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NUPLAZID® (pimavanserin): Effect on Motor Function in Parkinson's Disease Psychosis

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

Relevant Labeling Information[1]
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia who experience psychosis unless their hallucinations and delusions are related to Parkinson's disease.**

Summary

- The 4-week, **Phase 2 study ACP-103-006** (N=60) demonstrated that once daily (QD) doses up to 51 mg of pimavanserin did not worsen motor function 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. Similar results were observed for the UPDRS Parts II and III analyzed as separate scores.[2]
- In **pooled analysis** of three placebo-controlled, 6-week, Phase 2b/3 and Phase 3 studies in PD psychosis (Studies 012, 014 and 020), pimavanserin 34 mg QD did not show treatment-related worsening of motor function compared to placebo in participants with PD psychosis, as measured using the UPDRS Parts II+III. Similar results were observed for the UPDRS Parts II and III analyzed as separate scores.[3]
- In a **post hoc subgroup analysis** of the HARMONY Phase 3 study, participants with PD psychosis with PD dementia who received pimavanserin 34 mg in the open-label period (N=49) showed no worsening of motor function relative to placebo over 26 weeks in the double-blind period, as measured by the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A).[3]
- Rates of motor-related treatment-emergent adverse events (TEAEs) were similar between pimavanserin-treated and placebo-treated patients across studies.[2,3]

Clinical Studies in PD Psychosis

The effect of pimavanserin on motor function in participants with PD psychosis has been evaluated in four short-term placebo-controlled studies (one Phase 3 trial [ACP-103-020], two Phase 2b/3 trials [ACP-103-012 and -014], and one Phase 2 trial [ACP-103-006]) and in a post hoc subgroup analysis of the **HARMONY** Phase 3 double-blind, placebo-controlled, randomized discontinuation study.[2,3]

ACP-103-006

Study 006 was a Phase 2, randomized, double-blind, placebo-controlled, multi-center trial conducted in the U.S. to determine the safety of pimavanserin in 60 participants with PD psychosis. During the four-week trial, PD psychosis participants were randomized 1:1 to receive placebo or pimavanserin daily starting at 17 mg on study Day 1. The daily dose could be subsequently increased to 34 or 51 mg daily on study Days 8 and 15, respectively, based on clinical responsiveness. In order to be included in the study, participants had to have visual and/or auditory moderate-to-severe hallucinations and/or delusions for at least 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. The primary endpoint was the change from baseline to Day 28 in the combined score of UPDRS Parts II and III.[2]

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%). Baseline characteristics were similar between the two groups except there were more female participants in the placebo group (**Table 1**).[2] All enrolled participants received concomitant carbidopa-levodopa, and were on a stable dose of carbidopa-levodopa by at least 2 weeks prior to study baseline.[4] Of the 60 participants enrolled, 28 in each group completed the four-week study. 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.[5,6]

Table 1. Selected Demographic and Baseline Characteristics (Safety Population; ACP-103-006)[2,4]

Parameter	Pimavanserin (N=29)	Placebo (N=31)
Age, mean years (SE)	72.3 (1.43)	69.6 (1.68)
Female gender, n (%)	3 (10.3)	11 (35.5)
Caucasian, n (%)	28 (96.6)	31 (100.0)
NPI total score of delusions and hallucinations, mean (SE)	10.2 (1.05)	11.6 (1.07)
Modified Hoehn and Yahr staging score, mean (SE)	3.0 (0.17)	3.0 (0.13)
UPDRS II+III composite, mean (SE)	47.81 (2.587)	49.69 (2.782)

Abbreviations: NPI=Neuropsychiatry Inventory; SE=standard error; UPDRS=Unified Parkinson's Disease Rating Scale.

Results

For the primary endpoint, the combined score of UPDRS Parts II and III, the least squares mean (LSM) 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 analyzed as separate scores (**Table 2**).[2]

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

	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.

