independent interim analysis was the failure of all ramelteon SL doses to achieve a conditional power ≥ 30% compared with placebo.

*Results:* No significant differences between any dose of ramelteon SL and placebo were observed. The study was terminated after meeting the futility criteria. Ramelteon SL was well tolerated, with a safety profile consistent with that for oral ramelteon.

*Limitations:* A low rate of relapse events precluded detection of any statistically significant difference between groups.

*Conclusions:* The study failed to demonstrate the efficacy of ramelteon SL as adjunctive maintenance therapy for bipolar disorder. Interim analyses for futility in clinical studies are valuable in preventing unnecessary exposure of subjects to interventions.

## 1. Introduction

Bipolar disorder is a chronic condition characterized by severe disturbances in mood and levels of energy and activity (Vázquez et al., 2015). It typically follows a lifelong episodic course, with multiple recurrences of mania/hypomania, depressive or psychotic episodes, or mixed states (Vázquez et al., 2015). Multiple relapses are associated with a poor prognosis, including psychiatric and clinical morbidity, and increased suicidality (Peters et al., 2016). The principal aim of pharmacologic intervention is to achieve remission from acute symptoms and restabilize the patient by preventing future episodes of mood disturbances or reducing the frequency and severity of episodes; this

*Abbreviations:* AE, adverse event; CGI-S, Clinical Global Impression – Severity; CP, conditional power; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ECT, electroconvulsive therapy; FAS, full analysis set; HAM-A, Hamilton Anxiety Scale; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; MT1, melatonin receptor type 1; MT2, melatonin receptor type 2; PTE, pretreatment event; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; RSQ-W, Response Style Questionnaire; SD, standard deviation; SE, standard error; SL, sublingual; TEAE, treatment-emergent adverse event; YMRS, Young Mania Rating Scale

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requires long-term preventative or so-called maintenance treatments (Grunze et al., 2013; Malhi et al., 2015). However, the likelihood of relapse during maintenance therapy has been found to be greater for patients with a higher number of previous episodes of mania or depression (Berk et al., 2011), and the interval between episodes is inversely related to the number of previous episodes (Kessing et al., 1998). In clinical practice, several medications are routinely prescribed for maintenance therapy (Grunze et al., 2013; Post et al., 2010), with options that include mood stabilizers, anticonvulsants, antipsychotics, and antidepressants (Goodwin et al., 2016; Grunze et al., 2013; Yatham et al., 2013). However, the success rates of current maintenance therapies remain inadequate: annual recurrence rates from pooled real-world and controlled clinical trials are estimated to be 26.3% and 21.9%, respectively (Vázquez et al., 2015). In the analysis by Vázquez et al. (2015), rates of recurrence for different treatment types ranged from 14.6% per year for an antipsychotic combined with a mood stabilizer, to 40.3% per year for imipramine. The central importance of maintenance therapy in bipolar I disorder and the limitations of existing treatments highlight the need for new treatments with different therapeutic targets. More effective maintenance treatments for bipolar patients will help establish the optimal long-term management strategy that is currently lacking (Goodwin et al., 2016).

Sleep and circadian rhythm disruption are hallmarks of bipolar I disorder (Abreu and Bragança, 2015; McClung, 2007). Clinical evidence indicates that these abnormalities become more marked before the onset of both manic and depressive episodes, and that they contribute to relapse (Harvey, 2008; Harvey et al., 2009). Observations with existing therapies also provide a rationale for investigating the modulation of circadian rhythms as a target for maintenance therapy in bipolar I disorder. Clinical and preclinical studies have shown that both lithium and valproate have a stabilizing effect on circadian rhythms, which has been linked to their therapeutic effect in patients with bipolar I disorder (Landgraf et al., 2016; Moreira and Geoffroy, 2016). New, more effectively targeted pharmacologic treatments could help regulate circadian rhythms as a targeted maintenance strategy in bipolar patients.

Melatonin is a key hormone in sleep–wake regulation (Pandi-Perumal et al., 2006), and studies have shown changes in the levels and phases of melatonin secretion in bipolar individuals (Lam et al., 1990; Nurnberger Jr. et al., 2000; Robillard et al., 2013; Srinivasan et al., 2006). By directly binding to melatonin receptor type 1 (MT1) and type 2 (MT2) (Reppert et al., 1995; Rodriguez et al., 2004), melatonin influences the central clock located in the suprachiasmatic nucleus of the hypothalamus (Reppert and Weaver, 2001), and alters the phase and amplitude of circadian cycles (Dijk et al., 2012). A lack of MT1 signaling has been shown to contribute to behavioral abnormalities, including an increase in depressive-like behaviors in a murine model (Weil et al., 2006). Moreover, evidence from interventions in clinical trials suggests that resynchronization of circadian rhythms through modulation of the melatonin receptors may provide a specific and effective means of treating bipolar disorder, and may help to reduce cognitive/mood impairment (Calabrese et al., 2007; McElroy et al., 2011; Norris et al., 2013). To date, the evidence for agomelatine, an MT1 and MT2 agonist, has been mixed. In an open-label study of acute therapy, agomelatine demonstrated some efficacy as an adjunctive treatment for patients with bipolar I disorder experiencing a major depressive episode (Calabrese et al., 2007). However, a more recent randomized, double-blinded, placebo-controlled trial found that there was no difference between adjunctive agomelatine treatment and placebo in the improvement of depressive symptoms in patients with bipolar I disorder (Yatham et al., 2016).

