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NUPLAZID® (pimavanserin) Clinical Development Program in Parkinson's Disease Psychosis

This letter is provided in response to your specific request for information regarding the pimavanserin clinical development program in Parkinson's Disease (PD) psychosis.

Summary

- The 4-week, Phase 2 proof-of-concept study (**Study 006**, N=60) demonstrated that once daily (QD) doses up to 51 mg of pimavanserin did not worsen motor control in participants with PD psychosis compared with placebo, as assessed by the primary endpoint, the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III.[1]
- Two 6-week, Phase 2b/3 studies with almost identical design evaluated pimavanserin dosing regimens of 8.5 mg and 34 mg QD (**Study 012**, N=298),[2] and 8.5 and 17 mg QD (**Study 014**; N=123) in participants with PD psychosis.[3] When the primary endpoint of change from baseline in the Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions (SAPS-H+D) score at Day 42 was not met in Study 012 due to a high placebo response,[2,4] Study 014 was discontinued early with about half of the intended participant enrollment.[3,5]
- Key learnings from the Phase 2b/3 trials contributed to the study design of the 6-week pivotal Phase 3 trial (**Study 020**).[5]
- In **Study 020**, participants with PD psychosis treated with pimavanserin 34 mg QD exhibited a statistically significant improvement in hallucinations and delusions, as assessed by the Scale for Assessment of Positive Symptoms for Parkinson's disease (**SAPS-PD**), compared with placebo at Day 43.
    - Pimavanserin did not show treatment-related impairment in motor function compared to placebo, as measured using the **UPDRS Parts II+III** (key secondary endpoint).
    - **Treatment-emergent adverse events** (TEAEs) occurring in at least 5% of participants included nausea, peripheral edema, urinary tract infection (UTI), fall, confusion, headache, and hallucination.[6]

Clinical Studies in PD Psychosis

The efficacy and safety of pimavanserin for the treatment of PD psychosis have been evaluated in four short-term placebo-controlled studies: one Phase 3 trial, two Phase 2b/3 trials, and one Phase 2 trial (**Table 1**). In these studies, a range of pimavanserin doses was evaluated (8.5 to 51 mg) and participants received a fixed daily dose of pimavanserin (except for Study 006, in which participants underwent dose escalation at periodic intervals).[5]

Table 1. Pimavanserin Phase 2b/3 Studies in PD Psychosis[5]

Study Type	Study #	Participants, N	Design (Primary Endpoint)	Treatment
Concept Phase 2	006	60	4-week, multi-center, randomized, double-blind, placebo-controlled trial in the U.S. (UPDRS Parts II+III)	17, 34, or 51 mg dose of pimavanserin daily with flexible dose titration vs. placebo
Phase 2b/3	012	298	6-week multi-center, randomized, double-blind, placebo-controlled trial in the U.S., Europe and India (SAPS-H+D)	8.5 or 34 mg dose of pimavanserin daily vs. placebo
Phase 2b/3	014	123	6-week multi-center, randomized, double-blind, placebo-controlled trial in the U.S. and Europe (SAPS-H+D)	8.5 or 17 mg dose of pimavanserin daily vs. placebo
Pivotal Phase 3	020	199	6-week, multi-center, randomized, double-blind, parallel group, placebo-controlled trial in the U.S. and Canada (SAPS-PD)	34 mg dose of pimavanserin daily vs. placebo

Abbreviations: PD=Parkinson's disease; SAPS-H+D=Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions subscales; SAPS-PD=PD-adapted Scale for the Assessment of Positive Symptoms; UPDRS=Unified Parkinson's Disease Rating Scale.

