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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): Efficacy and Safety in Parkinson's Disease Psychosis

This letter is provided in response to your specific request for information regarding the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated 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

- In the 6-week pivotal Phase 3 study ACP-103-020 (**Study 020**), participants treated with pimavanserin 34 mg once daily demonstrated a statistically significant improvement in hallucinations and delusions associated with PD psychosis, as assessed by the Scale for Assessment of Positive Symptoms for Parkinson's disease (**SAPS-PD**) compared with placebo at Day 43.[2]
    - Pimavanserin did not show an effect on **motor function** compared to placebo, as measured using the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III.[2]
    - **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.[2]
    - In a **post hoc analysis** of Study 020, the change from baseline to Week 6 in SAPS-PD score in the pimavanserin group was similar between participants with a screening Mini-Mental State Examination (MMSE) score 21–24 and those with a screening MMSE score ≥25.[2,3]
- A **post hoc subgroup analysis** of ACP-103-045, or the HARMONY study, was conducted in participants with PD psychosis with PD dementia who received pimavanserin 34 mg in the open-label period (N=49). HARMONY was a Phase 3, double-blind, placebo-controlled, randomized discontinuation study.[4]
    - In the double-blind period and at the time the study was stopped early for positive efficacy, 7.7% (1/13) of pimavanserin-treated participants and 52.9% (9/17) of placebo-treated participants met relapse criteria for PD psychosis and were **adjudicated as relapses** by the study's independent adjudication committee.[4]
    - In the double-blind period, **TEAEs** were observed in 31.3% (5/16) of participants on pimavanserin and 45.0% (9/20) on placebo; discontinuations due to TEAEs

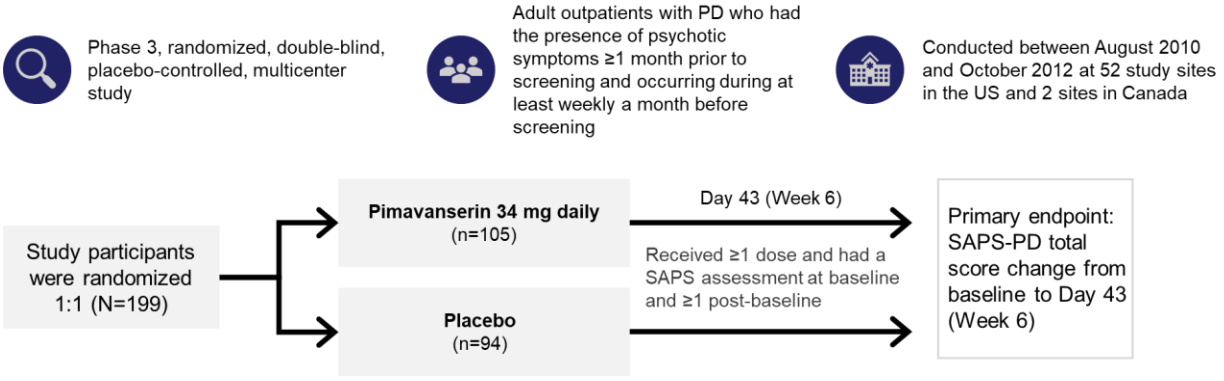
were 6.3% (1/16) for pimavanserin and 10.0% (2/20) for placebo, and no serious TEAEs were reported.[4]
- These results should be interpreted cautiously since the study was not designed or powered to demonstrate an effect in the subgroup.

Study 020: Pivotal Phase 3 Study

Study Design

Study 020 was a Phase 3 study evaluating treatment of pimavanserin 34 mg once daily in adult outpatients with PD psychosis (with or without dementia) (**Figure 1**).[1,2] Participants entered a 2-week lead-in period after screening, during which nonpharmacological brief psychosocial therapy adapted for PD was used, then randomized.[2] Of those randomized, 185 participants (95 in the pimavanserin arm and 90 in the placebo arm) met the requirements to be included in the full analysis. SAPS-PD assessments were performed remotely by live video conference with an independent rater with no knowledge of participant treatment assignment.

Figure 1. Study Design and Randomization (Study 020)[1,2]



Abbreviations: PD=Parkinson's disease; SAPS=Scale for the Assessment of Positive Symptoms; SAPS-PD=Scale for Assessment of Positive Symptoms for Parkinson's disease.

Selected inclusion and exclusion criteria are shown in **Table 1**. Antidementia medications were allowed if the dose was stable for at least 21 days prior to baseline and during the study.[5]

Table 1. Selected Inclusion and Exclusion Criteria (Study 020)[2,5]

Selected inclusion criteria
• Forty years of age or older • At least 1 year of confirmed PD diagnosis based on United Kingdom Brain Bank criteria • Presence of psychotic symptoms that developed after PD diagnosis and were present for at least one month prior to screening and occurred at least weekly during the month before screening • Psychotic symptoms severe enough to warrant treatment with antipsychotics (combined score of ≥6 or an individual score of ≥ 4 on the NPI items A [delusions] and/or B [hallucinations]) • Had clear sensorium at study entry (i.e., oriented to time, person, and place) • Participants were required to be on a stable dose of anti-PD medication for 1 month prior to baseline

Selected exclusion criteria
• Psychosis secondary to other causes • Dementia diagnosed concurrent with or before PD • Psychosis that occurred after ablative stereotactic surgery • Use of antipsychotic drugs or centrally acting anticholinergics • MMSE <21 at screening • Delirium • History of stroke that impairs ability to complete the MMSE • Uncontrolled serious medical illness • Myocardial infarction within six months of baseline • Congestive heart failure • History of long QT syndrome • QTcB >460 milliseconds for men or >470 milliseconds for women

Abbreviations: MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; PD=Parkinson's disease; QTcB=Bazett's corrected QT.