Ramelteon is a highly selective MT1 and MT2 agonist (Kato et al., 2005), and it is approved as an oral 8 mg tablet formulation in the (US) for the treatment of insomnia (Takeda Pharmaceuticals America Inc, 2010). Clinical data indicate that ramelteon can induce sleep in patients with insomnia without producing general central nervous system depressant effects or substance abuse and dependence symptoms that are associated with other treatments for insomnia (Erman et al., 2006; Miyamoto, 2009; Pandi-Perumal et al., 2011; Rush et al., 1999). Thus, it seems a better treatment option for bipolar patients because this patient population has high rates of substance abuse: a prevalence rate of 60.7% was reported in the US epidemiological study by Regier et al. (Maremmani et al., 2012; Quello et al., 2005; Regier et al., 1990), and the lifetime prevalence rate was 32% in a recent Danish population-based study (Toftdahl et al., 2016). In a randomized study, ramelteon improved depressive symptoms in bipolar patients with manic symptoms and sleep disturbance (McElroy et al., 2011). More recently, in an investigator-initiated, double-blind, randomized study in patients with euthymic bipolar disorder and sleep disturbances, ramelteon-treated participants were approximately twice as likely to remain stable throughout the 24-week trial as participants treated with placebo. These results suggest the potential benefit of ramelteon maintenance therapy (Norris et al., 2013).

Building upon these preliminary results, the current study was conducted to evaluate the efficacy and safety of ramelteon maintenance therapy as an adjunct to existing medication options in preventing relapse in stable patients with bipolar I disorder. The study used an investigational sublingual formulation of ramelteon (ramelteon SL, previously known as TAK-375SL) that was developed to overcome the low absolute oral bioavailability of ramelteon, which results from extensive first-pass metabolism (Karim et al., 2006; Takeda Pharmaceuticals America Inc, 2010).

## 2. Methods

### 2.1. Design

The study was performed in accordance with Good Clinical Practice guidelines and adhered to the principles of the Declaration of Helsinki. The protocol was approved by the appropriate central or local independent Institutional Review Board. All subjects were required to provide written informed consent before study participation. The written consent embodied all the elements of informed consent as described in the World Medical Association Declaration of Helsinki and the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and applicable local or regional regulatory requirements.

This was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study conducted between December 2011 and March 2015. Subjects were screened for eligibility within 30 days before randomization into a 12-month, double-blind treatment period. Eligible subjects were randomized in a 1:1:1:1 ratio via an interactive voice/web response system to one of four treatment groups: ramelteon SL 0.1, 0.4, or 0.8 mg, or sublingual placebo. These doses were selected for three reasons. Firstly, in a previous study, subjects treated with an oral ramelteon formulation at a dose of 8 mg for the maintenance therapy of bipolar I disorder were less likely to relapse than those receiving placebo (Norris et al., 2013). Secondly, in light of the hypothesis that lower doses of melatonin are more effective chronobiotic agents, as supported by circadian physiology and the mechanism of action of melatonin (Anwar et al., 2015; Hack et al., 2003; Lewy et al., 2001). Finally, results from a prior pharmacokinetic study show that the exposure (measured as area under the concentration–time curve) attained with 0.5 mg ramelteon was similar to the exposure attained with a ramelteon 8 mg oral formulation. Subjects took ramelteon SL every evening at bedtime. Study medication was adjunctive to ongoing non-study treatment, defined as the use of the following approved medications with an indication for maintenance treatment of bipolar I disorder: antidepressants (except fluvoxamine); mood stabilizers (including lithium, valproate, and lamotrigine); and atypical antipsychotics (including risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole).

### 2.2. Subjects

Subjects were enrolled and randomized at 67 sites in the US and 33 sites in Latin America, between 2011 and 2015. Male and female subjects were enrolled if they were aged 18–75 years; met the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for bipolar I disorder; and had been stable for at least 8 weeks before baseline, with the most recent mood episode between 8 weeks and 9 months before screening.