Motor function TEAEs occurred infrequently in both treatment arms, were mild, and did not lead to drug discontinuation. They included balance disorder (two pimavanserin-treated patients, 6.9%), bradykinesia (two placebo-treated patient, 3.2%), freezing phenomenon (two pimavanserin-treated patients, 6.9%), on and off phenomenon (one pimavanserin-treated patient, 3.4%), tremor (one placebo-treated patient, 3.2%), and walking disability (one placebo-treated patient, 3.2%).[2]

Pooled Analysis from Placebo-Controlled Phase 2b/3 And Phase 3 Studies

Motor function evaluation and safety data were pooled for participants who received pimavanserin 34 mg QD or placebo from three randomized, double-blind, placebo-controlled, 6-week, outpatient, Phase 2b/3 and Phase 3 studies in PD psychosis (Studies 012, 014 and 020).[3] The pooled analysis included 202 participants treated with pimavanserin 34 mg and 231 participants treated with placebo. Baseline characteristics are shown in **Table 3**.

Table 3. Selected Demographic and Baseline Characteristics (Pooled Studies 012, 014, and 020)[3]

	Pimavanserin 34 mg (N=202)	Placebo (N=231)
Age (y), mean (SD)	71.1 (7.33)	71.5 (8.84)
Male gender, n (%)	144 (71.3)	134 (58.0)
Race, n (%)		
White	183 (90.6)	209 (90.5)
Black	2 (1.0)	3 (1.3)
Asian	11 (5.4)	12 (5.2)
Other	6 (3.0)	7 (3.0)
Non-Hispanic ethnicity, n (%)	196 (97.0)	226 (97.8)
UPDRS II + III, mean (SD)	52.0 (19.26)	52.5 (19.32)
UPDRS II, mean (SD)	18.3 (6.85)	18.5 (7.17)
UPDRS III, mean (SD)	33.6 (14.40)	34.0 (13.99)

Abbreviations: SD=standard deviation; UPDRS=Unified Parkinson's Disease Rating Scale.

Results

The LSM [standard error (SE)] change from baseline to Week 6 in UPDRS II + III was -2.4 (0.69) for the pimavanserin 34 mg group and -2.3 (0.6) for placebo (95% CI: -1.9, 1.6). When evaluated independently, the UPDRS II LSM (SE) change from baseline to Week 6 was -0.8 (0.28) in pimavanserin-treated patients and -1.1 (0.24) in placebo-treated patients (95% CI: -0.4,

1.0), and the UPDRS III LSM (SE) change from baseline to Week 6 was -1.7 (0.54) in pimavanserin-treated patients and -1.2 (0.47) in placebo-treated patients (95% CI: -1.8, 0.9).[3]

Motor-related TEAEs for the pooled studies are shown in **Table 4**. Falls occurred in 6.4% of pimavanserin-treated patients and 9.1% of placebo-treated patients. Orthostatic hypotension TEAEs occurred in 1.0% of pimavanserin-treated patients and 5.2% of placebo-treated patients. Motor-related events (Parkinson-like events) occurred in 4.5% of pimavanserin-treated patients and 6.1% of placebo-treated patients. Gait disturbance occurred in 2.5% of pimavanserin-treated patients and 0.4% of placebo-treated patients.[3]

Table 4. Motor-related TEAEs (Pooled Studies 012, 014, and 020)[3]

	Pimavanserin (N=202)	Placebo (N=231)
Fall	13 (6.4)	21 (9.1)
Orthostatic hypotension		
Vital sign criteria[a]	58/196 (29.6)	88/229 (38.4)
TEAE PT orthostatic hypotension	2/202 (1.0)[b]	12/231 (5.2)
Either vital sign criteria[a] or TEAE PT orthostatic hypotension	58/202 (28.7)[b]	95/231 (41.1)
Parkinson-like events	9 (4.5)	14 (6.1)
Gait disturbance	5 (2.5)	1 (0.4)
Parkinson's disease	3 (1.5)	1 (0.4)
Tremor	1 (0.5)	4 (1.7)
Freezing phenomenon	1 (0.5)	2 (0.9)
Hypertonia	1 (0.5)	0 (0.0)
Muscle rigidity	1 (0.5)	0 (0.0)
Musculoskeletal stiffness	1 (0.5)	1 (0.4)
Parkinsonism	0 (0.0)	0 (0.0)
Bradykinesia	0 (0.0)	1 (0.4)
Drooling	0 (0.0)	1 (0.4)
Parkinsonian gait	0 (0.0)	1 (0.4)
Sedation-related events	13 (6.4)	12 (5.2)
Sedation	0 (0.0)	0 (0.0)
Somnolence	5 (2.5)	6 (2.6)
Fatigue	5 (2.5)	5 (2.2)
Asthenia	3 (1.5)	1 (0.4)
Lethargy	2 (1.0)	0 (0.0)
Hypersomnia	0 (0.0)	0 (0.0)