Primary efficacy was evaluated based on change from baseline to Day 43 (Week 6) in the SAPS-PD total score.[2,5] A key secondary endpoint assessed parkinsonism with the UPDRS parts II and III. Secondary outcomes included change by Day 43 in Clinical Global Impression–Severity (CGI-S) and Improvement (CGI-I) scale scores, completed by a site investigator who was masked to SAPS-PD scores.[2,5] The MMSE was conducted on the first day of screening only.[1] The MMSE total score at screening was categorized as 21–24 (cognitive impairment) and ≥25 (no cognitive impairment).[3]

Baseline Characteristics

Among the 185 participants, the mean age was 72 years (**Table 2**).[2] 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. In the pimavanserin group, 69.5% of participants had an MMSE score ≥25 at screening compared with 76.7% in the placebo group.[3]

Table 2. Baseline Characteristics (Full Analysis Set; Study 020)[2]

	Placebo (n=90)	Pimavanserin 34 mg (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)
Stereotactic surgery	3 (3%)	10 (11%)
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)
Time since first PD psychosis symptoms, months	36.4 (39.57)	30.9 (30.01)
Antipsychotic exposure within 21 days before baseline	15 (17%)	18 (19%)
Clozapine	0	2 (2%)
Quetiapine	13 (14%)	16 (17%)
Risperidone	1 (1%)	0
Ziprasidone	1 (1%)	0
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)

	Placebo (n=90)	Pimavanserin 34 mg (n=95)
SAPS-H+D	15.8 (6.52)	17.5 (7.57)
CGI-S	4.32 (0.91)	4.27 (0.92)

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: CGI-S=Clinical Global Impression – Severity; H+D=hallucinations and delusions; MMSE=Mini-Mental State Examination; PD=Parkinson's disease; SAPS=Scale for the Assessment of Positive Symptoms; SAPS-PD=Scale for Assessment of Positive Symptoms for Parkinson's disease; SD=standard deviation; UPDRS=Unified Parkinson's disease rating scale.

History of Dementia

In the overall population, 20.2% (40/198) of participants in the safety analysis set had a history of dementia at screening, according to their medical history (**Table 3**).[5] A subset of participants in each MMSE subgroup had a history of dementia: 25.5% (14/55) of participants with screening MMSE 21–24, and 18.3% (26/142) of participants with screening MMSE ≥25.

Table 3. Medical History: Summary of Dementia and MMSE Status by Dementia Type (Safety Analysis Set; Study 020)[5]

	Placebo (n=94)	Pimavanserin 34 mg (n=104)	Total (N=198)
Baseline MMSE 21–24, n (%)	**23**	**32**	**55**
Dementia	6 (26.1)	7 (21.9)	13 (23.6)
Dementia with Lewy bodies	--	1 (3.1)	1 (1.8)
No dementia	17 (73.9)	24 (75.0)	41 (74.5)
Baseline MMSE ≥25, n (%)	**71**	**71**	**142**
Dementia	11 (15.5)	13 (18.3)	24 (16.9)
Dementia with Lewy bodies	--	1 (1.4)	1 (0.7)
Vascular dementia	--	1 (1.4)	1 (0.7)
No dementia	60 (84.5)	56 (78.9)	116 (81.7)

Abbreviation: MMSE=Mini-Mental State Examination.

Note that dementia was not specified or required for inclusion in the study, and participants who had a dementia diagnosis prior to or concomitantly with the diagnosis of PD that was inconsistent with a PD diagnosis were excluded.[5]

Use of Antidementia Medications

Of the 185 participants, 69 (37%) in the overall population (modified IIT analysis set) were taking cognitive-enhancing medications at baseline (**Table 4**), with 12 participants taking ≥1.[3] These medications were required to be stable for at least 21 days prior to baseline and throughout the study period.[5]

Table 4. Use of Cognitive Enhancing Medications at Baseline (mITT Analysis Set; Study 020)[3]

