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 ($HDRS_{17}$) insomnia items (sum of items 4, 5, and 6) and the Karolinska Sleepiness Scale (KSS). Outcomes included change from baseline in $HDRS_{17}$ insomnia factor score and KSS score, correlation between the $HDRS_{17}$ 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, $HDRS_{17}$ 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.

Trial Registration: ClinicalTrials.gov identifier: NCT03018340

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Sleep disturbances, including insomnia and daytime sleepiness, occur in about one-third of the general population[1] and adversely affect workplace performance.[2,3] As a core symptom domain of major depressive disorder (MDD),[4,5] sleep disturbances affect up to 90% of MDD patients[6,7] and are associated with poor treatment outcomes such as failure to achieve remission[8] and increased risk of relapse[6,9] and recurrence[5] along with impaired psychosocial functioning[10] and quality of life (QoL).[6,7] Insomnia is one of the most common residual symptoms of MDD[7,11,12] and may add to the economic burden of the disorder.[13] Treating insomnia in patients with MDD improves mood[14] 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 ($5\text{-}HT_{2A}$) receptor antagonist/inverse agonist with lesser activity as a $5\text{-}HT_{2C}$ 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

Clinical Points

- Adjunctive pimavanserin significantly improved depressive symptoms, reduced sleepiness, and improved functioning as measured by the Sheehan Disability Scale in patients with major depressive disorder and an inadequate response to antidepressants.
- Pimavanserin is not approved by the US Food and Drug Administration for treating major depression, and these results require further replication in a randomized clinical trial.

the improvement in depression and psychosocial function associated with pimavanserin.

METHODS

An independent ethics committee or institutional review board at each study site reviewed and approved the study protocol. The study was conducted following the principles of Good Clinical Practice derived from the Declaration of Helsinki and in accordance with local regulations and International Council of Harmonization guidelines. All patients provided written informed consent prior to any study procedures. This study was registered at ClinicalTrials.gov (NCT03018340).

Study Design

CLARITY was a multicenter, randomized, double-blind, placebo-controlled study in patients with MDD. The study was conducted between December 2016 and October 2018. The detailed study methodology was previously published.[18] In brief, after an 8- to 21-day screening period, patients entered a 10-week double-blind treatment period and a 30-day safety follow-up period. A 2-stage Sequential Parallel-Comparison Design (SPCD)[19] was used to randomize patients in Stage 1 in a 3:1 ratio to placebo or pimavanserin 34 mg added to current SSRI or SNRI therapy (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, duloxetine, or venlafaxine) for 5 weeks. Placebo nonresponders after 5 weeks (17-item Hamilton Depression Rating Scale [$HDRS_{17}$][20] total score > 14 and < 50% reduction in score from baseline) were re-randomized to placebo or pimavanserin 34 mg (1:1 ratio) added to current therapy for an additional 5 weeks.

Patient Selection

To be eligible, patients were at least 18 years of age, with a body mass index (BMI) of 19 to 35 kg/m^2, 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).[21] Also required was a history of MDD for ≥ 1 year prior to screening, a Montgomery-Asberg Depression Rating Scale (MADRS)[22] total score > 20, a Clinical Global Impressions—Severity of Illness scale (CGI-S)[23] 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

