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12830 El Camino Real • Suite 400. • San Diego, California 92130 • USA • Tel. 858.558.2871 • Fax 858.558.2872 • www.acadia-pharm.com

NUPLAZID® (pimavanserin): Outcomes from the HARMONY Study in Participants with Parkinson's Disease Dementia and Dementia with Lewy Bodies

This letter is provided in response to your specific request for information regarding clinical outcomes with pimavanserin from the Phase 3 HARMONY study for the pooled subgroup of participants with Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB).

Pimavanserin is approved by the U.S. Food and Drug Administration (FDA) as an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis and carries a **Boxed WARNING** for Increased Mortality in Elderly Patients with Dementia-Related Psychosis. Pimavanserin is not approved for the treatment of patients with dementia who experience psychosis unless their hallucinations and delusions are related to PD.[1]

Summary

- **HARMONY (ACP-103-045)** was a Phase 3, randomized discontinuation study that enrolled participants with dementia-related psychosis and met the primary endpoint at the Interim Analysis (hazard ratio [HR]=0.35, 95% CI: 0.17, 0.73; one-sided p=0.0023).[2,3]
- A post hoc subgroup analysis of HARMONY was conducted in **pooled participants with PDD and DLB** who received pimavanserin 34 mg in the open-label period (N=76).[4]
    - In the double-blind period, at the time the study was stopped early for positive efficacy, 5.3% (1/19) of pimavanserin-treated participants and 55.0% (11/20) of placebo-treated participants met relapse criteria and **were adjudicated as relapses** (hazard ratio [HR]: 0.03; 95% confidence interval [CI]: 0.01–0.10; 2-sided nominal p<0.0001).[4]
    - In the double-blind period, **treatment-emergent adverse events (TEAEs)** were observed in 40.9% (9/22) of participants on pimavanserin and 41.7% (10/24) on placebo, discontinuations due to TEAEs were 4.5% (1/22) for pimavanserin and 8.3% (2/24) for placebo, and a serious TEAE was reported in 1 participant in the pimavanserin group.[4]
- A second post hoc subgroup analysis was conducted for participants with **DLB only** who received pimavanserin 34 mg in the open-label period (N=27).[5]
    - In the double-blind period, at the time the study was stopped early for positive efficacy, 0% (0/6) of pimavanserin-treated participants and 66.7% (2/3) of placebo-treated participants met relapse criteria and were adjudicated as relapses.[5]
- These results should be interpreted cautiously since the study was not designed or powered to demonstrate an effect in these subgroups.

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

Background

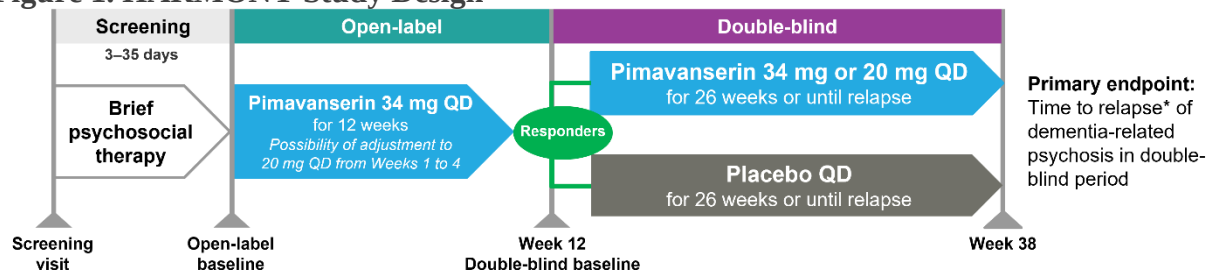
HARMONY was a Phase 3, double-blind, placebo-controlled, randomized withdrawal (relapse prevention) study, evaluating the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis.[2] A prespecified efficacy Interim Analysis (IA) was triggered after 40 relapse events occurred, and HARMONY was stopped early when the IA met stopping criteria for efficacy (i.e. a one-sided p-value less than 0.0033 on the study's primary endpoint).[3] 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; one-sided p=0.0023; two-sided p=0.005).[2,3]

