Effect of Adjunctive Pimavanserin on Sleep/Wakefulness in Patients With Major Depressive Disorder: Secondary Analysis From CLARITY

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ABSTRACT

Objective: This was an analysis of the effect of pimavanserin, a 5-hydroxytryptamine–2A antagonist and inverse receptor agonist, on dysregulated sleep in patients with major depressive disorder (MDD) by DSM-5 criteria and an inadequate antidepressant response.

Methods: For this analysis of CLARITY, a phase 2 study of adjunctive pimavanserin (N = 207) conducted between December 2016 and October 2018, sleep/wakefulness disturbances were measured with the 17-item Hamilton Depression Rating Scale (HDRS17) insomnia items (sum of items 4, 5, and 6) and the Karolinska Sleepiness Scale (KSS). Outcomes included change from baseline in HDRS17 insomnia factor score and KSS score, correlation between the HDRS17 insomnia factor score and KSS score, and change from baseline in the Sheehan Disability Scale (SDS) total score and Unproductive Days subscore in patients with a baseline KSS score ≥ 6.

Results: At baseline, HDRS17 insomnia factor score ≥ 3 occurred in 76% of patients receiving placebo and 85% of patients receiving pimavanserin. The overall least squares (LS) mean weighted difference (SE) was −0.5 (0.32) with a 95% CI of −1.2 to 0.1 (P = .088) at week 5. Improvement was observed with pimavanserin versus placebo at weeks 2, 3, and 4, with effect sizes (ESs) of 0.370 to 0.524 (P < .05). For KSS score, the LS mean difference (SE) at week 5 was −1.1 (0.30) (95% CI, −1.7 to −0.5; P = .0003; ES = 0.627) for pimavanserin versus placebo. Among those with a KSS score ≥ 6 at baseline (n = 120 placebo and n = 42 pimavanserin), the LS mean difference (SE) in the mean SDS score at week 5 was −1.1 (0.46) (95% CI, −2.0 to −0.2; P = .019; ES = 0.442) for pimavanserin versus placebo.

Conclusions: Adjunctive pimavanserin significantly improved sleep/wakefulness disturbance during treatment of MDD, an improvement that was associated with greater improvement in function.

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Sleep disturbances, including insomnia and daytime sleepiness, occur in about one-third of the general population and adversely affect workplace performance.2,3 As a core symptom domain of major depressive disorder (MDD),4 sleep disturbances affect up to 90% of MDD patients and are associated with poor treatment outcomes such as failure to achieve remission5 and increased risk of relapse6,9 and recurrence5 along with impaired psychosocial functioning10 and quality of life (QoL).6,7 Insomnia is one of the most common residual symptoms of MDD7,11,12 and may add to the economic burden of the disorder.13 Treating insomnia in patients with MDD improves mood14 and is a key factor in achieving remission.11 However, evidence for the effectiveness of antidepressants for treating insomnia is lacking.15 In fact, while select antidepressants such as doxepin, trazodone, and mirtazapine may improve insomnia, many commonly used antidepressants (such as selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and bupropion) may cause worsening of insomnia in a sizable number of patients. Worsening of insomnia in a substantial proportion (1 in 6) of patients with MDD may be associated with significantly lower likelihood of acute-phase remission.16 Pimavanserin is a 5-hydroxytryptamine–2A (5-HT2A) receptor antagonist/inverse agonist with lesser activity as a 5-HT2C antagonist and inverse agonist, but no activity at adrenergic, dopaminergic, histaminergic, or muscarinic receptors,17 and is approved in the United States for the treatment of hallucinations and delusions in patients with Parkinson’s disease psychosis. In CLARITY,18 a randomized, placebo-controlled trial of pimavanserin as adjunctive therapy in patients with MDD and an inadequate response to antidepressant treatment, pimavanserin demonstrated a significant reduction in symptoms of depression and improvement in function measured by the Sheehan Disability Scale (SDS). This secondary analysis of CLARITY was undertaken to evaluate the effects of adjunctive pimavanserin on sleep/wakefulness disturbances and whether improvement in these symptoms mediates
Depression Rating Scale [HDRS 17] total score > 14 and Placebo nonresponders after 5 weeks (17-item Hamilton desvenlafaxine, duloxetine, or venlafaxine) for 5 weeks. (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, pimavanserin 34 mg added to current SSRI or SNRI therapy, Clinician Version (SCID-5-CV). Also required DSM-5, and confirmed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and confirmation of treatment with a primary diagnosis of MDD and a current major depressive episode. To be eligible, patients were at least 18 years of age, with a body mass index (BMI) of 19 to 35 kg/m², and were required to have a primary diagnosis of MDD and a current major depressive episode (MDE), defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and confirmed by the Structured Clinical Interview for DSM-5, Clinician Version (SCID-5-CV). Also required was a history of MDD for ≥ 1 year prior to screening, a Montgomery-Asberg Depression Rating Scale (MADRS) total score > 20, a Clinical Global Impressions—Severity of Illness scale (CGI-S) score ≥ 4 (moderately ill or worse) at screening and baseline visits, and a history of inadequate response to 1 or 2 adequate trials with SSRI or SNRI antidepressant treatment during the current depression episode.