[a]Orthostatic hypotension was defined as a decrease of ≥20 mmHg in systolic blood pressure OR a decrease of ≥15 mmHg in diastolic blood pressure, OR an increase of ≥20 bpm in pulse rate; each measured from 5 min supine to 1 min standing at the same visit.
[b]Met p<0.05 level of significance using Fisher's Exact test by comparing the incidence rate for each pimavanserin group vs. placebo.
Abbreviations: PT=preferred term; TEAE=treatment-emergent adverse event.

Post Hoc Subgroup Analysis From ACP-103-045 (HARMONY)

HARMONY was a Phase 3, double-blind, placebo-controlled, randomized discontinuation study, evaluating the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis.[7] HARMONY was stopped early when a prespecified Interim Analysis (IA) met stopping criteria for efficacy (i.e. a two-sided p-value less than 0.0066 on the study's primary endpoint). Pimavanserin was associated with a significantly

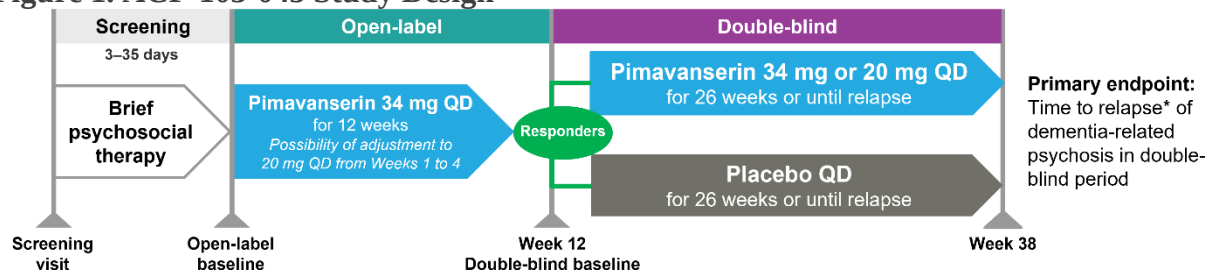
lower risk of relapse of symptoms of psychosis than placebo in the double-blind phase of the study (hazard ratio [HR]: 0.35; 95% CI: 0.17–0.73; p=0.005).

A post hoc analysis was conducted in a subgroup of participants with PD psychosis with PD dementia who received pimavanserin 34 mg in the open-label period.[8] Motor function was measured using the ESRS-A in a prespecified safety analysis.[3]

Study Design

The study included a 12-week, open-label period during which participants were treated with pimavanserin 34 mg once daily (**Figure 1**). Participants who responded to open-label treatment at Week 8 and sustained response at Week 12 by meeting prespecified criteria (≥30% reduction in Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions [SAPS-H+D] total score and Clinical Global Impression – Improvement [CGI-I] score of 1 [very much improved] or 2 [much improved] relative to baseline) were randomized into the double-blind period of the study to the same dose of pimavanserin (34 mg or 20 mg once daily) or placebo once daily, for up to 26 weeks, or until relapse. Participants who did not show a response to pimavanserin at Week 8 of the open-label period or achieved response criteria at Week 12 were discontinued from the study and entered the safety follow-up period. The primary endpoint in the study was time from randomization to relapse of psychosis in the double-blind period.[7]

Figure 1. ACP-103-045 Study Design[7]



**Relapse adjudicated by an Independent Adjudication Committee. Relapse was defined as one or more of the following: An increase from baseline (double-blind phase) of ≥30% in the SAPS-H+D total score AND a CGI-I score of 6 (much worse) or 7 (very much worse); Hospitalization for worsening symptoms of psychosis; Stopping the trial regimen or withdrawal from the trial owing to lack of efficacy; Use of other antipsychotics for the treatment of symptoms of psychosis.*
Dose adjustments (reduction to 20 mg daily based on tolerability, which could later be increased to 34 mg daily based on Investigator judgement) were permitted from Weeks 1 to 4, after which the dose remained fixed at 34 mg or 20 mg for the remainder of the open-label period.
Abbreviations: CGI-I=Clinical Global Impression – Improvement; QD=once daily; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

Demographics and Baseline Characteristics

A total of 392 participants were enrolled in HARMONY. Of the subgroup of 59 participants with PD psychosis with PD dementia in HARMONY, 49 received pimavanserin 34 mg in the open-label period.[8] Baseline characteristics and disease characteristics of the subgroup population in the open-label period and double-blind period are shown in **Table 5**.