A post hoc analysis was conducted in a pooled subgroup of participants with PDD and DLB, who received pimavanserin 34 mg in the open-label period.[6] Participants included here met clinical criteria for dementia,[7] and either PD dementia[8] or DLB.[9]

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 SAPS-H+D total score and 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.[2,10]

Figure 1. HARMONY Study Design[2]



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.
**Relapse adjudicated by an Independent Adjudication Committee*
Abbreviation: QD=once daily.

The intent-to-treat (ITT) population for the double-blind phase comprised patients randomized to continue pimavanserin or treatment with placebo. All efficacy data reflect the ITT analysis set at the time of the IA, which formed the basis for stopping the trial (data cutoff: July 31, 2019). Safety was also evaluated in the subgroup of patients who received at least 1 dose of the study drug for both the open-label and double-blind periods (Safety Analysis Sets).[10]

The primary endpoint in the study was time from randomization to relapse of psychosis in the double-blind period. Relapse was defined as one or more of the following:[2,10]

- 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

TEAEs were collected throughout the duration of the study. Cognitive function was evaluated using the MMSE and extrapyramidal symptoms were evaluated using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A).[2,10]

Selected inclusion and exclusion criteria are shown in **Table 1**.

Table 1. Selected Inclusion and Exclusion Criteria (ACP-103-045 Post Hoc)[2,10]

Selected inclusion criteria

• Male or female participants ≥50 and ≤90 years of age
• Met criteria for All-cause Dementia according to NIA-AA guidelines
• Met clinical criteria for dementia associated with Parkinson's disease OR dementia with Lewy bodies
• Had a MMSE score ≥6 and ≤24
• Had psychotic symptoms for ≥2 months
• Had all of the following scores at Screening and Visit 2 (open-label baseline):
  ○ SAPS-H+D total score ≥10 AND
  ○ SAPS-H+D global item (H7 or D13) score ≥4 AND
  ○ CGI-S score ≥4
• If the subject was taking a cholinesterase inhibitor, memantine, or both:
  ○ The dose of the medication(s) was stable for ≥12 weeks prior to Visit 2 (open-label baseline) and there was no current plan to change the dose; OR
  ○ If the medication(s) was discontinued, the discontinuation occurred no fewer than 2 weeks prior to Visit 2 (open-label baseline)
• If the subject was taking an antipsychotic medication at the time of screening, the antipsychotic must have been discontinued 2 weeks or 5 half-lives (whichever was longer) prior to Visit 2 (open-label baseline)

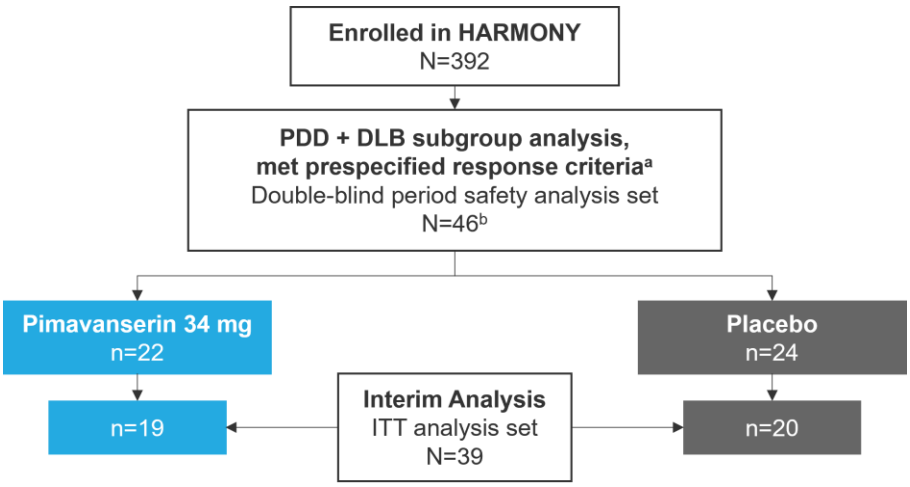
Selected exclusion criteria
• Had psychotic symptoms that were primarily attributable to a condition other than dementia • Had a current major depressive episode within 3 months of screening • Had experienced suicidal ideation or behavior within 3 months prior to study enrollment • Had evidence of non-neurologic medical comorbidity or medication use that could substantially impair cognition • Had a history of ischemic stroke within the last 12 months or any evidence of hemorrhagic stroke • Had a known history of cerebral amyloid angiopathy, epilepsy, CNS neoplasm, or unexplained syncope • Had any of the following: greater than New York Heart Association Class 2 congestive heart failure, Grade 2 or greater angina pectoris, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes, syncope due to an arrhythmia, an implantable cardiac defibrillator • Had a myocardial infarction within the last 6 months • Had a known personal or family history or symptoms of long QT syndrome • Had a significant unstable medical condition that could interfere with participant's ability to complete the study or comply with study procedures