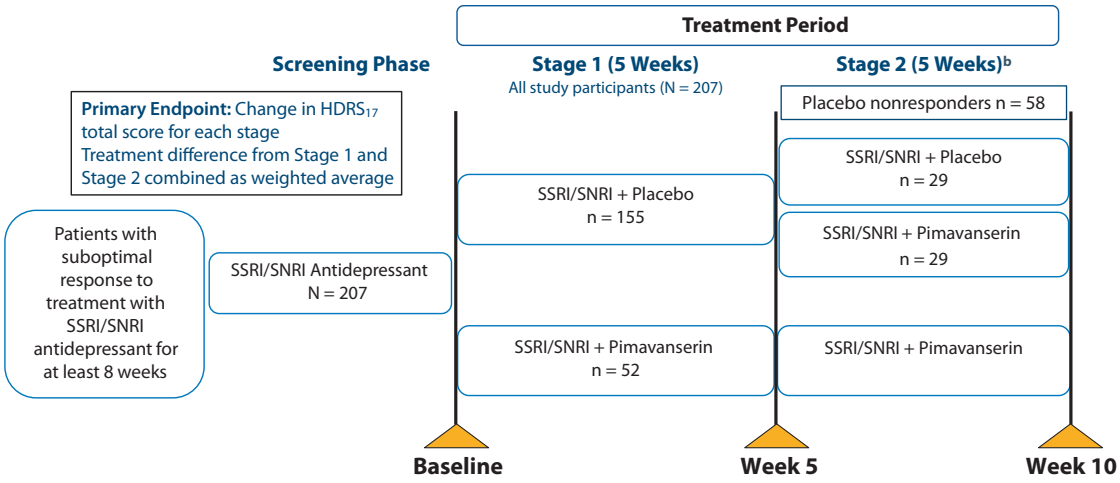
Clinic visits occurred weekly from baseline through week 10 (end of study). The $HDRS_{17}$ was administered by trained raters at each visit as a measure of depression severity. Participants completed the SDS[24] as a measure of disability and impairment in domains of work/school, social life, and family 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)[25] 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 $HDRS_{17}$ 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 $HDRS_{17}$ total score within each stage. Mean change from baseline was determined for the $HDRS_{17}$ 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 $HDRS_{17}$ total score and (1) $HDRS_{17}$ 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 $HDRS_{17}$ insomnia factor score and the KSS score. Mixed model for repeated measures (MMRM) analyses were used for comparisons with assessments of sleep/wakefulness disturbances ($HDRS_{17}$ 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 $HDRS_{17}$ 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

Figure 1. Study Design for CLARITY[a]



[a]For Stage 1, baseline is study week 0, and week 5 is study week 5. For Stage 2, baseline is study week 5, and week 5 is study week 10.
[b]Patients who had a response to placebo in Stage 1 continued taking placebo through week 10.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

the end of each stage and the corresponding 95% confidence intervals (CIs). An unstructured covariance matrix was used to model the within-patient errors. The denominator degrees of freedom were estimated using the Kenward-Rogers approximation. A 2-sided *P* value was calculated for the treatment difference from the stage-specific MMRM analysis. Cohen *d* effect size was calculated for comparisons between treatments.

Per methods proposed by Kraemer,[26] the mediator effect of early improvement in sleep/wakefulness disturbances was evaluated. To be defined as a mediator, (1) the symptom domain should exhibit differential change with treatment (versus placebo), (2) this change should precede or be concurrent to the ultimate treatment outcome, and (3) this change should significantly predict treatment outcome. As described in the previous paragraph, treatment effects from the aforementioned mixed model analyses were used to ascertain whether reduction in sleep/wakefulness disturbances from baseline to week 1 differed significantly between pimavanserin and placebo. If a significant difference was found, linear regression analyses with baseline-to–week 5 changes in SDS score as the outcome were used with baseline-to–week 1 changes in sleep/wakefulness disturbances (significantly different between pimavanserin and placebo) as the independent variable of interest. All analyses were performed using SAS version 9.3 (SAS Institute, Inc; Cary, North Carolina).

RESULTS

In the primary study, a total of 207 patients were randomized between December 2016 and October 2018.[18] 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.