Additional inclusion criteria were a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≤ 12, a Young Mania Rating Scale (YMRS) score ≤ 10, a Clinical Global Impression – Severity (CGI-S) score of ≤ 2, and a Hamilton Anxiety Scale score ≤ 21, at both screening and baseline visits, and that the subject had no change in psychotropic medications and no dose adjustment of psychotropic medications for bipolar I disorder for at least 8 weeks before randomization (stability criteria).

Subjects were excluded from the study if they had a current DSM-IV-TR diagnosis or history of schizophrenia or any other psychotic disorder; a history of rapid cycling bipolar disorder; a DSM-IV-TR diagnosis of alcohol or other substance abuse (excluding nicotine or caffeine) within 3 months of screening; any current DSM-IV-TR psychiatric disorder, other than bipolar I disorder, as the primary focus of treatment; any axis II disorder that might compromise the study; a current diagnosis or history of a clinically significant neurological disorder; any neurodegenerative disorder (including epilepsy); a significant risk of suicide, a MADRS score of ≥ 5 on suicidal thoughts, or a suicide attempt in the previous 6 months; or a clinically significant finding on medical history, physical examination, electrocardiogram, or laboratory testing. Additionally, subjects were excluded if they were receiving any medications other than antidepressants (except fluvoxamine), mood stabilizers (lithium, valproate, lamotrigine), or atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) for bipolar I disorder. If subjects were receiving any other psychotropic medications, withdrawal of these medications was allowed ≥ 2 weeks before baseline at the investigators' discretion. Subjects were not eligible if they were on no medication, taking only antidepressant medications, or taking only medications not commonly used as standard treatment for bipolar I disorder. The use of adequate contraception for the duration of the study and for 30 days after the last dose was required for sexually active male patients who were unsterilized and for female patients of childbearing potential.

### 2.3. Endpoints and assessments

The primary endpoint of the study was the time from randomization to relapse (i.e. study event), as determined by any of the following criteria during the 12-month study treatment period: depression (MADRS score ≥ 16); mania/hypomania (YMRS score ≥ 16); mixed episode (MADRS score ≥ 16 and YMRS score ≥ 16); psychiatric hospitalization for bipolar disorder; electroconvulsive therapy; any psychotropic medication change prescribed for the treatment of depressive, mania/hypomania, or mixed episodes; or as determined by the judgment of the principal investigator. Secondary endpoints included time to relapse due to any of the individual components of the primary endpoint, the time to study withdrawal for any reason, and the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) total score at Month 12. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests (including endocrine tests), vital signs, weight, electrocardiogram tests, and physical examinations. For data quality assurance, independent YMRS and MADRS scores were also obtained using a computer-simulated rater.

### 2.4. Statistical methods

The primary analysis was based on the full analysis set (FAS), which included all subjects who were randomized, received ≥ 1 dose of study drug, and had baseline and ≥ 1 valid post-baseline assessments for the primary efficacy endpoint. Comparisons of the survival functions between different ramelteon SL dose groups and placebo were conducted using the log-rank test. In the survival analysis, subjects who completed the study without relapse were censored at the time of study completion. Subjects who prematurely discontinued from the study before relapse and who relapsed were censored at the time of discontinuation. For the interim analysis, subjects who were ongoing without relapse were censored at the time of their last visit. The secondary endpoints were summarized using descriptive statistics based on the FAS.

#### 2.4.1. Determination of sample size

Assuming a hazard ratio of 0.6 between placebo and ramelteon SL, no fewer than 160 study events had to be observed in the combination of any one ramelteon SL treatment group and the placebo group to achieve approximately 80% power to detect a significant difference between a ramelteon SL dose and placebo at a two-sided 0.0167 significance level. It was estimated that approximately 50% of the randomized subjects would experience a relapse event during the 12-month double-blind treatment period. This estimate was based on evidence that an interval of ~ 1 year between episodes is predicted in patients who have experienced prior episode (Goodwin and Jamison, 2007). To control the overall type I error at 0.05 using Bonferroni adjustment, ≥ 640 subjects (160 subjects per treatment group) needed to be randomized into this study to achieve the 80% power to detect a significant difference between ramelteon SL doses and placebo.

#### 2.4.2. Interim analysis

As the study proceeded, the cumulative count of study events was lower than expected in the power calculations. For this reason, an independent Data Monitoring Committee was incorporated into the study to conduct an unblinded interim review to assess the likelihood of any ramelteon SL dose significantly reducing the time to relapse compared with placebo by the end of the study. At the cut-off date established, the review assessed subjects who had reached the 6-month post-baseline study visit, or who had completed or discontinued from the study before that visit. The Data Monitoring Committee was responsible for recommending whether the study should be stopped or continued as planned, or whether the sample size should be increased. A ramelteon SL dose was considered ineffective if the conditional power (CP) was < 30% for the comparison with placebo (the 'threshold' CP); if the CP was ≥ 80%, the dose was considered effective; if the CP was ≥ 30 to < 80%, an increase in sample size to achieve the planned power of 80% would be calculated. If no ramelteon SL dose achieved the 30% CP threshold, the futility criteria were met and the study was to be terminated. If at least one ramelteon SL dose achieved the threshold, the study would continue with all doses, but there would be no increase in the sample sizes of the ineffective doses. The maximum number of additional subjects permitted was 50% of the total planned number of subjects per treatment group.