Abbreviations: CGI-S=Clinical Global Impression – Severity; MMSE=Mini-Mental State Examination; NIA-AA=National Institute on Aging- Alzheimer's Association; 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.[2] Of the pooled subgroup of 87 participants with PDD and DLB in HARMONY,[5] 76 received pimavanserin 34 mg in the open-label period.[4] Of these, 46 (60.5%) met the prespecified response criteria and were randomized (placebo, n=24; pimavanserin, n=22) (**Figure 2**).[4]

Figure 2. Participant Disposition[4]



[a]Treatment response was defined as ≥30% reduction in the SAPS-H+D total score and as a CGI-I score of much improved (2) or very much improved (1).
[b]Participants met the response criteria at both Weeks 8 and 12.
Abbreviations: DLB=dementia with Lewy bodies; ITT=intent to treat; PDD=Parkinson's disease dementia.

Baseline characteristics and disease characteristics of the subgroup population in the open-label period and double-blind period are shown in **Table 2**. Overall, 55.3 % of participants were on concomitant cognitive-enhancing medications at open-label baseline (memantine, memantine hydrochloride, rivastigmine, or donepezil).[6]

Table 2. Baseline Demographics and Clinical Characteristics (ACP-103-045 Post Hoc; Open-label and Double-blind Safety Analysis Sets)[4]

	Open-label Period	Double-blind Period	
	PIM 34 mg N=76	Placebo N=24	PIM 34 mg N=22
Age, years (mean ± SE)	72.8 ± 0.87	73.2 ± 1.78	70.1 ± 1.39
Female, n (%)	29 (38.2)	11 (45.8)	8 (36.4)
White race, n/N (%)	69/72 (95.8)	22/22 (100)	20/22 (90.9)
Hispanic/Latino, n/N (%)	10/72 (13.9)	1/22 (4.5)	4/22 (18.2)
Dementia subtype, n (%)			
PDD	49 (64.5)	20 (83.3)	16 (72.7)
DLB	27 (35.5)	4 (16.7)	6 (27.3)
Dementia severity, n (%)			
Mild	20 (26.3)	7 (29.2)	8 (36.4)
Moderate	49 (64.5)	14 (58.3)	14 (63.6)
Severe	7 (9.2)	3 (12.5)	0
Age at cognitive impairment onset, years (mean ± SE)	69.0 ± 0.93	70.0 ± 1.79	66.5 ± 1.50
Duration of cognitive impairment, years (mean ± SE)	4.2 ± 0.33	3.6 ± 0.51	4.2 ± 0.49
Symptoms of psychosis, historical n/N (%)			