ACP-103-006

Participants in Study 006 had to have visual and/or auditory moderate-to-severe hallucinations and/or delusions for ≥4 weeks prior to study entry (i.e., score ≥4 as assessed by the hallucinations and delusions sections of the Neuropsychiatry Inventory [NPI] scale) and have been stable on an antiparkinsonian drug for ≥1 week prior to the study and through Week 4 of treatment.[1]

Results

Among the 60 participants enrolled (29 pimavanserin, 31 placebo), the overall mean age was 70.9 years. The majority of participants were male (76.7%) and white (98.3%). At baseline, the NPI total score of delusions and hallucinations was 10.9 (standard error [SE] 0.75).[1] Most subjects in the active arm escalated to the 34 mg dose level, without need for further escalation to 51 mg: the mean final daily dose was 38.1 mg.[4,5]

For the primary endpoint, the combined score of UPDRS Parts II (Activities of Daily Living) and III (Motor Examination), the LSM mean change from baseline to Day was -3.05 for pimavanserin and -3.86 for placebo. The difference in LSM between pimavanserin and placebo (-0.81) was not statistically significant (p=0.74, 95% confidence interval [CI]: –4.18, 5.80). Similar results were observed for the UPDRS Parts II and III scores analyzed as separate scores (**Table 2**).[1]

Table 2. UPDRS Scores: Change from Baseline to Day 28 and Estimated Treatment Effects for the PP-OC Participant Population (Study ACP-103-006)[1]

	Pimavanserin		Placebo		Estimated treatment effect		
	LSM	95% CI	LSM	95% CI	Difference in LSM	95% CI	P value
Part II	–1.68	–3.38, 0.02	–1.42	–3.05, 0.20	–0.26	–2.68, 2.17	0.83
Part III	–0.99	–3.72, 1.74	–2.64	–5.29, 0.01	1.65	–2.25, 5.55	0.40
Parts II and III	–3.05	–6.56, 0.46	–3.86	–7.20, –0.53	–0.81	–4.18, 5.80	0.74

Negative numbers represent improvement.
Abbreviations: CI=confidence interval; LSM=least square mean; OC=observed case; PP=per protocol; UPDRS=Unified Parkinson's Disease Rating Scale.

Overall, there was no significant difference in the incidence of TEAEs in the placebo- and pimavanserin-treated participants. In total, 133 TEAEs were reported in 21 (72.4%) participants receiving pimavanserin and 24 (77.4%) participants receiving placebo. The most common TEAEs in the pimavanserin group were somnolence, peripheral edema, and increase in blood urea nitrogen (10.3% each). In the placebo arm, the most commonly occurring TEAEs were hallucinations (five participants, 16.1%), dizziness (four participants, 12.9%), and fall, headache, confusional state and hypotension each occurring in three (9.7%) participants.[1]

ACP-103-012

All participants were ≥40 years of age with PD for ≥one year and had visual and/or auditory hallucinations and/or delusions (combined score of ≥4 on the NPI items A [delusions] and/or B [hallucinations], and a baseline SAPS-H+D score ≥5) occurring during the four weeks prior to study screening. These symptoms must have developed after PD diagnosis was established and participants were required to be on a stable dose of anti-PD medication for one month prior to baseline.[2]

Results

The mean age for the total population was 69.5 years, with a majority of male (63.1%) and white (86.1%) participants. The mean baseline SAPS-H+D score was 15.4 (SE 0.51).[2]

For the primary endpoint analysis, both pimavanserin treatment arms failed to demonstrate significant improvement in SAPS-H+D score compared with placebo (**Table 3**). All three arms showed improvement in least squares mean (LSM) SAPS-H+D scores at Day 42.[2] The high placebo response rate (42%) may have limited the ability to detect treatment effects.[7]

Assessment of the primary endpoint was performed by central raters in the U.S. and by site-based raters in India and the rest of the world. In an exploratory analysis by region, the placebo response rate for the mean change from baseline to Day 42 in the SAPS-H+D score was lowest in the U.S. region compared with other regions. In a post-hoc analysis of the primary endpoint, the 20-item SAPS-H+D data were analyzed using the SAPS-PD scale. Using this approach, the reported difference between the pimavanserin 34 mg group and placebo in the U.S. region was in favor of pimavanserin (treatment difference was 2.66 points [95% CI: -5.31 to 0.00]; p=0.0498). For sites outside of the U.S., there was no difference in SAPS-PD scores between treatment arms.[5]