Study Assessments
Clinic visits occurred weekly from baseline through week 10 (end of study). The HDRS17 was administered by trained raters at each visit as a measure of depression severity. Participants completed the SDS as a measure of disability and impairment in domains of work/school, social life, and family life/home responsibilities (responses summed as SDS total score) at each visit. Furthermore, participants also were asked to indicate the number of days in the past week that they felt their productivity to be reduced while at school or work (SDS Unproductive Days subscore). As a measure of daytime sleepiness, participants completed the Karolinska Sleepiness Scale (KSS) at each study visit, via which a retrospective assessment of the level of sleepiness during the past 7 days was recorded. For this secondary analysis, assessments of sleep/wakefulness disturbance included the insomnia items (items 4, 5, and 6) of the HDRS17 and the KSS.

Statistical Analysis
Efficacy data were analyzed for the full analysis set (FAS) for Stage 1 (placebo n = 152, pimavanserin n = 51) and for Stage 2 (placebo n = 29, pimavanserin n = 29), comprising all randomized patients who received ≥ 1 dose of blinded study drug and who had a baseline value and at least 1 postbaseline value for the HDRS17 total score within each stage. Mean change from baseline was determined for the HDRS17 insomnia factor score (sum of items 4, 5, and 6) among patients with a factor score ≥ 3 at baseline. In addition, mean change from baseline was determined for the KSS. For the SDS total score and Unproductive Days subscore, mean change from baseline was examined among the subgroup of patients with a baseline KSS score ≥ 6 (some signs of sleepiness).

The Pearson correlation coefficient was used to determine the relationship between the HDRS17 total score and (1) HDRS17 insomnia factor score and (2) KSS score for Stages 1 and 2 (and for 10 weeks in patients not randomized to pimavanserin in Stage 2) as well as association of change from baseline to week 5 in HDRS17 insomnia factor score and the KSS score. Mixed model for repeated measures (MMRM) analyses were used for comparisons with assessments of sleep/wakefulness disturbances (HDRS17 insomnia factor and KSS) as the outcome variable and treatment group, visit, and treatment-by-visit interaction as independent variables of interest. Analyses were done with baseline SDS total or Unproductive Days or baseline HDRS17 total or insomnia factor score--by-treatment interaction as factors. The treatment effect was assessed as the treatment difference in least squares (LS) mean change from baseline to
In the primary study, a total of 207 patients were randomized between December 2016 and October 2018. In Stage 1, 152 patients (98.1%) and 51 patients (98.1%) in the placebo and pimavanserin groups, respectively, were included in the FAS population. In Stage 2, 29 patients each in the placebo and pimavanserin groups were included in the FAS population (Figure 1). Treatment groups were generally comparable for demographic and clinical characteristics at baseline. Concomitant sedative/hypnotic medications were taken by <10% of patients during the study.

**HDQRS** Insomnia Factor

At baseline, an **HDQRS** insomnia factor score ≥3 was recorded in 118 patients (76% of FAS population) receiving placebo and 44 patients (85% of FAS population) receiving pimavanserin. The overall LS mean (standard error [SE]) weighted difference was –0.5 (0.32) with a 95% CI of –1.2 to 0.1 (P = .088). In Stage 1, improvement was observed with pimavanserin versus placebo for the insomnia factor score at weeks 2, 3, and 4, with effect sizes of 0.370 to 0.524 (P < .05) (Figure 2A). No significant differences were observed between pimavanserin (n = 25) and placebo (n = 22) during Stage 2 or for the overall weighted difference for Stages 1 and 2 (Table 1).