	Open-label Period	Double-blind Period	
	PIM 34 mg N=76	Placebo N=24	PIM 34 mg N=22
Visual hallucinations	71/75 (94.7)	24/24 (100)	18/21 (85.7)
Auditory hallucinations	53/75 (70.7)	20/24 (83.3)	15/21 (71.4)
Delusions	53/75 (70.7)	20/24 (83.3)	11/21 (52.4)
Previous treatment for dementia-related psychosis	34 (44.7)	9 (37.5)	10 (45.5)
SAPS-H+D score (mean ± SE)	24.2 ± 1.11	4.1 ± 0.93	4.0 ± 1.19
CGI-S score (mean ± SE)	4.7 ± 0.08	2.1 ± 0.21	2.0 ± 0.19
ESRS-A score (mean ± SE)	21.5 ± 1.53	22.8 ± 3.08	23.7 ± 3.24
MMSE total score (mean ± SE)	18.4 ± 0.55	19.5 ± 1.16	18.9 ± 1.10

Abbreviations: CGI-S=Clinical Global Impression – Severity; DLB=dementia with Lewy bodies; ESRS-A= Extrapyramidal Symptom Rating Scale-Abbreviated; MMSE=Mini-Mental State Examination; PD=Parkinson's disease; PDD=Parkinson's disease dementia; PIM=pimavanserin; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions; SE=standard error.

Outcomes: PDD and DLB

In the post hoc subgroup analysis of PDD and DLB, 60.5% of eligible participants (46/76) achieved response criteria to pimavanserin at Week 12 in the open-label treatment period, and were randomized to pimavanserin (N=22) or placebo (N=24) in the double-blind period.[4] Thirty (39.5%) participants were terminated early from the open-label period; reasons for early termination included lack of response in open-label (n=15), AE (n=4), non-compliance with study drug (n=2), participant withdrew consent (n=2), and death (n=1).[6]

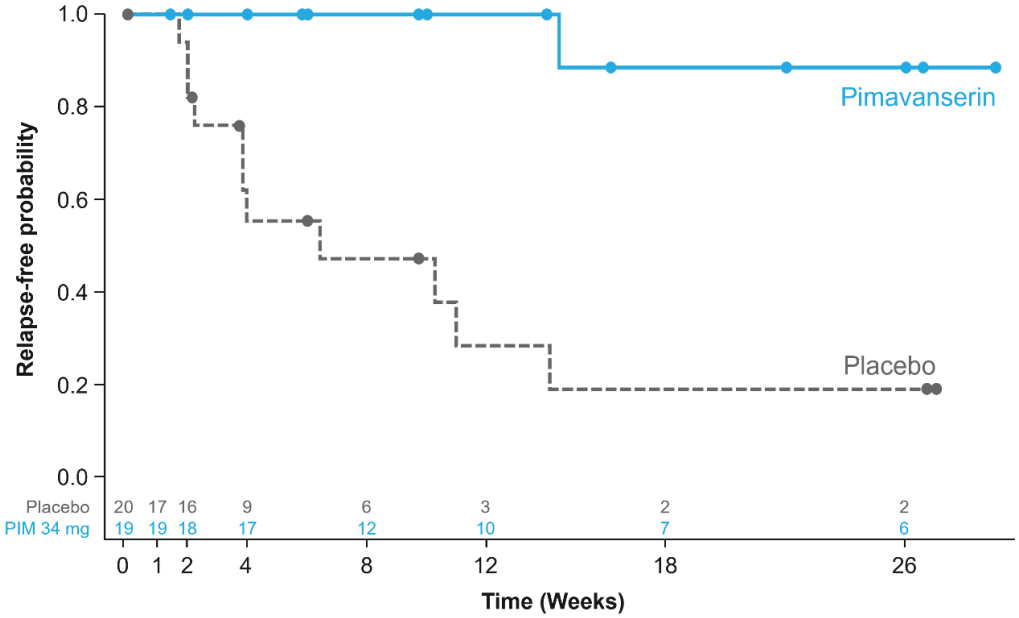
In the double-blind treatment period at the time of prespecified IA (N=39), 1 of 19 (5.3%) pimavanserin-treated participants and 11 of 20 (55.0%) placebo-treated participants had met relapse criteria and were adjudicated as relapses by the study's independent adjudication committee (HR: 0.03; 95% CI: 0.01–0.10; 2-sided nominal p<0.0001; **Table 3**, **Figure 3**).[4]