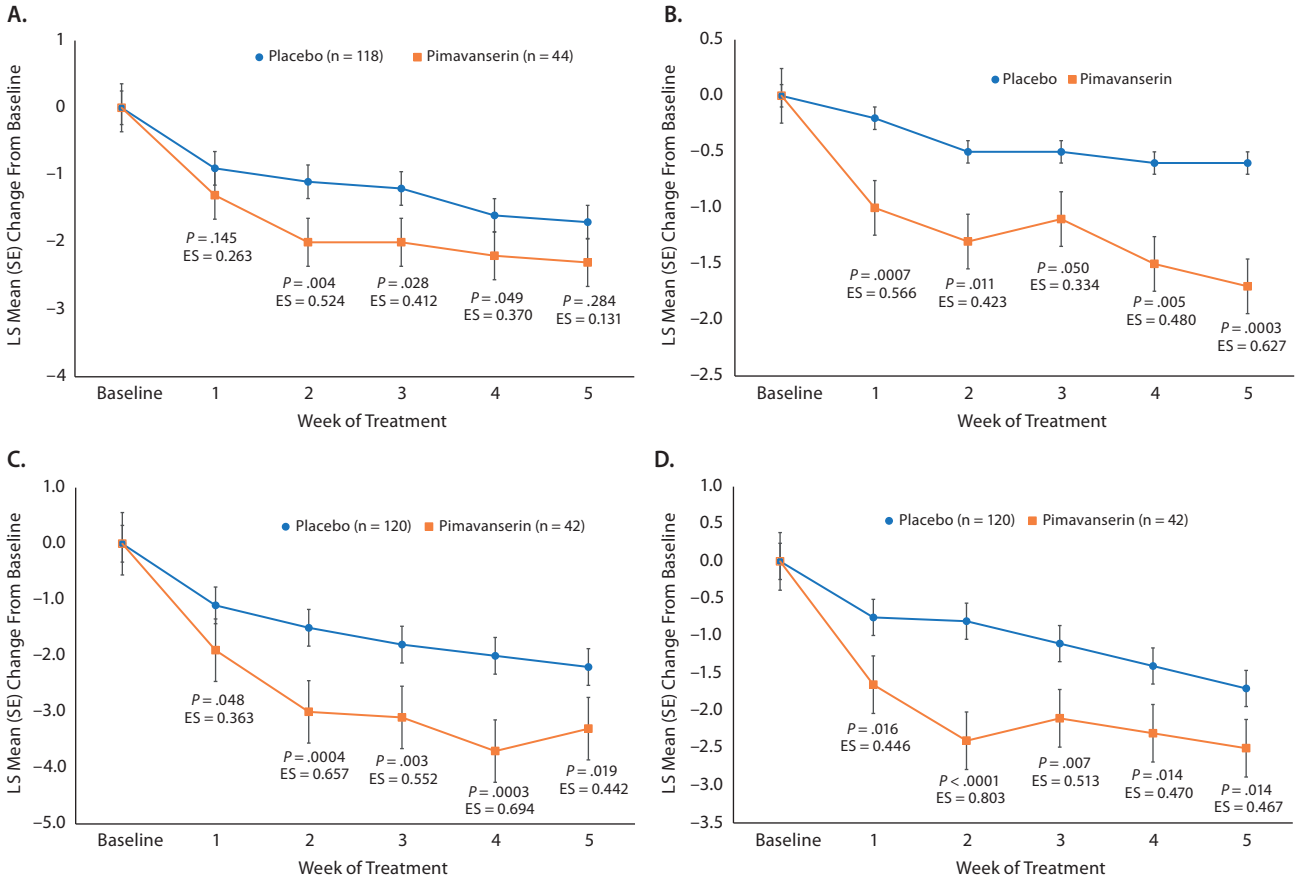
$HDRS_{17}$ Insomnia Factor

At baseline, an $HDRS_{17}$ 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

Figure 2. Mean (Standard Error) Change From Baseline to Week 5 in (A) $HDRS_{17}$ Insomnia Factor Score Among Patients With a Baseline Score of at Least 3, (B) Karolinska Sleepiness Scale Score, (C) Sheehan Disability Scale Total Score, and (D) Unproductive Days Subscale Among Patients With a KSS Score of at Least 6 (Sleepiness, but No Effort Needed to Keep Awake) at Baseline



Abbreviations: ES = effect size, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, KSS = Karolinska Sleepiness Scale, LS = least squares, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

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 (0.46) (95% CI, −2.0 to −0.2; P = .019; ES = 0.442) for pimavanserin versus placebo (Figure 2C). For SDS Unproductive Days, the LS mean difference in the mean score at week 5 was −0.86 (0.35) (95% CI, −1.6 to −0.2; P = .014; ES = 0.467) 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 $HDRS_{17}$ Total Score

For the subgroup of patients with a baseline KSS score ≥ 6, a significant correlation was observed for improvement in the $HDRS_{17}$ 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 $HDRS_{17}$ total score was

Table 1. Mean $HDRS_{17}$ Insomnia Factor Scores (for Patients With Score ≥ 3) and Change From Baseline to Week 5: Full Analysis Set for Stages 1 and 2