**Karolinska Sleepiness Scale**

At baseline, a KSS score ≥6 was recorded in 120 patients (77% of FAS population) with placebo and 42 patients (81% of FAS population) with pimavanserin. LS mean (SE) baseline scores on the KSS were 6.6 (0.14), and 6.7 (0.19) for placebo (n = 152) and pimavanserin (n = 51), respectively, during Stage 1 and 6.1 (0.30) and 6.7 (0.29) for placebo (n = 29) and pimavanserin (n = 29), respectively, during Stage 2. For KSS score during Stage 1, the LS mean (SE) difference at week 5 was –1.1 (0.30) (95% CI, –1.7 to –0.5; P = .0003; ES = 0.627) for pimavanserin versus placebo. During Stage 1, a significant (P < .05) reduction from baseline for the KSS score was observed with pimavanserin versus placebo from week 1 through week 5 with effect sizes of 0.4 or greater at each week (Figure 2B). No significant differences were
observed between treatments during Stage 2 (Table 2). However, the overall LS mean (SE) weighted difference was −0.6 (0.26) with a 95% CI of −1.1 to −0.1 (P = .021). Among those with a KSS score ≥6 (some sleepiness) at baseline (n = 120 for placebo and n = 42 for pimavanserin), the LS mean difference at week 5 was −1.1 (0.46) (95% CI, −2.0 to −0.2; P = .019; ES = 0.442) for pimavanserin versus placebo.

Sheehan Disability Scale

In Stage 1, among patients with a KSS score ≥6 (some sleepiness) at baseline (n = 120 for placebo and n = 42 for pimavanserin), the LS mean (SE) difference in the SDS mean score at week 5 was −1.09 (0.35) (95% CI, −2.0 to −0.2; P = .019; ES = 0.442) for pimavanserin versus placebo. A significant (P < .05) improvement versus placebo was observed from week 1 to week 5 for the SDS total score and Unproductive Days subscore (Figure 2D). Effect sizes for pimavanserin versus placebo were 0.363 or greater for the SDS mean score and 0.446 or greater for the SDS Unproductive Days subscore. No significant differences for the SDS mean score and Unproductive Days score were observed between treatments for Stage 2. For the SDS mean score, the overall LS mean (SE) weighted difference was −0.85 (0.34) with a 95% CI of −1.5 to −0.19 (P = .012). Among the subgroup of patients with baseline KSS score < 6, LS mean difference with pimavanserin versus placebo was significant (P = .008) only at week 4 for SDS mean score and not at any timepoint for Unproductive Days.

Correlation of Sleep/Wakefulness Disturbance With HDRS17 Total Score

For the subgroup of patients with a baseline KSS score ≥6, a significant correlation was observed for improvement in the HDRS17 total score during Stage 1 for both pimavanserin (P = .003; correlation = 0.467) and placebo (P = .029; correlation = 0.220) groups (Figure 3). Among those patients not re-randomized who remained on pimavanserin treatment in Stage 2, a significant correlation between baseline KSS score and the HDRS17 total score was observed between treatments during Stage 2 (Table 2). However, the overall LS mean (SE) weighted difference was −0.6 (0.26) with a 95% CI of −1.1 to −0.1 (P = .021). Among those with a KSS score ≥6 (some sleepiness) at baseline (n = 120 for placebo and n = 42 for pimavanserin), the LS mean difference at week 5 was −1.1 (0.46) (95% CI, −2.0 to −0.2; P = .019; ES = 0.442) for pimavanserin versus placebo.

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observed for pimavanserin ($P = .002$; correlation = 0.516) but not placebo (0.155; correlation = 0.177). For an analysis of mean change from baseline for the HDRS$_{17}$ insomnia factor score and KSS score, a significant correlation ($P = .014$; correlation = 0.188) was observed for improvement in the HDRS$_{17}$ insomnia factor because no significant difference was observed between pimavanserin and placebo at week 1.

**Mediator Analysis**

In Stage 1, regression analysis of the mean change from baseline to week 5 for the SDS was significantly correlated with a reduction in the KSS at week 1 ($F_{168} = 6.68, P = .011$) and at week 5 ($F_{169} = 18.18, P < .0001$) in the mediator analysis. Mediator analysis was not done with the HDRS$_{17}$ insomnia factor because no significant difference was observed between pimavanserin and placebo at week 1.