Table 3. Time from Randomization to Relapse of Psychosis in the Double-Blind Period (ACP-103-045 Post Hoc; ITT Population*)[4]

	Placebo N=20	PIM 34 mg N=19
Number of participants having a relapse event, n (%)	11 (55.0)	1 (5.3)
Number of participants censored from survival analysis, n (%)	9 (45.0)	18 (94.7)
Completed Week 26 without a relapse	2 (10.0)	6 (31.6)
Prematurely discontinued prior to Week 26	3 (15.0)	4 (21.1)
Ongoing at time of database cutoff	4 (20.0)	8 (42.1)

**Efficacy data reflect the ITT analysis set at the time of the IA (n=39). Seven additional participants had been randomized by the time the study was stopped based on the recommendation by the data safety monitoring board for positive efficacy. These 7 participants were not part of the efficacy analyses.[6]*
Abbreviations: IA=Interim Analysis; ITT=intent-to-treat; PIM=pimavanserin.

Figure 3. Kaplan-Meier Estimation of Time from Randomization to Relapse of Psychosis in the Double-Blind Period (ACP-103-045 Post Hoc*)[4]



**Efficacy data reflect the intention-to-treat analysis set at the time of the IA (n=39). Seven additional participants had been randomized by the time the study was stopped based on the recommendation by the data safety monitoring board for positive efficacy. These 7 participants were not part of the efficacy analyses.[6]*
Abbreviations: IA=interim analysis; PIM=pimavanserin.

Reasons for premature discontinuation in the double-blind period prior to Week 26 included participant withdrew consent (n=3), AE (n=1), and use of prohibited medications (n=1) in the pimavanserin group, and participant withdrew consent (n=1), AE (n=1), and other (n=1) in the placebo group.[6]

Outcomes: DLB

In a post hoc subgroup analysis of DLB only (N=27), 45.6% of eligible participants (10/22) achieved response criteria to pimavanserin at Week 12 in the open-label treatment period, and were randomized to pimavanserin (N=6) or placebo (N=4) in the double-blind period (5 participants were ongoing in the open-label period at the time the study was discontinued and were not included).[5,6] Relapse outcomes from the double-blind period at the time of prespecified IA are shown in **Table 4**.

Table 4. Time from Randomization to Relapse of Psychosis in the Double-Blind Period (ACP-103-045 Post Hoc; ITT Population*)[5]

	Placebo N=3	PIM 34 mg N=6
Number of participants having a relapse event, n (%)	2 (66.7)	0
Number of participants censored from survival analysis, n (%)	1 (33.3)	6 (100)
Completed Week 26 without a relapse	0	3 (50.0)
Prematurely discontinued prior to Week 26	0	1 (16.7)
Ongoing at time of database cutoff	1 (33.3)	2 (33.3)

**Efficacy data reflect the ITT analysis set at the time of the IA (n=9). One additional participant had been randomized by the time the study was stopped based on the recommendation by the data safety monitoring board for positive efficacy. This participant was not part of the efficacy analyses.*
Abbreviations: IA=interim analysis; ITT=intent-to-treat; PIM=pimavanserin.

Safety Results: PDD and DLB

In the open-label period (N=76), 46.1% (n=35) of participants included in the subgroup analysis experienced any TEAE and 7.9% (n=6) experienced a serious TEAE (9 events: 2 falls and 1 each of myocardial infarction, diarrhea, urinary tract infection, bone fissure, dehydration, agitation, and psychotic disorder); 7 (9.2%) discontinued due to TEAEs. One death was reported during the open-label period from myocardial infarction. According to the Investigator, the death was considered unrelated to the study drug.[4,6]

In the double-blind period (N=36), TEAEs were observed in 40.9% (n=9) of participants on pimavanserin and 41.7% (n=10) on placebo (**Table 5**). Discontinuations due to TEAEs were 4.5% (n=1) for pimavanserin and 8.3% (n=2) for placebo. A serious TEAE of prostate cancer metastatic (n=1, 4.5%) was reported in the pimavanserin group; no serious TEAEs were reported in the placebo group.[4,6] The incidence of TEAEs by study period is shown in **Table 6**.