Table 3. SAPS-H+D Score - Change from Baseline to Day 42 (LOCF): Intent-to-Treat Analysis Set (Study ACP-103-012)[2]

	Placebo (N=97)	Pimavanserin	
		8.5 mg QD (N=98)	34 mg QD (N=92)
Change from Baseline	n=95	n=96	n=91
LS mean	-5.9	-5.8	-6.7
Difference of LS mean (95% CI)		0.1 (-1.7, 2.0)	-0.8 (-2.7, 1.1)
p-value		0.8825	0.4184

Abbreviations: CI=confidence interval; LOCF=last observation carried forward; LS=least squares; SAPS-H+D=Scale for the Assessment of Positive Symptoms- Hallucinations and Delusions subscales; SE=standard error.

On Day 42, a decrease from baseline in the UPDRS Parts II+III score (key secondary endpoint) was observed across the treatment groups (LSM placebo, -2.94 vs. pimavanserin 8.5 mg, -1.41 and pimavanserin 34 mg, -3.13), and the magnitude of the treatment difference (pimavanserin minus placebo) was 1.53 (95% CI, -1.24, 4.31) in the 8.5 mg group and -0.19 (95% CI, -2.99, 2.62) in the 34 mg group. Since the upper limit of the 2-sided 95% CI for the treatment difference was ≤5, non-inferiority of the pimavanserin 8.5 mg and 34 mg groups compared to placebo was concluded for the change from baseline to Day 42.[2]

Overall, TEAEs were experienced by 61.2% of subjects in the placebo group, 59.6% in the pimavanserin 8.5 mg, and 51.0% in the pimavanserin 34 mg group. TEAEs occurring in at least 5% of participants in any treatment group are summarized in **Table 4**.[2]

Table 4. TEAEs Experienced by ≥5% of Subjects in Any Treatment Group: Safety Analysis Set (ACP-103-012)[2]

	Placebo (N=98) n (%)	Pimavanserin	
		8.5 mg QD (N=99) n (%)	34 mg QD (N=98) n (%)
Dizziness	4 (4.1)	7 (7.1)	7 (7.1)
Headache	6 (6.1)	4 (4.0)	4 (4.1)
Nausea	4 (4.1)	4 (4.0)	8 (8.2)
Constipation	3 (3.1)	4 (4.0)	5 (5.1)
Edema	1 (1.0)	2 (2.0)	7 (7.1)
Confusional state	3 (3.1)	5 (5.1)	5 (5.1)
Fall	11 (11.2)	5 (5.1)	4 (4.1)
Orthostatic hypotension	9 (9.2)	4 (4.0)	2 (2.0)

Abbreviations: QD=once daily; TEAE=treatment-emergent adverse event.

Two (2.0%) subjects in the placebo group, five (5.1%) in the pimavanserin 8.5 mg group, and five (5.1%) in the pimavanserin 34 mg group experienced a serious TEAE. Three (3.1%) subjects in the placebo group, seven (7.1%) in the pimavanserin 8.5 mg group, and six (6.1%) in the pimavanserin 34 mg group discontinued due to a TEAE. The most common TEAE that led to discontinuation was confusional state in two (2.0%) subjects in the pimavanserin 8.5 mg group. Two participants died during the study: 1 subject in the 8.5 mg group due to myocardial infarction, and 1 subject in the 34 mg group due to respiratory. Both deaths were considered by the Investigator to be unrelated to study drug.[2]

ACP-103-014

Study 014 was stopped early on the basis of the results from Study 012. Of the planned sample size of 280 participants, a total of 123 participants were enrolled before study termination and the intent-to-treat (ITT) analysis set included 117 participants.[3,5] The mean age for the total population was 72.3 years, with a majority of participants being male (63.2%) and white (97.4%). The mean baseline SAPS-H+D score was 16.1 (SE 0.78).[3]