## 3. Results

### 3.1. Subject disposition and baseline characteristics

Of the 1247 subjects who were screened, 642 were randomized to ramelteon SL at doses of 0.1, 0.4, or 0.8 mg, or to placebo (Fig. 1). Subject demographics and baseline characteristics are presented in Table 1. Treatment groups were generally well balanced, with similar mean baseline scores for the primary and secondary endpoint

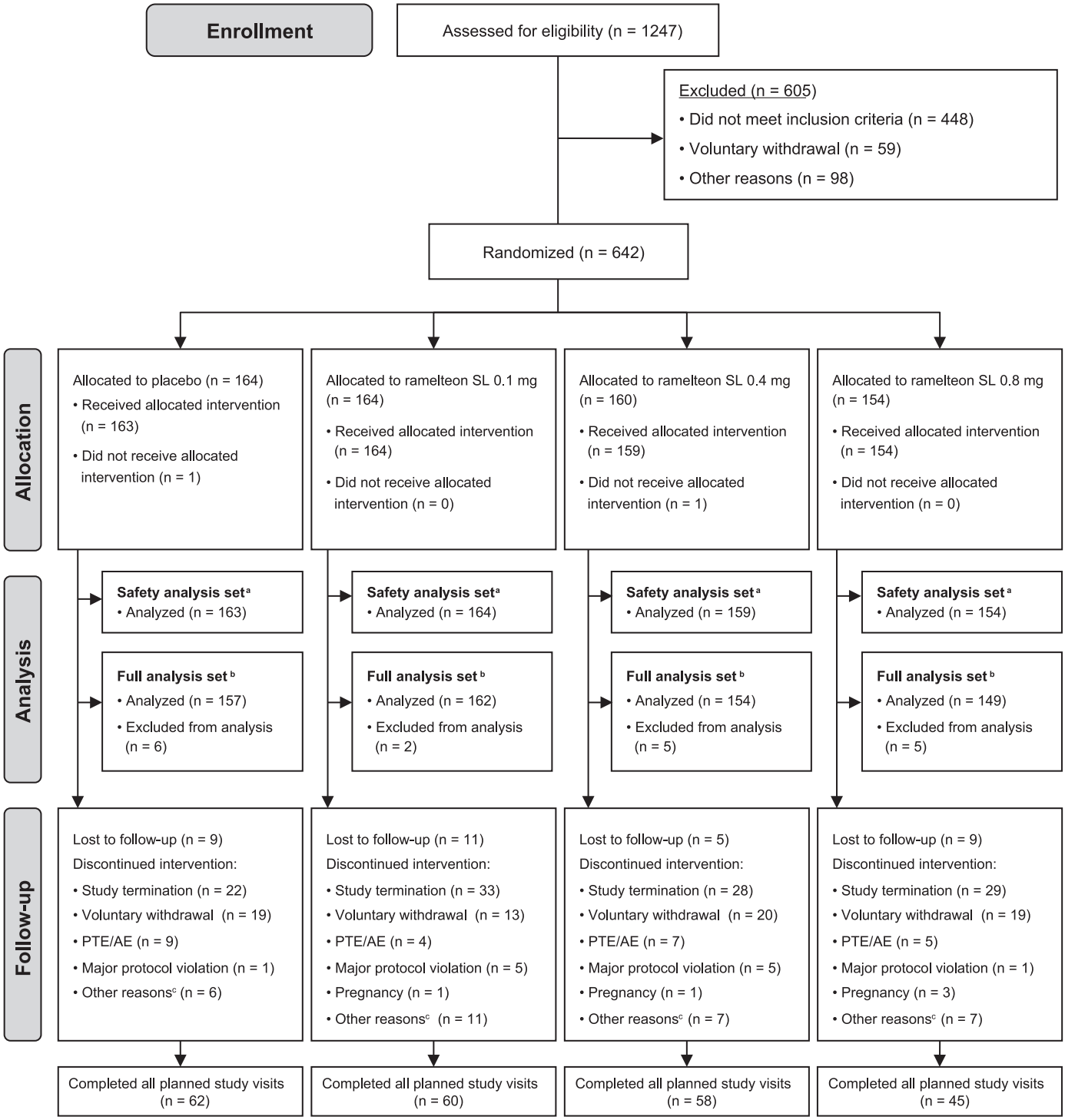



**Fig. 1.** Participant flow. [a] All randomized subjects who received at least one dose of double-blind study medication. [b] All randomized subjects who received at least one dose of double-blind study medication and had at least one valid post-baseline value for assessment of primary efficacy. [c] Other reasons included: subject noncompliance, did not meet inclusion/exclusion criteria, principal investigator or sponsor decision, lost to follow-up or withdrew consent. AE, adverse event; PTE, pretreatment event.

parameters, as well as similar concomitant medication use.