Table 5. Incidence of TEAEs in the Open-label Period and Double-blind Period (ACP-103-045 Post Hoc; Open-label and Double-blind Safety Analysis Sets)[4]

	Number (%) of Participants		
	Open-label Period	Double-blind Period	
	PIM 34 mg N=76	Placebo N=24	PIM 34 mg N=22
Any TEAE	35 (46.1)	10 (41.7)	9 (40.9)
Serious TEAE	6 (7.9)	0	1 (4.5)
Related TEAE	9 (11.8)	3 (12.5)	1 (4.5)
TEAE leading to discontinuation	7 (9.2)	2 (8.3)	1 (4.5)
TEAE resulting in death	1 (1.3)	0	0

Events with a missing relationship were counted as related.
Abbreviations: PIM=pimavanserin; TEAE=treatment-emergent adverse event.

Table 6. TEAEs Occurring in ≥2 Participants in Either Study Period (ACP-103-045 Post Hoc; Open-label and Double-blind Safety Analysis Sets)[6]

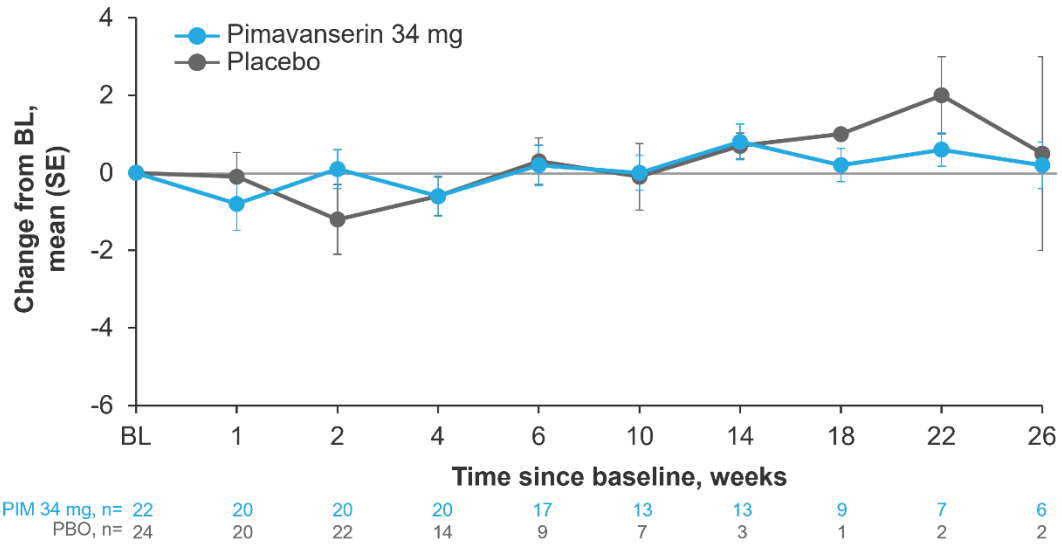
	Number (%) of Participants		
	Open-label Period	Double-blind Period	
	PIM 34 mg N=76	Placebo N=24	PIM 34 mg N=22
Weight decreased	5 (6.6)	2 (8.3)	0
Decreased appetite	5 (6.6)	1 (4.2)	0
Urinary tract infection	5 (6.6)	1 (4.2)	1 (4.5)
Somnolence	4 (5.3)	1 (4.2)	0
Insomnia	4 (5.3)	0	0
Confusional state	4 (5.3)	0	0
Fall	3 (3.9)	0	0
Fatigue	3 (3.9)	0	0
Psychotic disorder	2 (2.6)	0	1 (4.5)
Agitation	2 (2.6)	0	0
Electrocardiogram QT prolonged	1 (1.3)	0	2 (9.1)
Anxiety	1 (1.3)	0	2 (9.1)
Hypertension	1 (1.3)	2 (8.3)	0

Abbreviations: PIM=pimavanserin; TEAE=treatment-emergent adverse event.