	Stage 1		Stage 2	
$HDRS_{17}$ Variable	Placebo (n = 118)	Pimavanserin (n = 44)	Placebo (n = 22)	Pimavanserin (n = 25)
Baseline insomnia factor score, mean (SE)	4.6 (0.10)	4.7 (0.16)	4.1 (0.41)	3.6 (0.32)
Change from Baseline to Week 5				
LS mean (SE)[a]	−1.7 (0.18)	−2.3 (0.30)	−0.4 (0.39)	−1.0 (0.35)
95% CI of LS mean	(−2.1 to −1.4)	(−2.8 to −1.7)	(−1.2 to 0.4)	(−1.7 to −0.3)
LS mean (SE) difference (pimavanserin 34 mg – placebo)		−0.5 (0.35)		−0.6 (0.53)
95% CI of difference		(−1.2 to 0.2)		(−1.6 to 0.5)
P value[b]		.131		.301
Effect size (Cohen *d*)		0.284		0.319
Overall Treatment Comparison at Week 5 (linear combination test)				
Weighted difference in LS mean (SE)				−0.5 (0.32)
95% CI of weighted difference				(−1.2 to 0.1)
P value[b]				.088

[a]LS mean from the stage-specific analysis with the change from baseline as the outcome, treatment group as a factor, and the corresponding baseline value as a covariate.
[b]Two-sided *P* value for treatment difference from the stage-specific analysis.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, LS mean = least squares, SE = standard error.

Table 2. Mean KSS Scores and Change From Baseline to Week 5: Full Analysis Set for Stages 1 and 2

	Stage 1		Stage 2	
KSS Variable	Placebo (n = 152)	Pimavanserin (n = 51)	Placebo (n = 29)	Pimavanserin (n = 29)
Baseline score, mean (SE)	6.6 (0.14)	6.7 (0.19)	6.1 (0.30)	6.7 (0.29)
Change From Baseline to Week 5				
LS mean (SE)[a]	−0.6 (0.15)	−1.7 (0.26)	−0.3 (0.30)	−0.4 (0.28)
95% CI of LS mean	(−0.9 to −0.2)	(−2.2 to −1.2)	(−0.9 to 0.3)	−1.0 to 0.1)
LS mean (SE) difference (pimavanserin 34 mg – placebo)		−1.1 (0.30)		−0.1 (0.42)
95% CI of difference		(−1.7 to −0.5)		(−0.9 to 0.8)
P value[b]		.0003		.842
Effect size (Cohen *d*)		0.627		0.056
Overall Treatment Comparison at Week 5 (linear combination test)				
Weighted difference in LS mean (SE)				−0.6 (0.26)
95% CI of weighted difference				(−1.1 to −0.1)
P value[b]				.021

[a]LS mean from the stage-specific analysis with the change from baseline as the outcome, treatment group as a factor, and the corresponding baseline value as a covariate.
[b]Two-sided *P* value for treatment difference from the stage-specific analysis.
Abbreviations: KSS = Karolinska Sleepiness Scale, LS = least squares.

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 KSS score with improvement in the $HDRS_{17}$ insomnia factor score.

