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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).