Prespecified Safety Analyses

No worsening of cognitive function (as measured by MMSE) or 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 4** and **Figure 5**).[4,6]

Figure 4. MMSE Score Change from Double-Blind Baseline (ACP-103-045 Post Hoc; Double-blind Safety Analysis Set)[4]



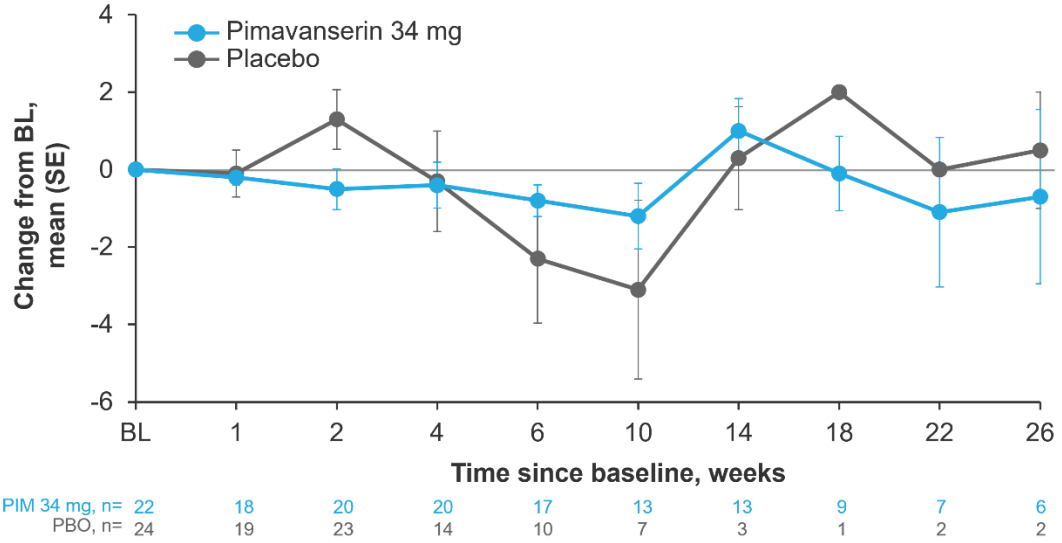
Abbreviations: BL=baseline; MMSE=Mini-Mental State Examination; PBO=placebo; PIM=pimavanserin; SE=standard error.

The mean MMSE score at open-label baseline was 18.4 (SE, 0.55), and the mean change from baseline to Week 12 was 0.6 (SE, 0.55). Participants randomized to pimavanserin and placebo had similar mean MMSE scores at double-blind baseline (pimavanserin, 18.9 [SE, 1.10];

placebo, 19.5 [SE, 1.16]). Mean MMSE score changes from baseline to Week 26 are shown in **Figure 4**.[4]

The mean ESRS-A score at open-label baseline was 21.5 (SE, 1.5), and the mean change from baseline to Week 12 was -1.6 (SE, 0.60). Mean ESRS-A scores at double-blind baseline (pimavanserin, 23.7 [SE, 3.2]; placebo, 22.8 [SE, 3.1]). Mean ESRS-A score changes from baseline to Week 26 are shown in **Figure 5**.[4]

Figure 5. ESRS-A Total Score Change from Double-Blind Baseline (ACP-103-045 Post Hoc; Double-blind Safety Analysis Set)[4]



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

These results should be interpreted cautiously since the study was not designed or powered to demonstrate an effect in these subgroups.

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