Safety of Pimavanserin for Parkinson's Disease Psychosis: Exploratory Analysis of Sedation and Sleep Data From Clinical Studies

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BACKGROUND

- Parkinson's disease is a common progressive neurodegenerative disorder characterized by motor symptoms of bradykinesia, rigidity, resting tremor, and disturbances of balance and posture[1]; additionally, patients can experience neuropsychiatric and non-motor symptoms, including psychosis (PDP) and sleep disturbances[1,2]
- Sleep disorders are a major cause of disability in Parkinson's disease, affecting 60%-98% of all patients[3]; sleep impairments can also occur in association with PDP[4,5]
- Pimavanserin, a 5-HT_{2A} receptor inverse agonist/antagonist, is the only FDA-approved treatment for hallucinations and delusions associated with PDP[6,7]; however, other atypical antipsychotics, such as quetiapine, are often used off-label[8-10]
- Sedation is a prominent side effect of other atypical antipsychotics[10,11] increasing the risk of falls and fractures in a population already prone to frequent daytime somnolence and sleep attacks[12]
- The objective of this analysis was to summarize the sleep and sedation-related safety and tolerability of pimavanserin for the treatment of PDP

METHODS

- Pimavanserin safety data were gathered from previously completed clinical studies (multiple study designs and treatment doses), which included treatment durations of ≥6 weeks and various exploratory outcome measures relevant to sleep and sedation (**Table 1**)

Table 1. Pimavanserin Studies Included for Safety and Sleep Analysis

Study	Description	Sedation/sleep exploratory endpoints
CONCEPT 2 (ACP-103-006)	A phase 2, 8-week (4 weeks of double-blind treatment), dose-escalation study of patients with PDP (N=60) randomized to pimavanserin (20 mg with possible increase to 40 or 60 mg[a]) or placebo with an OLE (ACP-103-010)	• Lightheadedness/ dizziness and nighttime sleep quality (Symptom Questionnaire) • Situational sleepiness (ESS)
Studies in PDP with ≥6-week treatment duration[b] (ACP-103-012/ ACP-103-014, and ACP-103-020)	A phase 2b/3, 6-week, international, randomized study of patients with PDP (N=298) randomized to pimavanserin (10 mg or 40 mg[a]) or placebo	• Nighttime sleep quality and daytime sleepiness (SCOPA-Sleep) • TEAEs
	A phase 3, 6-week, randomized, double-blind study of patients with PDP (N=199) randomized to pimavanserin (40 mg[a]) or placebo with an OLE (ACP-103-015)	• Nighttime sleep quality and daytime sleepiness (SCOPA-Sleep) • TEAEs
OLE studies[b] (ACP-103-010 and ACP-103-015)	An OLE of CONCEPT 2 (ACP-103-006) (N=39)	• TEAEs
	An OLE of the phase 3, 6-week study (ACP-103-020) (N=459)	• TEAEs
Older participants with neuropsychiatric symptoms related to NDD (ACP-103-046)	A phase 3b, 8-week (study duration of up to 16 weeks), multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study of patients with neuropsychiatric symptoms related to NDD[c] (N=784) randomized to pimavanserin (34 mg) or placebo	• Sleep disturbance (SDI)
Older, healthy participant sleep study (ACP-103-011)	A 13-day, double-blind, randomized study of older (mean age >51 years) healthy adults (N=45) randomized to pimavanserin (1, 2.5, 5, or 20 mg in morning)[d] or placebo	• Nighttime sleep quality (SWS measured by polysomnography)

ESS, Epworth Sleepiness Scale; NDD, neurodegenerative disease; OLE, open-label extension; PDP, Parkinson's disease psychosis; SCOPA-Sleep, Scales for Outcomes in Parkinson's Disease – Sleep; SDI, Sleep Disorders Inventory; SWS, slow-wave sleep; TEAEs, treatment-emergent adverse events.
[a]The dosages of pimavanserin tartrate correspond to the dosages of pimavanserin free base as follows: 20 mg pimavanserin tartrate is equivalent to 17 mg pimavanserin free base; 40 mg pimavanserin tartrate is equivalent to 34 mg pimavanserin free base.[6]
[b]An integrated summary of safety study was conducted, which consisted of the ≥6-week treatment duration studies (ACP-103-012, ACP-103-014, and ACP-103-020) and the OLE studies (ACP-103-010 and ACP-103-015).
[c]NDDs assessed included Alzheimer's disease, vascular dementia, Parkinson's disease (with or without dementia), frontotemporal dementia, and dementia with Lewy bodies.

