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NUPLAZID® (pimavanserin): Sleep Effects in Patients with Parkinson's Disease Psychosis

> This letter is provided in response to your specific request for information regarding the effect of pimavanserin on sleep in patients with Parkinson's disease (PD) psychosis.

Summary

- Pimavanserin's effect on sleep was assessed as an exploratory endpoint in **Study 020**, a randomized, double-blind, placebo-controlled, multi-center, Phase 3 study of pimavanserin 34 mg in 199 adult participants with hallucinations and delusions associated with PD psychosis, as measured with the Scales for Outcomes in Parkinson's Disease (SCOPA) Nighttime and Daytime sleep subscales.[1]
    - For the **SCOPA Nighttime exploratory endpoint**, the least squares mean (LSM) change from baseline to Day 43 was -1.42 with pimavanserin and -0.49 with placebo. The treatment difference (pimavanserin minus placebo) was -0.93 points.[1]
    - For the **SCOPA Daytime exploratory endpoint**, the LSM change from baseline to Week 6 was -2.21 for pimavanserin versus -0.99 for placebo, with the treatment difference (pimavanserin minus placebo) of -1.22 points.[1]
- An **exploratory post hoc analysis** of Study 020 analyzed the effect of baseline sleep disturbances on SCOPA Nighttime and Daytime sleep score changes from baseline to Day 43.[2]

Background

The effects of pimavanserin on sleep were evaluated as an exploratory endpoint in the pivotal Phase 3 study, ACP-103-020, using the SCOPA-Sleep scale,[1,3] which is a short questionnaire consisting of separate scales that evaluate nighttime sleep (SCOPA Nighttime) and daytime wakefulness (SCOPA Daytime). This scale was developed and validated for use in subjects with PD.[3]

ACP-103-020

ACP-103-020 was a randomized, double-blind, placebo-controlled, multi-center, Phase 3 study of pimavanserin 34 mg in 199 adult participants with hallucinations and delusions associated with PD psychosis.[1] Study participants had a diagnosis of PD (with or without dementia) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis, were present for at least one month, and were severe and frequent enough to warrant treatment with an antipsychotic. Participants were allowed to be on dopaminergic medications but were required to be on a stable dose for one month prior to baseline.[1,4]

Following a 2-week nonpharmacological lead-in period, participants were randomized to receive pimavanserin 34 mg/day (N=105) or placebo (N=94). Of those, 185 participants (95 in the

pimavanserin arm and 90 in the placebo arm) met the requirements to be included in the full analysis.[1]

Primary efficacy was evaluated based on change from baseline to Day 43 (Week 6) in the PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) total score. Participants in the pimavanserin 34 mg group experienced a statistically significant improvement in SAPS-PD scores from baseline to Day 43 compared with placebo (-5.79 vs. -2.73).[1,4] The treatment difference (pimavanserin minus placebo) was -3.06 (95% confidence interval [CI], -4.91 to -1.20; p=0.0014).[1] Although the primary endpoint was at Day 43, a statistically significant difference between pimavanserin and placebo was observed as early as Day 29 (p=0.0369).

Concomitant Sleep Medications

Table 1 summarizes the hypnotics and sedatives used as concomitant medications by study participants.[5]

Table 1. Concomitant Hypnotics and Sedatives: Safety Analysis Set[5]

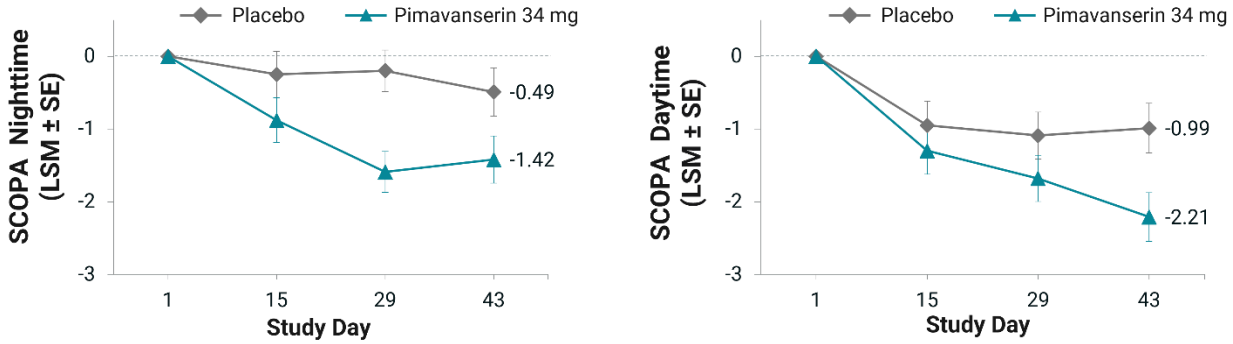
	Placebo (N=94) n (%)	Pimavanserin 34 mg (N=104) n (%)
Temazepam	6 (6.4%)	2 (1.9%)
Melatonin	5 (5.3%)	5 (4.8%)
Zolpidem	3 (3.2%)	4 (3.9%)
Ramelteon	1 (1.1%)	0
Diphenhydramine hydrochloride	0	1 (1.0%)
Doxepin hydrochloride	0	1 (1.0%)

