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NUPLAZID® (pimavanserin): Individual Domains of the SAPS-PD used in Parkinson's Disease Psychosis Pivotal Study

This letter is provided in response to your specific request for information regarding the outcomes for the individual domains of the Parkinson's disease (PD)-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) from the pimavanserin pivotal study in PD psychosis.

Summary

- In a **supportive analysis** of the pivotal Phase 3 study of pimavanserin in participants with hallucinations and delusions associated with PD psychosis (N=199), an effect was seen on both the hallucinations and delusions components of the SAPS-PD.[1]
- For the **SAPS-PD Hallucinations domain**, the auditory (H1), visual (H6), and global (H7) items were the main contributors to the score change from baseline.[2]
- For the **SAPS-PD Delusions domain**, the persecutory (D1) item was the main contributor to the score change from baseline.[2]

Pivotal Phase 3 Study (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.[3] 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. Primary efficacy was evaluated based on change from baseline to Day 43 (Week 6) in the SAPS-PD total score.[1,3]

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.[3]

Baseline Characteristics

Baseline demographics and clinical characteristics were similar between the two groups. Among the 185 participants, the mean age was 72 years (**Table 1**). The majority of participants were male (63%) and white (95%). The SAPS-PD score at baseline was 14.7 (standard deviation [SD] 5.55) and 15.9 (6.12) in the placebo and pimavanserin arms, respectively.[3]

Table 1. Selected Baseline Characteristics (Full Analysis Set)[3]

	Placebo (n=90)	Pimavanserin (n=95)
Age, years	72.4 (7.92)	72.4 (6.55)
Sex, female	38 (42%)	31 (33%)
Ethnic group, white	85 (94%)	90 (95%)
Body-mass index, kg/m²	26.4 (5.65)	26.2 (4.57)
MMSE score	26.6 (2.40)	26.0 (2.61)
Time since first PD psychosis symptoms, months	36.4 (39.57)	30.9 (30.01)
SAPS-PD	14.7 (5.55)	15.9 (6.12)
CGI-S	4.32 (0.91)	4.27 (0.92)

Data are mean (SD) or n (%). The full analysis set consisted of all patients who received ≥1 dose and had SAPS assessments at baseline and ≥1 post-baseline.
Abbreviations: CGI-S=Clinical Global Impression-Severity; MMSE=Mini-Mental State Examination; PD=Parkinson's disease; SAPS=Scale for the Assessment of Positive Symptoms; SAPS-PD=PD-adapted Scale for the Assessment of Positive Symptoms; SD=standard deviation.

Results

Primary Efficacy

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).[1,3] The treatment difference (pimavanserin minus placebo) was -3.06 (95% confidence interval [CI], -4.91 to -1.20; p=0.0014).[3] 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).

Supportive Efficacy

An effect was seen on both the hallucinations and delusions components of the SAPS-PD (**Table 2**).[1]

Table 2. Change from Baseline to Day 43 in SAPS-PD Hallucinations and Delusions Components (N=185)[1]

Endpoint	Treatment group	Mean baseline score (SD)	LSM change from baseline (SE)	Placebo-subtracted difference* (95% CI)
SAPS-PD Hallucinations†	Pimavanserin	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	
SAPS-PD Delusions†	Pimavanserin	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	

**Difference (drug minus placebo) in least-squares mean change from baseline.*
†Supportive analysis.
Abbreviations: CI=confidence interval; LSM=least squares mean; SAPS-PD=PD-adapted Scale for the Assessment of Positive Symptoms; SD=standard deviation; SE=standard error.

Table 3 summarizes the score changes from baseline to Day 43 for individual items in the SAPS-PD Hallucinations domain.[2] The auditory (H1), visual (H6), and global (H7) items were the main contributors to the score change from baseline in the SAPS-PD Hallucinations domain.

Table 3. Hallucinations Domain: SAPS-PD Individual Item Score Change from Baseline to Day 43 (OC, MMRM; ITT Analysis Set*)[2]

Item	Treatment group	Mean baseline score (SD)	LSM change from baseline (SE)	Placebo-subtracted difference† (95% CI)
H1 - Auditory hallucinations	Pimavanserin	1.7 (1.86)	-0.64 (0.16)	-0.56 (-1.01, -0.11)
	Placebo	1.0 (1.48)	-0.08 (0.16)	
H3 - Voices conversing	Pimavanserin	1.1 (1.73)	-0.29 (0.12)	0.09 (-0.24, 0.43)
	Placebo	0.5 (1.18)	-0.38 (0.12)	
H4 - Somatic or tactile hallucinations	Pimavanserin	0.7 (1.28)	-0.31 (0.09)	-0.00 (-0.24, 0.24)
	Placebo	0.6 (1.43)	-0.30 (0.09)	
H6 - Visual hallucinations	Pimavanserin	3.9 (1.39)	-1.31 (0.18)	-0.61 (-1.12, -0.11)
	Placebo	4.1 (1.32)	-0.69 (0.18)	
H7 - Global rating of severity of hallucinations	Pimavanserin	3.8 (0.96)	-1.16 (0.15)	-0.66 (-1.08, -0.25)
	Placebo	3.7 (1.04)	-0.50 (0.15)	

**95 participants in the pimavanserin arm, and 90 in the placebo arm.*
†Difference (drug minus placebo) in LSM change from baseline.
Abbreviations: CI=confidence interval; ITT=intent-to-treat; LSM=least squares mean; MMRM=mixed model repeated measures analysis; OC=observed cases; SAPS-PD=PD-adapted Scale for the Assessment of Positive Symptoms; SD=standard deviation; SE=standard error.

Table 4 summarizes the score changes from baseline to Day 43 for items in the SAPS-PD Delusions domain.[2] The persecutory (D1) item contributes the bulk of the change from baseline score of the SAPS-PD Delusions domain.

Table 4. Delusions Domain: SAPS-PD Individual Item Score Change from Baseline to Day 43 (OC, MMRM; ITT Analysis Set*)[2]

Item	Treatment group	Mean baseline score (SD)	LSM change from baseline (SE)	Placebo-subtracted difference† (95% CI)
D1 - Persecutory delusions	Pimavanserin	1.4 (1.63)	-0.66 (0.14)	-0.50 (-0.89, -0.10)
	Placebo	1.2 (1.57)	-0.16 (0.14)	
D2 - Delusions of jealousy	Pimavanserin	0.5 (1.09)	-0.31 (0.07)	-0.17 (-0.37, 0.04)
	Placebo	0.6 (1.19)	-0.14 (0.07)	
D7 - Ideas and delusions of reference	Pimavanserin	0.3 (0.96)	-0.20 (0.08)	-0.03 (-0.24, 0.19)
	Placebo	0.5 (1.15)	-0.17 (0.08)	
D13 - Global rating of severity of delusions	Pimavanserin	2.5 (1.61)	-0.80 (0.15)	-0.27 (-0.68, 0.14)
	Placebo	2.5 (1.55)	-0.53 (0.15)	

**95 participants in the pimavanserin arm, and 90 in the placebo arm.*
†Difference (drug minus placebo) in LSM change from baseline.
Abbreviations: CI=confidence interval; ITT=intent-to-treat; LSM=least squares mean; MMRM=mixed model repeated measures analysis; OC=observed cases; SAPS-PD=PD-adapted Scale for the Assessment of Positive Symptoms; SD=standard deviation; SE=standard error.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. [Link]
2. Acadia Pharmaceuticals Inc. Data on file. ACP-103-020 SAPS-PD Individual Item Analysis. 2016.
3. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet.* 2014;383(9916):533-540. [PubMed]