RESULTS

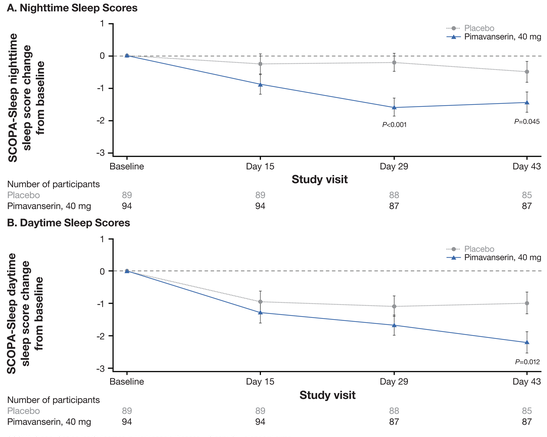
- In CONCEPT 2 (ACP-103-006), Symptom Questionnaire event rates and Epworth Sleepiness Scale scores were similar between pimavanserin and placebo groups (**Table 2**)
- In study ACP-103-020, pimavanserin demonstrated significant improvements over placebo in both nighttime (**Figure 1A**) and daytime (**Figure 1B**) sleep scores on the Scales for Outcomes in Parkinson's Disease (SCOPA)-Sleep. In ACP-103-012, significant improvements with pimavanserin vs placebo were observed in nighttime (**Figure 2A**) but not daytime (**Figure 2B**) sleep scores

Table 2. Symptom Questionnaire and ESS Scores (ACP-103-006)

Events and severity, n (%)	Pimavanserin		Placebo	
	Week 4	Week 8	Week 4	Week 8
Symptom Questionnaire	(n=29)		(n=31)	
Lightheadedness/dizziness				
None	14 (48.3)	6 (20.7)	9 (29.0)	10 (32.3)
Mild	9 (31.0)	12 (41.4)	13 (41.9)	10 (32.3)
Moderate	2 (6.9)	2 (6.9)	7 (22.6)	4 (12.9)
Severe	0	0	0	0
Poor sleeping at night				
None	7 (24.1)	7 (24.1)	13 (41.9)	12 (38.7)
Mild	5 (17.2)	5 (17.2)	6 (19.4)	6 (19.4)
Moderate	11 (37.9)	6 (20.7)	5 (16.1)	4 (12.9)
Severe	2 (6.9)	2 (6.9)	5 (16.1)	2 (6.5)
Epworth Sleepiness Scale	(n=28)		(n=31)	
Total score, mean (SE)	13.1 (0.87)		11.5 (0.99)	
Change from baseline to week 4	−0.5 (0.79)		−0.3 (0.70)	

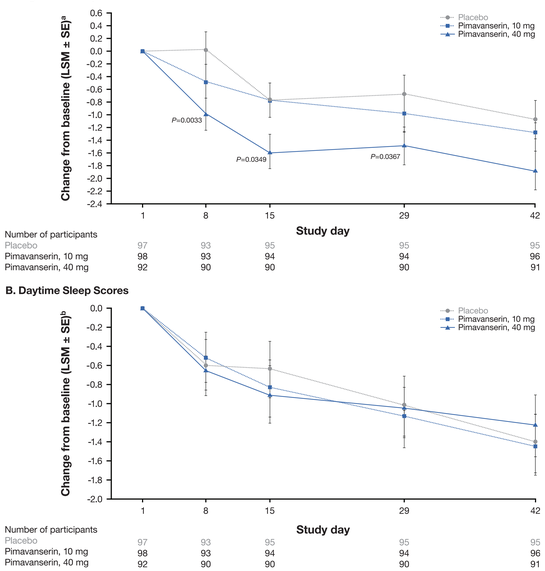
ESS, Epworth Sleepiness Scale; SE, standard error.

Figure 1. Change From Baseline to Week 6 for Pimavanserin (40 mg) and Placebo Groups for the SCOPA-Sleep Scores (ACP-103-020; Intent-to-Treat Population)



SCOPA-Sleep, Scales for Outcomes in Parkinson's Disease – Sleep; SE, standard error.
[a]SCOPA-Sleep nighttime sleep score range is 0-15; a negative change in score indicates improvement in nighttime sleep.
[b]SCOPA-Sleep daytime sleep score range is 0-18; a negative change in score indicates improvement in sleepiness.

Figure 2. Change From Baseline to Week 6 for Pimavanserin (10 and 40 mg) and Placebo Groups for the SCOPA-Sleep Scores (ACP-103-012; Intent-to-Treat Population)



LSM, least squares mean; SCOPA-Sleep, Scales for Outcomes in Parkinson's Disease – Sleep.
Missing data were corrected using the last observation carried forward.
[a]SCOPA-Sleep nighttime sleep score range is 0-15; a negative change in score indicates improvement in nighttime sleep.
[b]SCOPA-Sleep daytime sleep score range is 0-18; a negative change in score indicates improvement in sleepiness.