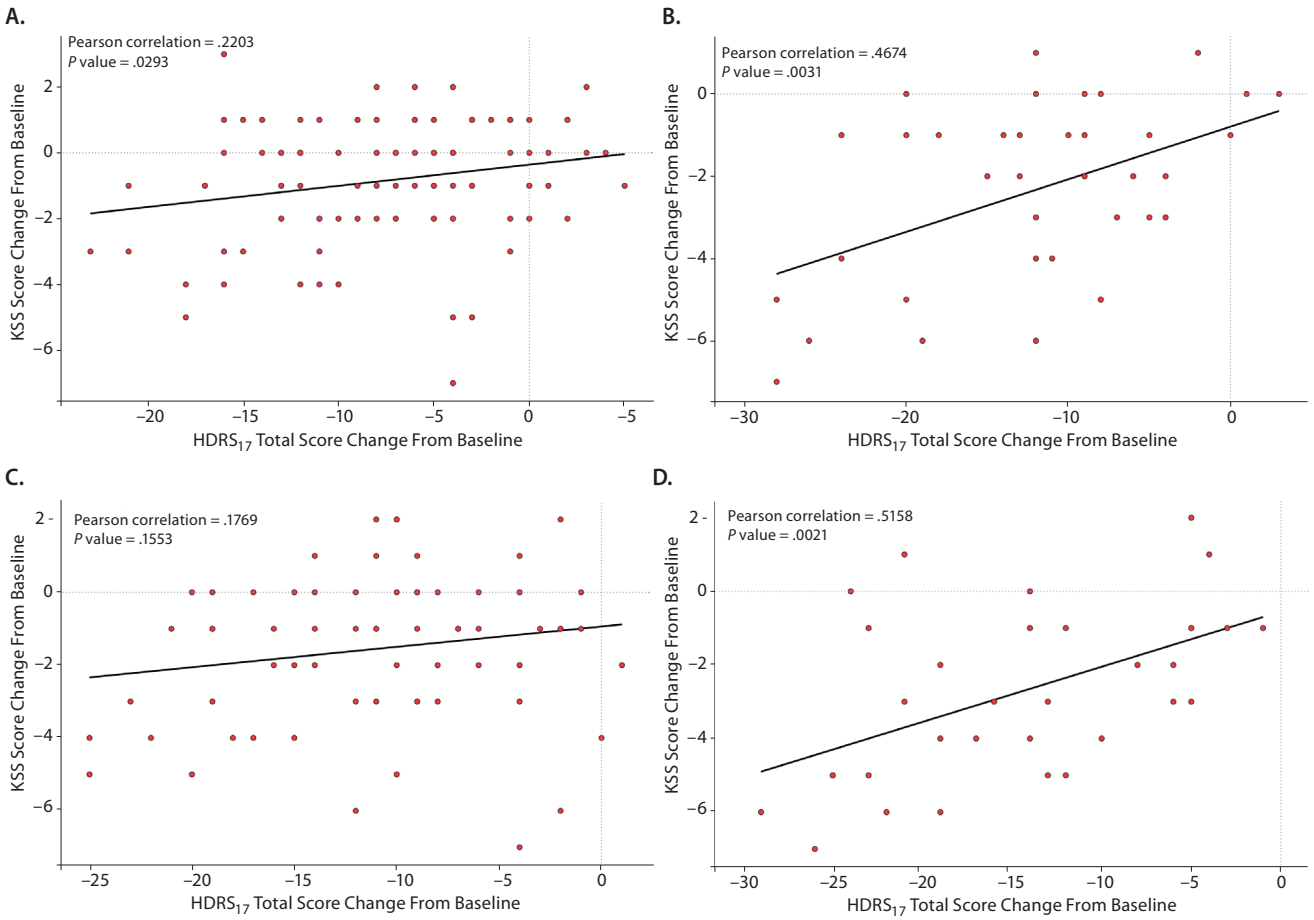
Mediator Analysis

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 ≥ 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 ≥ 6. Significant improvement with pimavanserin versus placebo was observed at each week

Figure 3. Correlation Between Change From Baseline to Week 5 for KSS and $HDRS_{17}$ 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 $HDRS_{17}$ 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: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, KSS = Karolinska Sleepiness Scale.

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 $HDRS_{17}$ total score were correlated with improvements in the $HDRS_{17}$ 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,[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 $HDRS_{17}$ 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[7–9] and an important residual symptom of MDD.[11] In a longitudinal study of depressed outpatients,[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*D trial[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[10,30,31] as well as on the risk for depression. A number of studies[14,30–32] have shown the effects of insomnia and sleep disturbances on MDD and the benefits of treating

insomnia on MDD outcomes including QoL. In longitudinal studies,[1,4] the presence of sleep disturbance in older women or men was associated with an increased risk for depression. In contrast, among patients with MDD and a baseline $HDRS_{17}$ insomnia factor score ≥ 4, a reduction in the insomnia factor score was associated with improvement in symptoms of MDD.[11,33] In addition to being a risk factor for MDD, insomnia also has been identified as an independent risk factor for suicide.[34–36] In a 6-year longitudinal study of patients with MDD,[37] the presence of insomnia and presence of suicidal ideation at baseline were risk factors for suicide attempts. Results from meta-analyses[34,38] have shown an association between the presence of sleep disorders and suicidal behavior in patients with psychiatric diagnoses, including MDD.