The results of the interim analysis met the predefined efficacy criterion for futility for all three doses of ramelteon SL (CP < 30% for the comparison of each treatment arm with placebo), and the study was prematurely terminated in February 2015, with a total of 226 subjects (35.2%) completing the 12-month double-blind treatment period.

### 3.2. Efficacy

Overall, 129 subjects (20.7%) in the FAS had relapsed at the time the study was terminated. No statistical difference was observed for the primary endpoint of time from randomization to relapse for any comparison between the treatment groups (Fig. 2). Mean time to any

**Table 1**
Demographics and baseline characteristics (all randomized subjects).

| | | Ramelteon SL dose | | |
|---|---|---|---|---|
| | **Placebo (n = 164)** | **0.1 mg (n = 164)** | **0.4 mg (n = 160)** | **0.8 mg (n = 154)** |
| Age, mean, years (SD) | 44.2 (12.22) | 43.0 (13.26) | 42.9 (11.67) | 41.7 (12.53) |
| Female, n (%) | 96 (58.5) | 89 (54.3) | 92 (57.5) | 90 (58.4) |
| BMI, mean, kg/m$^2$ (SD) | 30.7 (7.35) | 30.7 (6.38) | 31.5 (7.11) | 30.1 (6.70) |
| Race, n (%) | | | | |
| Caucasian | 118 (72.0) | 116 (70.7) | 117 (73.1) | 104 (67.5) |
| Black | 36 (22.0) | 34 (20.7) | 34 (21.3) | 36 (23.4) |
| Other | 10 (6.1) | 14 (8.5) | 9 (5.6) | 14 (9.1) |
| **Concomitant psychotropic medications**[a] | | | | |
| Anti-epileptics, n (%) | 76 (46.3) | 73 (44.5) | 68 (42.5) | 67 (43.5) |
| Lamotrigine | 33 (20.1) | 37 (22.6) | 35 (21.9) | 36 (23.4) |
| Valproate or valproic acid | 44 (26.8) | 36 (22.0) | 34 (21.3) | 31 (20.1) |
| Psychoanaleptics, n (%) | 64 (39.0) | 54 (32.9) | 56 (35.0) | 51 (33.1) |
| Psycholeptics, n (%) | 129 (78.7) | 128 (78.0) | 120 (75.0) | 124 (80.5) |
| Aripiprazole | 32 (19.5) | 33 (20.1) | 27 (16.9) | 27 (17.5) |
| Lithium/lithium carbonate | 42 (25.6) | 39 (23.8) | 39 (24.4) | 32 (20.8) |
| Quetiapine/quetiapine fumarate | 32 (19.5) | 39 (23.8) | 32 (20.0) | 36 (23.4) |
| **Baseline parameters, mean (SD)** | | | | |
| MADRS score | 5.3 (3.70) | 5.4 (3.75) | 4.8 (3.59) | 5.1 (3.75) |
| YMRS score | 2.8 (2.49) | 2.9 (2.55) | 2.6 (2.61) | 2.8 (2.46) |
| Q-LES-Q-SF total score[b] | 65.2 (16.90) | 65.4 (16.86) | 68.5 (15.88) | 65.4 (14.78) |
| HAM-A total score | 4.3 (3.74) | 4.1 (3.40) | 4.0 (3.27) | 3.7 (3.47) |
| CGI-S score | 1.5 (0.50) | 1.5 (0.50) | 1.5 (0.50) | 1.5 (0.50) |
| RSQ-W total score | 59.2 (20.82) | 60.7 (19.18) | 61.4 (20.62) | 55.8 (19.88) |

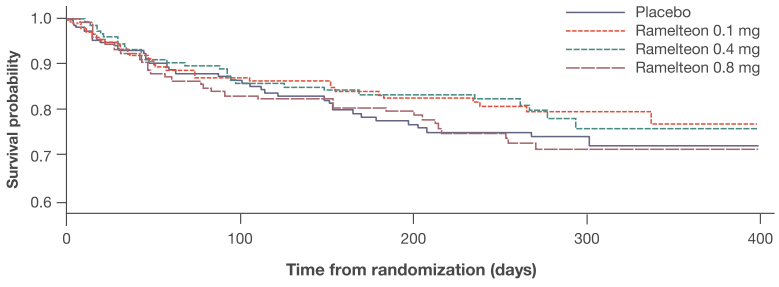
BMI, body mass index; CGI-S, Clinical Global Impression – Severity; HAM-A, Hamilton Anxiety Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; RSQ-W, Response Style Questionnaire; SD, standard deviation; YMRS, Young Mania Rating Scale.
[a] Concomitant medication was defined as medication taken on or after the screening visit date and before the last dose of study medication.
[b] Data are not included for 119 subjects whose data were not included in the clinical dataset.