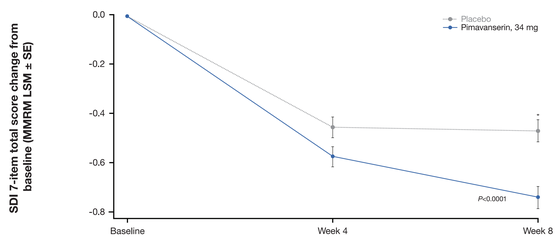
Table 3. Select TEAEs in ≥2% Participants (All Pimavanserin or Placebo Groups) From Studies With ≥6-Week Treatment Duration and Partial Data From OLE Studies[a]

Events, n (%)	All pimavanserin doses (10, 20, and 40 mg) (n=383)	Pimavanserin 40 mg OLE[b] (n=184)	Placebo (n=231)
Somnolence	11 (2.9)	4 (2.2)	6 (2.6)
Insomnia	10 (2.6)	4 (2.2)	7 (3.0)
Orthostatic hypotension	6 (1.6)	4 (2.2)	12 (5.2)
Dizziness	17 (4.4)	3 (1.6)	10 (4.3)

OLE, open-label extension; TEAE, treatment-emergent adverse event.
[a]An integrated summary of safety study was conducted, which consisted of the ≥6-week treatment duration studies (ACP-103-012, ACP-103-014, and ACP-103-020) and the OLE studies (ACP-103-010 and ACP-103-015).
[b]Includes adverse events up to day 72 for participants in OLE Study 015 (ACP-103-015) who were in the placebo group in the ≥6-week treatment duration studies (ACP-103-012/ACP-103-014, and ACP-103-020).

- For the ≥6-week dataset, rates of relevant treatment-emergent adverse events were similar between groups (**Table 3**)
- In patients with neuropsychiatric symptoms related to neurodegenerative disease, pimavanserin was associated with significant improvements in Sleep Disorders Inventory scores compared to placebo by week 8 (**Figure 3**)
- For the healthy volunteer study (ACP-103-011), pimavanserin was associated with increases in slow-wave sleep duration (**Table 4**)

Figure 3. Change From Baseline to Weeks 4 and 8 for Pimavanserin and Placebo Groups for the SDI Total Score (ACP-103-046)



LSM, least squares mean; MMRM, mixed model for repeated measures; SDI, Sleep Disorders Inventory.
[a]MMRM LSM difference (SE) at week 8: −0.3 (0.06), *P*<0.0001; LSM from MMRM with fixed categorical effects of region (ie, North America, Europe, or rest of world), planned treatment, visit, treatment-by-visit interaction, and fixed continuous covariates of baseline SDI score and baseline SDI score-by-visit interaction.
[b]40 mg pimavanserin tartrate is equivalent to 34 mg pimavanserin free base.

Table 4. Effects of Pimavanserin Versus Placebo on Duration (min) of SWS[a] (ACP-103-011)

Time Point	Pimavanserin				Placebo (n=9)
	1 mg (n=9)	2.5 mg (n=9)	5 mg (n=9)	20 mg (n=9)	
Baseline	63.39±26.12	54.00±30.88	57.61±33.06	83.94±21.44	67.39±32.06
Day 1	69.78±32.14	75.83±50.91	94.89±39.84	129.94±36.29	56.22±19.12
DLS mean[b]	17.3	32.4	48.1	57.9	
P value[c]	0.178	**0.013**	**<0.001**	**<0.001**	
Day 13	68.78±31.01	73.61±50.82	99.56±49.64	122.94±44.69	64.28±13.96
DLS mean[b]	8.3	22.2	44.7	42.8	
P value[c]	0.519	0.088	**<0.001**	**<0.001**	
Overall treatment effect					
DLS mean[b]	12.8	27.3	46.4	50.4	
P value[d]	0.160	**0.004**	**<0.001**	**0.001**	

ANCOVA, analysis of covariance; DLS, difference between least squares; SWS, slow-wave sleep.
Data are presented as mean ± SD unless otherwise noted. The overall ANCOVA for treatment was *P*<0.001.
Bolded *P* values indicate statistical significance.
[a]SWS was measured via polysomnography.
[b]The DLS mean represents the difference between least squares means for each pimavanserin and placebo dose (pimavanserin – placebo).
[c]The *P* value for the treatment effect from ANCOVA model at the time point.
[d]The *P* value for the overall treatment effect (averaged over study days 1 and 13).

CONCLUSIONS

- These data suggest that pimavanserin may be associated with low levels of sedation and other sleep-related adverse events, as well as improvements in nighttime sleep and sleep architecture
- Results should be interpreted with caution because the data were analyzed post hoc from various prior clinical studies of pimavanserin

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