Table 5. Selected Baseline Demographics and Clinical Characteristics (ACP-103-045 Post Hoc)[3]

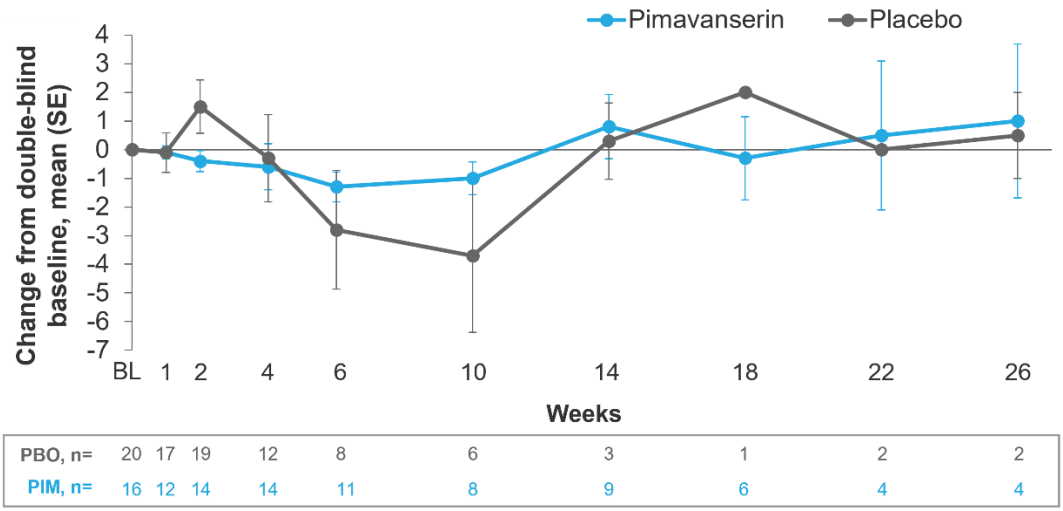
	Open-label Period	Double-blind Period	
	PIM 34 mg N=49	Placebo N=20	PIM 34 mg N=16
Age (y), mean (SD)	72.6 (7.59)	72.3 (8.61)	69.6 (7.12)
Female, n (%)	19 (38.8)	8 (40.0)	6 (37.5)
White race, n/N (%)	47/47 (100)	19/19 (100)	16/16 (100)
Hispanic/Latino, n/N (%)	6/47 (12.8)	1/19 (5.3)	3/16 (18.8)
ESRS-A, mean (SD)	26.2 (13.24)	26.3 (14.03)	27.4 (15.96)

Abbreviations: ESRS-A= Extrapyramidal Symptom Rating Scale-Abbreviated; PIM=pimavanserin; SD=standard deviation.

Results

In a pre-specified safety analysis, no worsening of motor function (as measured by ESRS-A) was observed relative to placebo over 26 weeks in the double-blind period (treatment duration up to 38 weeks) (**Figure 2**).[3,8]

Figure 2. ESRS-A Total Score Change from Double-Blind Baseline (ACP-103-045 Post Hoc)[3]



Abbreviations: BL=baseline; ESRS-A=Extrapyramidal Symptom Rating Scale-Abbreviated; SE=standard error.

In the open-label period of HARMONY (N=49), 1 participant (2.0%) reported dysphonia, 1 participant (2.0%) reported psychomotor hyperactivity, and 3 participants (6.1%) reported falls. Two participants (4.1%) reported orthostatic hypotension. Somnolence [n=4 (8.2%)], fatigue [n=2 (4.1%)], and asthenia [n=1 (2.0%)] were the only sedation-like events reported. In the double-blind period of HARMONY (pimavanserin, n=16; placebo, n=20), dyskinesia, tremor, orthostatic hypotension, hypersomnia, and somnolence were reported by 1 (5.0%) placebo-treated participant each. No motor-related TEAEs were reported in pimavanserin-treated participants in the double-blind period.[3]

References

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