relapse ( ± standard error) was 248.3 ( ± 8.11) days in the placebo group, 287.7 ( ± 8.83) days for ramelteon SL 0.1 mg, 253.1 ( ± 7.52) days for ramelteon SL 0.4 mg, and 223.9 ( ± 7.60) days for ramelteon SL 0.8 mg. Outcomes for the secondary endpoints are shown in Table 2. The only secondary endpoint to show a significant difference between placebo and any of the ramelteon SL doses was the Q-LES-Q-SF total score at Month 12, in which a nominal difference was observed for the ramelteon SL 0.1 mg treatment group ($p = 0.037$).

### 3.3. Safety

Overall, 434 of 640 subjects (67.8%) experienced 1231 TEAEs, with most experiencing TEAEs of mild or moderate severity (Table 3). A total of 63 subjects (9.8%) experienced one or more severe TEAEs, and 189 subjects (29.5%) experienced TEAEs that were assessed by investigators to be related to the study drug. Thirty-eight subjects (5.9%) experienced 53 serious TEAEs; of the 10 events considered to be related to the study drug, nine were associated with the underlying bipolar disorder (affective disorder, manic episode, bipolar manic disorder, depression relapse, suicidal ideation [two subjects], worsening of manic episode, and bipolar disorder mixed episode) and one was a general tonic–clonic convulsion that resolved after study drug withdrawal (0.1 mg ramelteon SL). Sixteen subjects (2.5%) experienced serious TEAEs leading to discontinuation of study drug. One death was reported in the placebo group. The subject died on Day 95 after experiencing a non-traumatic cardiopulmonary arrest. The investigator considered this event to be unrelated to the study drug or procedure. The rates of ≥ 7% weight gain in subjects with at least one weight measurement post baseline were 9.4% (14/149) in the placebo group and 10.1% (15/148), 10.3% (15/146), and 7.2% (10/139) in the ramelteon 0.1 mg, 0.4 mg, and 0.8 mg groups, respectively. Akathisia was reported in one subject receiving placebo (0.6%) and two subjects treated with ramelteon SL 0.4 mg (1.3%).

There were no apparent clinically important differences or trends in




Number of subjects at risk

| | | | | | |
|---|---|---|---|---|---|
| Placebo | 157 | 119 | 95 | 36 | 0 |
| Ramelteon 0.1 mg | 162 | 117 | 103 | 39 | 0 |
| Ramelteon 0.4 mg | 154 | 110 | 96 | 31 | 0 |
| Ramelteon 0.8 mg | 149 | 100 | 87 | 28 | 0 |

**Fig. 2.** Kaplan–Meier curves for time to any relapse (full analysis set). Kaplan–Meier curves for time to any relapse in the full analysis set with numbers of subjects at risk shown. Relapse was determined by any of the following criteria during the 12-month study treatment period: depression (Montgomery–Åsberg Depression Rating Scale [MADRS] score ≥ 16); mania/hypomania (Young Mania Rating Scale [YMRS] score ≥ 16); mixed episode (MADRS score ≥ 16 and YMRS score ≥ 16); psychiatric hospitalization for bipolar disorder; electroconvulsive therapy; any psychotropic medication change prescribed for the treatment of depressive, mania/hypomania, or mixed episodes; or as determined by judgment of the principal investigator.