Limitations of this study included its basis as a post hoc analysis with endpoints that were not prespecified. The sample size calculation for Stage 2 was not achieved, which most likely is the explanation for the lack of statistical significance for comparisons in Stage 2. In addition, sleep disturbances and daytime sleepiness were based on patient report, and objective sleep measures were not administered. Further, in this study, the KSS was used retrospectively to assess sleepiness, although this instrument was designed and validated for prospective use to assess the level of sleepiness at a particular time of the day and is a measure of situational sleepiness.[39] Nevertheless, results showed a robust effect of adjunctive pimavanserin on sleep/wakefulness disturbances in MDD patients and suggest that an improvement in depressive symptoms accompanies improvements in sleep/wakefulness 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/m^2, 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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Potential conflicts of interest: **Dr Freeman**, in the past 36 months, has conducted investigator initiated trials/research for Takeda, JayMac, and Sage; has been on advisory boards for Otsuka, Alkermes, Janssen, Sage, and Sunovion; has served on an independent data safety and monitoring committee for Janssen (Johnson & Johnson); has performed medical editing for the GOED newsletter; has done speaking for/received honoraria from US Psychiatric Congress and Medscape; is an employee of Massachusetts General Hospital (MGH); and works with the MGH National Pregnancy Registry (Current Registry Sponsors: Teva [2019–present], Alkermes, Inc [2016–present]; Otsuka America Pharmaceutical, Inc [2008–present]; Forest/Actavis [2016–present], and Sunovion Pharmaceuticals, Inc [2011–Present]). As an employee of MGH, Dr Freeman works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and the National Institute of Mental Health [NIMH]. All (lifetime) disclosures for **Dr Fava** can be viewed online at http://mghcme.org/faculty/faculty-detail/maurizio_fava. 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REFERENCES