Although there were some suggestions of positive efficacy signals with the 17 mg dose, very little can be concluded from the completed analysis due to the premature termination of the study and the small size of the dataset. The primary endpoint based on the SAPS-H+D showed a favorable trend for the 17 mg dose but failed to achieve significance (treatment difference of -2.1 [95% CI, -4.9 to 0.8]; LSM change from baseline -6.5 for pimavanserin).[3,5]

On Day 42, a decrease from baseline in the UPDRS Parts II+III score (key secondary endpoint) was observed across the treatment groups (LSM placebo, -1.8 vs. pimavanserin 17 mg, -3.9), and the magnitude of the treatment difference (pimavanserin 20 mg minus placebo) was -2.1 (95% CI, -5.9, 1.8). Since the upper limit of the 2-sided 95% CI for the treatment difference was ≤5, non-inferiority of the pimavanserin 17 mg group compared to placebo was concluded.[3]

ACP-102-020: Pivotal Phase 3 Study[6]

Several key findings from the Phase 2b/3 studies led to the modifications of the methodology for Study 020. Specific protocol refinements to Study 020 intended to optimize study design, and reduce variability and placebo response included:[5]

- Enrollment of subjects with moderate-to-severe symptoms that were sufficiently frequent (i.e., occurring weekly) to be accurately measured over a 6-week treatment period.
- Independent centralized and blinded ratings procedure for the primary outcome measure
- Nonpharmacologic, brief psychosocial therapy adapted for PD (BPST-PD) used during the 2-week screening period to screen out subjects who did not require pharmacological intervention
- Two-arm design and fewer number of study visits in order to minimize expectancy bias
- Use of the SAPS-PD for the primary endpoint measure, which captures those symptoms that are characteristic of the symptoms expressed in PD psychosis

Participants in Study 020 had a diagnosis of PD (with or without dementia) established ≥1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis, were present for ≥one month, and were severe and frequent enough to warrant treatment with an antipsychotic.[6,8,9]

After screening, participants entered a 2-week lead-in period during which nonpharmacological BPST-PD was used. Following confirmation of eligibility at baseline, 199 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 (received ≥1 dose and had a SAPS assessment at baseline and ≥1 post-baseline).[6]

Baseline Characteristics

Baseline demographics and clinical characteristics were similar between the two groups. Among the 185 participants, the mean age was 72 years (**Table 5**). 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 groups, respectively.[6]

Table 5. Selected Baseline Characteristics: Full Analysis Set (ACP-103-020)[6,8]

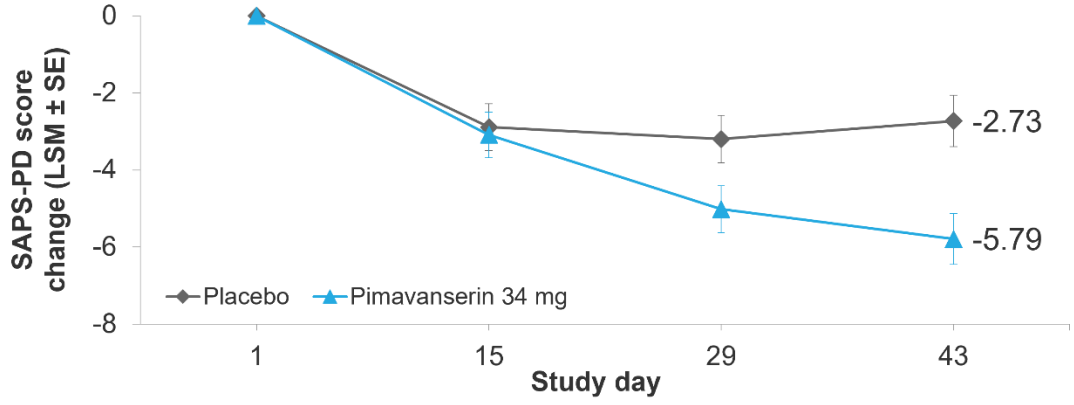
	Placebo (n=90)	Pimavanserin (n=95)
Age, years	72.4 (7.92)	72.4 (6.55)
Sex, female	38 (42%)	31 (33%)
Ethnic group, white	85 (94%)	90 (95%)
MMSE score	26.6 (2.40)	26.0 (2.61)
UPDRS-II score	19.3 (6.77)	18.7 (6.62)
UPDRS-III score	33.3 (12.23)	32.8 (12.86)
Use of dopaminergic drugs at baseline and throughout trial	89 (99%)	94 (99%)
Use of cholinesterase inhibitors at baseline and throughout trial	32 (36%)	31 (33%)
SAPS-PD	14.7 (5.55)	15.9 (6.12)