Exploratory Endpoint

The effect of pimavanserin on nighttime sleep and daytime wakefulness was assessed as an exploratory endpoint using two outcome measures: the SCOPA Nighttime and Daytime sleep subscales.[1,3,6] The baseline mean SCOPA Nighttime score was 5.84 (standard deviation [SD], 3.84; n=94) for the pimavanserin group and 5.48 (SD, 3.82; n=89) for the placebo group.[5] The baseline mean SCOPA Daytime score was 7.65 (SD, 4.25; n=94) for the pimavanserin group and 7.33 (SD, 3.94; n=89) for the placebo group.[5]

Results for this exploratory analysis are shown in **Figure 1**. For SCOPA Nighttime, the LSM (standard error [SE]) change from baseline to Day 43 was -1.42 (0.32) with pimavanserin and -0.49 (0.33) with placebo (LSM [SE] treatment change: -0.93 [0.46]).[1] For SCOPA Daytime, the LSM (SE) change from baseline to Day 43 was -2.21 (0.34) with pimavanserin and -0.99 (0.34) with placebo (LSM [SE] treatment change: -1.22 [0.48]).[1]

Figure 1. SCOPA Nighttime Score and SCOPA Daytime Score Change from Baseline (LSM±SE) Over Time (MMRM; OC): Intent-to-Treat Analysis[1,5,6]



Abbreviations: LSM=least squares mean; MMRM=mixed-effect model repeated measures; OC=observed cases; SCOPA=Scales for Outcomes in Parkinson's Disease; SE=standard error.

Exploratory Post Hoc Analysis

SCOPA Nighttime and Daytime sleep score changes from baseline to Day 43 were stratified by the presence or absence of baseline nighttime sleep impairment or daytime sleepiness at baseline (**Table 2**) using the following definitions:[2]

- Nighttime sleep impairment: SCOPA Nighttime score <7 (absence) or ≥7 (presence)
- Daytime sleepiness: SCOPA Daytime score <5 (absence) or ≥5 (presence)

Table 2. SCOPA Nighttime and SCOPA Daytime Score Change from Baseline to Day 43 Stratified by Baseline Nighttime Sleep Impairment or Daytime Sleepiness (MMRM; OC): Intent-to-Treat Population[2]

	BL nighttime sleep impairment				BL daytime sleepiness			
	Absence (SCOPA Nighttime <7)		Presence (SCOPA Nighttime ≥7)		Absence (SCOPA Daytime <5)		Presence (SCOPA Daytime ≥5)	
LSM (SE)	PBO (n=56)	PIM (n=61)	PBO (n=34)	PIM (n=33)	PBO (n=26)	PIM (n=24)	PBO (n=63)	PIM (n=70)
SCOPA Nighttime								
n	52	56	33	31	24	22	61	65
Change from BL	0.27 (0.40)	0.22 (0.38)	−1.82 (0.56)	−4.35 (0.57)	−0.24 (0.57)	−0.78 (0.60)	−0.56 (0.40)	−1.66 (0.39)
Difference vs placebo*	−0.06 (0.55)		−2.54 (0.80)		−0.54 (0.83)		−1.10 (0.56)	
95% CI of difference	−1.15, 1.04		−4.14, −0.93		−2.20, 1.12		−2.21, 0.00	
SCOPA Daytime								
n	52	56	33	31	24	22	61	65
Change from BL	−1.05 (0.43)	−2.19 (0.42)	−0.92 (0.56)	−2.19 (0.58)	0.85 (0.53)	0.22 (0.56)	−1.67 (0.43)	−3.10 (0.41)
Difference vs placebo*	−1.14 (0.60)		−1.27 (0.81)		−0.62 (0.77)		−1.43 (0.59)	
95% CI of difference	−2.33, 0.05		−2.90, 0.35		−2.20, 0.95		−2.61, −0.26	

**Difference vs placebo indicates difference between LSMs (pimavanserin – placebo) from the MMRM analysis.*
Abbreviations: BL=baseline; CI=confidence interval; LSM=least squares mean; MMRM=mixed-effect model repeated measures; OC=observed cases; PBO=placebo; PIM=pimavanserin; SCOPA=Scales for Outcomes in Parkinson's Disease; SE=standard error.

These results should be interpreted cautiously since the analysis was not powered to detect differences between subgroups.

References

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