**Table 2**
Outcomes for secondary endpoints (full analysis set).

| | | Ramelteon SL dose | | |
|---|---|---|---|---|
| | Placebo (n = 157) | 0.1 mg (n = 162) | 0.4 mg (n = 154) | 0.8 mg (n = 149) |
| Subjects with any relapse, n (%) | 37 (23.6) | 29 (17.9) | 28 (18.2) | 35 (23.5) |
| Subjects with relapse due to, n (%) | | | | |
| Depression[a] | 31 (19.7) | 19 (11.7) | 21 (13.6) | 24 (16.1) |
| Mania/hypomania or mixed episode[b] | 6 (3.8) | 10 (6.2) | 7 (4.5) | 10 (6.7) |
| Depression (MADRS score ≥ 16 or investigator judgment) | 25 (15.9) | 17 (10.5) | 20 (13.0) | 24 (16.1) |
| Mania/hypomania (YMRS score ≥ 16 or investigator judgment) | 4 (2.5) | 5 (3.1) | 3 (1.9) | 5 (3.4) |
| Mixed episode (MADRS score ≥ 16 and YMRS score ≥ 16 or investigator judgment) | 2 (1.3) | 3 (1.9) | 3 (1.9) | 4 (2.7) |
| Psychiatric hospitalization for bipolar disorder | 4 (2.5) | 3 (1.9) | 2 (1.3) | 2 (1.3) |
| ECT administration | 0 | 0 | 0 | 0 |
| Any psychotropic medication change for bipolar disorder | 5 (3.2) | 3 (1.9) | 3 (1.9) | 2 (1.3) |
| Kaplan–Meier estimate for time to study withdrawal for any reason during the 12-month treatment period | | | | |
| Mean time, days (SE) | 240.6 (11.44) | 226.8 (10.48) | 226.9 (10.88) | 208.7 (11.01) |
| Q-LES-Q-SF total score at Month 12 (LOCF)[c] | | | | |
| Month 12 change from baseline (mean, SD) | 1.8 (18.14) | 5.8 (16.56)* | 1.4 (17.35) | 1.0 (16.79) |

ECT, electroconvulsive therapy; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; PI, principal investigator; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SD, standard deviation; SE, standard error; YMRS, Young Mania Rating Scale.

[a] Based on investigator judgment, MADRS score ≥ 16, psychiatric hospitalization, ECT or any psychotropic medication change prescribed for the treatment of depressive episodes.

[b] Based on investigator judgment, mania/hypomania (YMRS score ≥ 16), mixed episode (MADRS score ≥ 16 and YMRS score ≥ 16), psychiatric hospitalization, ECT or any psychotropic medication change prescribed for the treatment of mania/hypomania or mixed episode.

[c] Data are not included for 119 subjects whose data were not included in the clinical dataset.

* $p = 0.037$ (all other comparisons vs placebo were non-significant).

**Table 3**
Summary of TEAEs.

| Number of subjects (%) | | Ramelteon SL dose | | |
|---|---|---|---|---|
| | Placebo (n = 163) | 0.1 mg (n = 164) | 0.4 mg (n = 159) | 0.8 mg (n = 154) |
| **Any TEAE** | 120 (73.6) | 103 (62.8) | 106 (66.7) | 105 (68.2) |
| Discontinuation due to TEAE | 30 (18.4) | 22 (13.4) | 28 (17.6) | 30 (19.5) |
| **Serious AEs** | 10 (6.1) | 14 (8.5) | 6 (3.8) | 8 (5.2) |
| Discontinuation due to serious AE | 5 (3.1) | 4 (2.4) | 4 (2.5) | 3 (1.9) |
| Death | 1 (0.6) | 0 | 0 | 0 |
| **TEAE in ≥ 3% subjects in any treatment group** | | | | |
| Headache | 13 (8.0) | 14 (8.5) | 14 (8.8) | 10 (6.5) |
| Depression | 10 (6.1) | 7 (4.3) | 7 (4.4) | 16 (10.4) |
| Nasopharyngitis | 11 (6.7) | 6 (3.7) | 10 (6.3) | 13 (8.4) |
| Insomnia | 11 (6.7) | 8 (4.9) | 10 (6.3) | 7 (4.5) |
| Upper respiratory tract infection | 11 (6.7) | 7 (4.3) | 9 (5.7) | 6 (3.9) |
| Diarrhea | 7 (4.3) | 10 (6.1) | 2 (1.3) | 5 (3.2) |
| Influenza | 3 (1.8) | 6 (3.7) | 8 (5.0) | 5 (3.2) |
| Somnolence | 5 (3.1) | 3 (1.8) | 7 (4.4) | 7 (4.5) |
| Nausea | 6 (3.7) | 5 (3.0) | 4 (2.5) | 6 (3.9) |
| Weight increased | 4 (2.5) | 5 (3.0) | 6 (3.8) | 2 (1.3) |
| Back pain | 6 (3.7) | 4 (2.4) | 2 (1.3) | 4 (2.6) |
| Dry mouth | 6 (3.7) | 4 (2.4) | 5 (3.1) | 1 (0.6) |
| Mania | 5 (3.1) | 3 (1.8) | 5 (3.1) | 2 (1.3) |
| Depressive symptom | 5 (3.1) | 1 (0.6) | 4 (2.5) | 4 (2.6) |
| Fatigue | 4 (2.5) | 5 (3.0) | 1 (0.6) | 4 (2.6) |
| Anxiety | 1 (0.6) | 8 (4.9) | 1 (0.6) | 3 (1.9) |
| Arthralgia | 6 (3.7) | 5 (3.0) | 1 (0.6) | 1 (0.6) |
| Irritability | 5 (3.1) | 3 (1.8) | 2 (1.3) | 2 (1.3) |
| Dizziness | 3 (1.8) | 5 (3.0) | 1 (0.6) | 2 (1.3) |
| Dyspepsia | 5 (3.1) | 2 (1.2) | 2 (1.3) | 2 (1.3) |
| Cough | 1 (0.6) | 3 (1.8) | 0 | 6 (3.9) |
| Urinary tract infection | 6 (3.7) | 1 (0.6) | 1 (0.6) | 2 (1.3) |
| Vomiting | 3 (1.8) | 5 (3.0) | 1 (0.6) | 0 |