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

Primary Efficacy Results

Participants in the pimavanserin group experienced a statistically significant improvement in SAPS-PD scores from baseline to Day 43 compared with placebo (-5.79 vs. -2.73; **Figure 1**).[6,9] The treatment difference (pimavanserin minus placebo) was -3.06 (95% CI, -4.91 to -1.20; p=0.0014).[6] 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). Sensitivity analyses that included all randomized participants were consistent with the findings in the full analysis set.

Figure 1. SAPS-PD Score Change from Baseline (LSM ± SE) Over Time (MMRM; OC): Intent-to-Treat Analysis Set (ACP-103-020)[9]



Abbreviations: LSM=least squares mean; MMRM=mixed model repeated measures analysis; OC=observed cases; PD=Parkinson's disease; SAPS-PD=PD-adapted Scale for the Assessment of Positive Symptoms; SE=standard error.

Supportive Analyses

Among participants receiving pimavanserin compared with placebo, an effect was seen on both the hallucinations (-3.81 vs. -1.80) and delusions (-1.95 vs. -1.01) components of the SAPS-PD.[9] Participants in the pimavanserin group also showed statistically significant improvement in the SAPS-H (p=0.0032) and SAPS-D (p=0.0325) components of the SAPS-H+D, separately.[6]

Key Secondary Efficacy Results

For the key secondary endpoint, non-inferiority of pimavanserin 34 mg compared to placebo for motor function was concluded from the treatment difference in the mean change from baseline to Day 43 in the combined UPDRS Parts II+III score (-1.40 vs. -1.69; 95% CI, -2.14 to 2.72). In supportive analyses, participants receiving pimavanserin experienced no change compared to placebo in the individual UPDRS II (-0.55 vs. -0.84; 95% CI, -0.66 to 1.24), and UPDRS III scores (-0.81 vs. -0.84; 95% CI, -2.00 to 2.05).[8]

Safety Results

TEAEs occurring in ≥5% of participants in either treatment group are summarized in **Table 6**. Eleven (11%) participants in the pimavanserin group and four (4%) participants in the placebo group had a serious adverse event. Ten participants in the pimavanserin group discontinued due to an adverse event compared with two in the placebo group. Six discontinuations in the pimavanserin group were for psychosis, but discontinuations did not influence the primary outcome in a sensitivity analysis. Three deaths occurred (one in the placebo group from sudden cardiac death and two in the pimavanserin group from sepsis and septic shock); all were regarded as unrelated to study drug.[6]

Table 6. TEAEs Experienced by ≥5% of Subjects in Either Treatment Group: Safety Analysis Set (ACP-103-020)[8]

	Placebo (N=94) n (%)	Pimavanserin 34 mg QD (N=104) n (%)
Nausea	6 (6.4)	6 (5.8)
Peripheral edema	3 (3.2)	7 (6.7)
Urinary tract infection	11 (11.7)	14 (13.5)
Fall	8 (8.5)	11 (10.6)
Confusional state	3 (3.2)	6 (5.8)
Headache	5 (5.3)	1 (1.0)
Hallucination	1 (1.1)	7 (6.7)

Abbreviations: QD=once daily; TEAE=treatment-emergent adverse event.

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