**Effect of Adjunctive Pimavanserin on Insomnia and Function in Patients With Major Depressive Disorder: Secondary Analysis From CLARITY**

**BACKGROUND**

- Sleep disturbances are a core symptom of major depressive disorder (MDD) that occur in up to 90% of patients.1,2
- Sleep disturbances are often associated with poor outcomes in MDD, including increased relapse1,3 and recurrence.4,5 and are associated with a need to achieve remission.

**Pimavanserin** is a 5-hydroxytryptamine (5-HT2A) receptor agonist or inverse agonist with low affinity at the 5-HT2A receptor, with no appreciable activity at adrenergic, dopaminergic, histaminergic, or muscarinic receptors.6

- Pimavanserin is approved by the US Food and Drug Administration for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. 

In the phase 2 CLARITY study (NCT01318340), pimavanserin demonstrated a significant reduction in symptoms of depression and improvement in function in patients with MDD and an inadequate response to antidepressant treatment.7

This post hoc analysis of CLARITY evaluated the effects of adjunctive pimavanserin on insomnia and sleepiness, and whether improvement in these symptoms mediate the improvement in depression and psychosocial function associated with pimavanserin.

**METHODS**

- **CLARITY** was a multicenter, randomized, double-blind, placebo-controlled study in patients with MDD.8
- A 2-stage sequential parallel-comparison design was used to randomize patients in Stage 1 in a 3:1 ratio to placebo or pimavanserin 34 mg per day daily added to current serotonin-norepinephrine reuptake inhibitor (SNRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) therapy for 5 weeks.9
- Placebo nonresponders after 5 weeks (17-item Hamilton Depression Rating Scale [HAMD]; 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**

- 18-55 years of age.
- Body mass index of 18-35 kg/m².
- Primary diagnosis of MDD and a current major depressive episode defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and confirmed by the Structured Clinical Interview for DSM-5 for Clinician Version (SCID-CV).
- History of MDD for ≥1 year before screening.
- Montgomery-Asberg Depression Rating Scale (total score ≤25; 11-point scale) on day of the screening visit and baseline visits.
- History of inadequate response to 1 or 2 adequate trials with an SSRI or SNRI antidepressant during the current depressive episode.

**Study Assessments/Outcomes**

- Level scores are change from baseline for the HAMD (insomnia factor score [items 4, 5, and 6]) and in patients with a score ≥5 at baseline.
- LSR score change from baseline.
- LSR score change from baseline in Kainiska Sleepiness Scale (KSS) score.
- LSR score change from baseline in Somnolence Diary Scale (SDS) total score and SDS Unproductive Days subscale for patients with a baseline KSS score of ≥6 (at least some signs of sleepiness).

**RESULTS**

- **HAMD Insomnia Factor**
  - In Stage 1, a significant (P < 0.05) improvement from baseline was observed with pimavanserin vs placebo at Weeks 2, 3, and 4 (Figure 1).
  - At Week 5, no differences were observed between Stage 2 between pimavanserin and placebo (n = 22) or for the overall weighted difference between treatments for Stages 1 and 2 (Table 1).

- **Kainiska Sleepiness Scale**
  - During Stage 1, a significant (P < 0.05) reduction from baseline for the KSS was observed with pimavanserin vs placebo from Week 1 to 5 (Figure 2).
  - No significant differences from baseline to Week 5 were observed between treatments for Stage 2.
  - For the SDS total score, the overall LSR (SE) weighted difference between treatments for Stages 1 and 2 at Week 5 was −0.63 (0.69) with a 95% CI of −1.92 to 0.65 (P = 0.342).

- **Sheean Disability Scale**
  - In Stage 1, patients with baseline KSS ≥6, a significant (P < 0.05) improvement from baseline was observed from Weeks 1 to 5 for the SDS total score (Figure 3, top) and Unproductive Days Subscale score (Figure 3, bottom).
  - No significant differences were observed between treatments for Stage 2.
  - For the SDS total score, the overall LSR (SE) weighted difference between treatments for Stages 1 and 2 at Week 5 was −0.15 (0.74) with a 95% CI of −1.6 to 1.3 (P = 0.82)

**CONCLUSIONS**

- Adjunctive pimavanserin significantly improved insomnia and sleepiness vs placebo as measured by the KSS and HAMD insomnia factor during treatment of MDD.
- This 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 insomnia or sleep disturbances.
- Limitations of the study were its post hoc analysis with endpoints that were not prespecified.
- A small sample size for some of the subgroups may have hindered findings of significance of Stage 2 of the study.
- **CLARITY** was a single, phase 2 study and results require replication.
- Nevertheless, results showed a greater effect of adjunctive pimavanserin vs placebo on sleep disturbance in patients with MDD, and suggest an improvement in depressive symptoms accompanies improvements in sleep/insomnia.
- **Phase 3 studies of adjunctive pimavanserin in patients with MDD will provide additional findings about its beneficial effects on insomnia and sleep disturbances.**

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**DISCLOSURES**

The authors report no conflicts of interest. ClinicalTrials.gov: NCT01318340. ClinicalTrials.gov: NCT01742718.

**REFERENCES**

4. Primary data are available on the ACADIA-Pharm.com website and in an additional file (1020303_web.pdf).