AE, adverse event; TEAE, treatment-emergent adverse event.

the frequency of TEAEs among the four treatment groups. The most frequently reported study drug-related TEAEs (≥ 3% of subjects in any treatment group) were somnolence (3.4%), insomnia (3.0%), headache (2.8%), diarrhea (2.3%), and dry mouth (1.6%).

## 4. Discussion

This study did not demonstrate the efficacy of adjunctive ramelteon SL for the prevention of relapse in stable adult patients with bipolar I

disorder; none of the doses showed a statistically significant difference compared with placebo for the primary endpoint. The study was terminated when the interim analysis established that the prespecified futility criteria were met: the relapse event rates were too low for a statistically significant difference to be demonstrated between the subject groups, even if the study was to continue with up to a 50% sample size increase. Of the secondary endpoints, the Q-LES-Q-SF score showed a nominal statistical difference ($p = 0.037$) in favor of subjects treated with ramelteon SL versus placebo at Week 12.

An oral formulation of ramelteon is approved for the treatment of insomnia (Takeda Pharmaceuticals America Inc, 2010) and has a well-established safety profile. In this study, 0.1, 0.4, and 0.8 mg doses of ramelteon SL were also all well tolerated. The type and severity of adverse events were consistent with those reported for the oral formulation of ramelteon in insomnia clinical studies, in previous studies in bipolar disorder I, and in post-marketing experience (Takeda Pharmaceuticals America Inc, 2010). The favorable safety profile in this study was observed against a background of multiple concomitant therapies.

### 4.1. Limitations

The primary limitation of this study was the lower-than-predicted number of relapse events that made it impossible to detect a difference between different doses of ramelteon SL and placebo. A possible reason for this may be that the study population was selected for stability, and hence had a lower rate of relapse than that predicted from the literature. Notably, Norris et al. (2013) reported an overall relapse rate of 48% in their study of oral ramelteon in patients with euthymic bipolar disorder. However, their eligibility criteria required subject stability for 7–28 days between screening and randomization compared with the 8 weeks to 9 months of stability before screening required by this study. In addition, in contrast to this study, documented sleep disturbances were a specific eligibility criterion for the study by Norris et al. (2013).

## 5. Conclusions

Although the study did not meet primary or secondary endpoints, these results highlight the utility of interim analyses for futility in clinical studies, and how they can be used to prevent the unnecessary exposure of subjects to interventions that would not reach a prespecified endpoint, and additionally can save time, costs, and resources.

The results of the current study also build on the known safety profile of ramelteon SL in patients with insomnia, expanding the clinical experience to patients with bipolar I disorder who were receiving numerous concomitant medications.

## Author disclosures

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## Contributors

ARM contributed to the final study design, study conduct, and data interpretation in addition to the development of the manuscript. JRC, TAM, KB, AA, XD, EH, and GSS contributed to the conception, study design, and protocol development in addition to the development of the manuscript. All authors have approved the final article.

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## Conflict of interest

ARM, TAM, AA, XD, and EH are employees of Takeda Pharmaceuticals International, Inc. GSS received financial support, consulting fees, and honoraria from Allergan, Janssen, Intracellular Therapies, Lundbeck, Merck, Otsuka, Pfizer, Sunovion, and Takeda, and has shares in Express Scripts, Oracle, and Amyris. JRC has been a consultant, advisory board member, and speaker for Abbott Laboratories, Allergan, AstraZeneca, Bristol-Myers Squibb, Cephalon (Teva Pharmaceutical Industries), Dainippon Sumitomo Pharma, GlaxoSmith*Kl*ine, Janssen Pharmaceuticals, H. Lundbeck A/S, Merck & Co, Otsuka Pharmaceutical, Pfizer, Repligen Corporation, Servier, Sunovion Pharmaceuticals, Solvay Pharmaceuticals, and Takeda Pharmaceuticals. JRC has received grant support from Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Cephalon (now Teva Pharmaceutical Industries.), Dainippon Sumitomo Pharma, GlaxoSmith*Kl*ine, Janssen Pharmaceuticals, Eli Lilly and Company, Intra-Cellular Therapies, Pfizer, H. Lundbeck A/S, Sunovion Pharmaceuticals, and Takeda Pharmaceuticals. KB is an employee of AbbVie.

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