1. Paudel ML, Taylor BC, Diem SJ, et al; Osteoporotic Fractures in Men Study Group. Association between depressive symptoms and sleep disturbances in community-dwelling older men. *J Am Geriatr Soc*. 2008;56(7):1228–1235.
2. Geiger-Brown J, Rogers VE, Trinkoff AM, et al. Sleep, sleepiness, fatigue, and performance of 12-hour-shift nurses. *Chronobiol Int*. 2012;29(2):211–219.
3. Wilson M, Permito R, English A, et al. Performance and sleepiness in nurses working 12-h day shifts or night shifts in a community hospital. *Accid Anal Prev*. 2019;126:43–46.
4. Maglione JE, Ancoli-Israel S, Peters KW, et al; Study of Osteoporotic Fractures Research Group. Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women. *Sleep*. 2014;37(7):1179–1187.
5. Maglione JE, Ancoli-Israel S, Peters KW, et al. Depressive symptoms and subjective and objective sleep in community-dwelling older women. *J Am Geriatr Soc*. 2012;60(4):635–643.
6. Paterson LM, Nutt DJ, Wilson SJ. NAPSAQ-1: National Patient Sleep Assessment Questionnaire in depression. *Int J Psychiatry Clin Pract*. 2009;13(1):48–58.
7. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci*. 2008;10(3):329–336.
8. Fava M. Daytime sleepiness and insomnia as correlates of depression. *J Clin Psychiatry*. 2004;65(suppl 16):27–32.
9. Mendlewicz J. Sleep disturbances: core symptoms of major depressive disorder rather than associated or comorbid disorders. *World J Biol Psychiatry*. 2009;10(4):269–275.
10. Cutler AJ. The role of insomnia in depression and anxiety: its impact on functioning, treatment, and outcomes. *J Clin Psychiatry*. 2016;77(8):e1010.
11. Fava M, Ball S, Nelson JC, et al. Clinical relevance of fatigue as a residual symptom in major depressive disorder. *Depress Anxiety*. 2014;31(3):250–257.
12. Sakurai H, Suzuki T, Yoshimura K, et al. Predicting relapse with individual residual symptoms in major depressive disorder: a reanalysis of the STAR*D data. *Psychopharmacology (Berl)*. 2017;234(16):2453–2461.
13. Sunderajan P, Gaynes BN, Wisniewski SR, et al. Insomnia in patients with depression: a STAR*D report. *CNS Spectr*. 2010;15(6):394–404.
14. Gebara MA, Siripong N, DiNapoli EA, et al. Effect of insomnia treatments on depression: a systematic review and meta-analysis. *Depress Anxiety*. 2018;35(8):717–731.
15. Everitt H, Baldwin DS, Stuart B, et al. Antidepressants for insomnia in adults. *Cochrane Database Syst Rev*. 2018;5:CD010753.
16. Jha MK, Minhajuddin A, South C, et al. Worsening anxiety, irritability, insomnia, or panic predicts poorer antidepressant treatment outcomes: clinical utility and validation of the Concise Associated Symptom Tracking (CAST) Scale. *Int J Neuropsychopharmacol*. 2018;21(4):325–332.
17. Vanover KE, Weiner DM, Makhay M, et al. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N′-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. *J Pharmacol Exp Ther*. 2006;317(2):910–918.
18. Fava M, Dirks B, Freeman MP, et al. A phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder and an inadequate response to therapy (CLARITY). *J Clin Psychiatry*. 2019;80(6):19m12928.
19. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3):115–127.
20. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
21. First MB, Williams JBW, Karg RS, et al. *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association; 2016.
22. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
23. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. DHEW Publication No. ADM 76–338. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:218–222.
24. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996;11(suppl 3):89–95.
25. Kaida K, Takahashi M, Akerstedt T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol*. 2006;117(7):1574–1581.
26. Kraemer HC. A mediator effect size in randomized clinical trials. *Int J Methods Psychiatr Res*. 2014;23(4):401–410.
27. Patel N, LeWitt P, Neikrug AB, et al. Nighttime sleep and daytime sleepiness improved with pimavanserin during treatment of Parkinson's disease psychosis. *Clin Neuropharmacol*. 2018;41(6):210–215.
28. Nil R, Lütolf S, Seifritz E. Residual symptoms and functionality in depressed outpatients: a one-year observational study in Switzerland with escitalopram. *J Affect Disord*. 2016;197:245–250.
29. Nierenberg AA, Husain MM, Trivedi MH, et al. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychol Med*. 2010;40(1):41–50.
30. McCall WV, Blocker JN, D'Agostino R Jr, et al. Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression. *J Clin Sleep Med*. 2010;6(4):322–329.
31. McCall WV, Reboussin BA, Cohen W. Subjective measurement of insomnia and quality of life in depressed inpatients. *J Sleep Res*. 2000;9(1):43–48.
32. Murphy MJ, Peterson MJ. Sleep disturbances in depression. *Sleep Med Clin*. 2015;10(1):17–23.
33. Trivedi MH, Bandelow B, Demyttenaere K, et al. Evaluation of the effects of extended release quetiapine fumarate monotherapy on sleep disturbance in patients with major depressive disorder: a pooled analysis of four randomized acute studies. *Int J Neuropsychopharmacol*. 2013;16(8):1733–1744.
34. Malik S, Kanwar A, Sim LA, et al. The association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses: a systematic review and meta-analysis. *Syst Rev*. 2014;3(1):18.
35. McCall WV, Black CG. The link between suicide and insomnia: theoretical mechanisms. *Curr Psychiatry Rep*. 2013;15(9):389.
36. McCall WV, Blocker JN, D'Agostino R Jr, et al. Insomnia severity is an indicator of suicidal ideation during a depression clinical trial. *Sleep Med*. 2010;11(9):822–827.
37. Eikelenboom M, Beekman ATF, Penninx BWJH, et al. A 6-year longitudinal study of predictors for suicide attempts in major depressive disorder. *Psychol Med*. 2019;49(6):911–921.
38. Wang X, Cheng S, Xu H. Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behaviour in patients with depression. *BMC Psychiatry*. 2019;19(1):303.
39. Kaida K, Akerstedt T, Kecklund G, et al. Use of subjective and physiological indicators of sleepiness to predict performance during a vigilance task. *Ind Health*. 2007;45(4):520–526.