**DISCUSSION**

In this secondary analysis from CLARITY, significant improvements in sleep/wakefulness disturbances were observed with adjunctive pimavanserin when assessed with the HDRS$_{17}$ insomnia factor and the KSS. Importantly, the results showed significant improvement over 5 weeks with pimavanserin versus placebo in functionality measured by the SDS among patients with a baseline KSS score $\geq 6$ (some sleepiness), with robust effect sizes of 0.4 or greater, which suggests that improvement in daytime sleepiness in patients with MDD is associated with improved function. This association was further explored by assessing the effects on the SDS Unproductive Days subscore among patients with a baseline KSS score $\geq 6$. Significant improvement with pimavanserin versus placebo was observed at each week.
with robust effect sizes that exceeded 0.4. These results suggest that patients with MDD and baseline insomnia or daytime sleepiness have improved functioning and greater productivity with pimavanserin. Improvements in the HDRS\textsubscript{17} total score were correlated with improvements in the HDRS\textsubscript{17} insomnia factor score and with KSS score. In total, these results suggest a statistically significant and clinically relevant effect of adjunctive pimavanserin on sleep/wakefulness disturbances in patients with MDD. These results with pimavanserin are supported by findings from a small study of patients with Parkinson’s Disease and psychosis,\textsuperscript{27} for whom a significant improvement in nighttime sleep was observed with pimavanserin among those with baseline impaired nighttime sleep.

The regression and correlation analyses attempted to explore the relationship between change in KSS score and change in SDS score as well as the correlation between change in SDS score and change in HDRS\textsubscript{17} score. The results suggest that improvement in the mean SDS score and SDS Unproductive Days score was mediated by improvement in the KSS score. Pimavanserin had a greater effect on the KSS score versus placebo at week 1, and the reduction in KSS score from baseline to week 1 was significantly correlated with a change in SDS score from baseline to week 5. Although the trial was not designed to evaluate mediator effects, findings of this report do suggest that improvement in psychosocial function with pimavanserin is mediated by an improvement in KSS score. Future studies are needed for further confirmation.

Insomnia has been identified as a core symptom of depression\textsuperscript{7–9} and an important residual symptom of MDD.\textsuperscript{11} In a longitudinal study of depressed outpatients,\textsuperscript{28} the majority had residual symptoms of depression after 1 year of treatment, and 13.9% reported insomnia as a residual symptom. Analyses from the STAR\textsuperscript{*}D trial\textsuperscript{11–13,29} found that insomnia was common in outpatients with MDD, and insomnia or sleep disturbances were among the most common residual symptoms. Presence of insomnia or sleep disturbances was associated with an increased rate of relapse.

Insomnia has a significant impact on QoL and daytime functioning\textsuperscript{10,30,31} as well as on the risk for depression. A number of studies\textsuperscript{4,30–32} have shown the effects of insomnia and sleep disturbances on MDD and the benefits of treating insomnia.

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**Figure 3.** Correlation Between Change From Baseline to Week 5 for KSS and HDRS\textsubscript{17} Total Score During Stage 1 With (A) Placebo and (B) Pimavanserin Among Patients With a Baseline KSS Score at Least 6 and Correlation Between Change From Baseline to Week 10 for KSS and HDRS\textsubscript{17} Total Score With (C) Placebo and (D) Pimavanserin Among Patients With a Baseline KSS at Least 6, Among Patients not Randomized to Pimavanserin in Stage 2

**Abbreviations:** HDRS\textsubscript{17} = 17-item Hamilton Depression Rating Scale, KSS = Karolinska Sleepiness Scale.
in contrast, among patients with MDD and a baseline or men was associated with an increased risk for depression. While apnea. We also observed prospectively that pimavanserin kg/m², excluding those at highest risk of obstructive sleep disturbances. Another limitation of this study is that it was not designed to assess BMI or obesity as an important variable in sleep dysregulation in the context of depression and treatment with pimavanserin. Notably, study eligibility was restricted to individuals with BMI under 35 kg/m², excluding those at highest risk of obstructive sleep apnea. We also observed prospectively that pimavanserin was associated with low rates of weight gain.18 While understanding the role of obesity within the context of depression is important, we believe analyses focused on BMI are outside the scope of this report and should be considered an important variable in future studies.

In summary, adjunctive pimavanserin significantly improved sleep/wakefulness disturbances versus placebo during treatment of MDD, which appeared to be associated with greater improvements in function and productivity. Adjunctive pimavanserin may represent an option for the treatment of MDD, especially in the presence of sleep/wakefulness disturbances. Ongoing phase 3 studies of adjunctive pimavanserin in patients with MDD will provide additional findings about its beneficial effects on sleep/wakefulness disturbances.

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