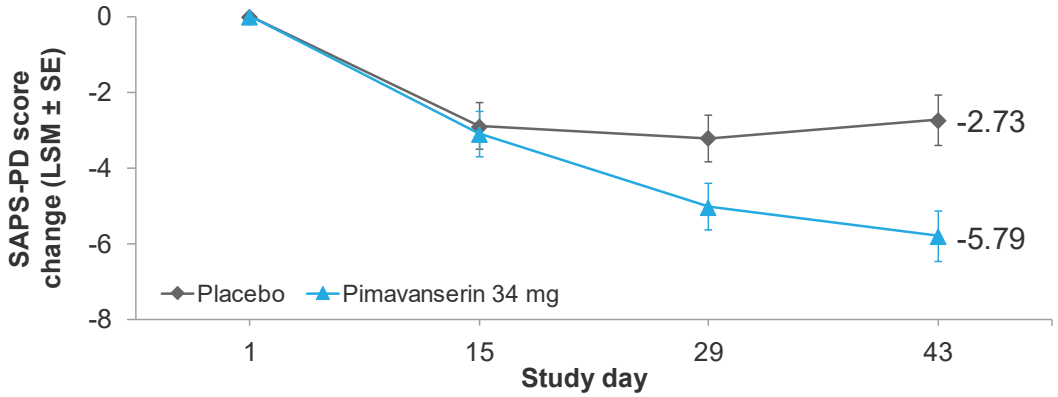
n (%)	Placebo (n=90)	Pimavanserin 34 mg (n=95)
Any cognitive-enhancing medication	36 (40)	33 (35)
Cholinesterase inhibitors	32 (36)	31 (33)
Memantine	12 (13)	6 (6)

Abbreviation: mITT=modified intent to treat.

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 2**).[1,2] The treatment difference (pimavanserin minus placebo) was -3.06 (95% confidence interval [CI], -4.91 to -1.20; *p*=0.0014).[2] 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 findings in the full analysis set.

Figure 2. SAPS-PD Score Change from Baseline (LSM ± SE) Over Time (MMRM; OC; ITT Analysis Set; Study 020)[1]



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

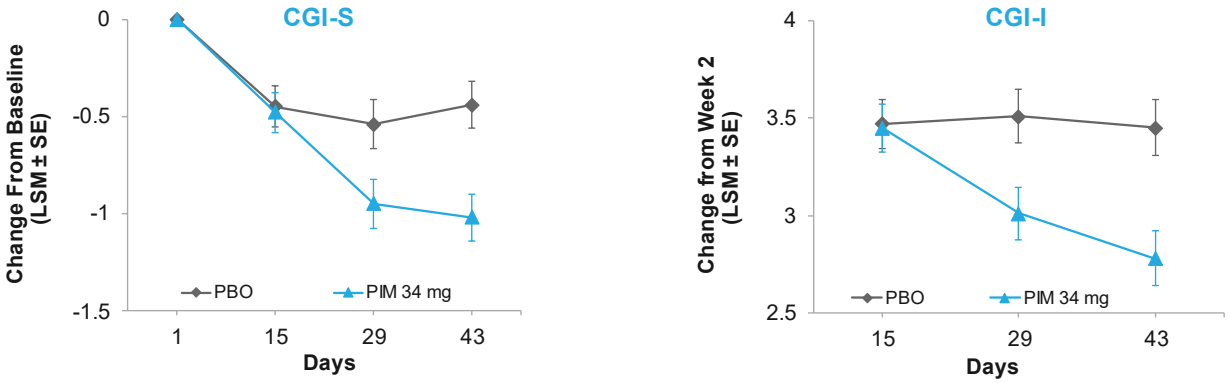
Supportive Analyses

Among participants receiving pimavanserin compared with placebo, an effect was seen on both the hallucination (-3.81 vs -1.80) and delusion (-1.95 vs -1.01) items of the SAPS-PD.[1] Participants in the pimavanserin group also showed statistically significant improvement in the SAPS-H (*p*=0.0032) and SAPS-D (*p*=0.0325) domains of the Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions (SAPS-H+D), separately.[2]

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).[5] 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). Compared with placebo, participants in the pimavanserin group had significantly greater improvements in measures of antipsychotic benefit, including CGI-S (*p*=0.0007) and CGI-I (*p*=0.0011; **Figure 3**).[2]

Figure 3. CGI Score Change from Baseline (LSM ± SE) Over Time (MMRM; OC; ITT Analysis Set; Study 020)[6]



Abbreviations: CGI-I=Clinical Global Impression Scale–Improvement; CGI-S=Clinical Global Impression Scale–Severity; ITT=intent to treat; LSM=least squares mean; MMRM=mixed model repeated measures analysis; OC=observed cases; PBO=placebo; PIM=pimavanserin; SE=standard error.

Safety Results

TEAEs occurring in ≥5% of participants in either treatment group are summarized in **Table 5**. Eleven percent (11%; 11/104) of participants in the pimavanserin group and 4% (4/94) in the placebo group had a serious adverse event (AE).[2] Ten (10) participants in the pimavanserin group discontinued due to an AE compared with 2 in the placebo group. Six (6) discontinuations in the pimavanserin group were for psychosis, but discontinuations did not influence the primary outcome in a sensitivity analysis. Three (3) deaths occurred (1 in the placebo group from sudden cardiac death and 2 in the pimavanserin group from sepsis and septic shock); all were regarded as unrelated to study drug.

Table 5. TEAEs Experienced by ≥5% of Participants in Either Treatment Group (Safety Analysis Set; Study 020)[5]

n (%)	Placebo (n=94)	Pimavanserin 34 mg (n=104)
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)

Abbreviation: TEAE=treatment-emergent adverse event.

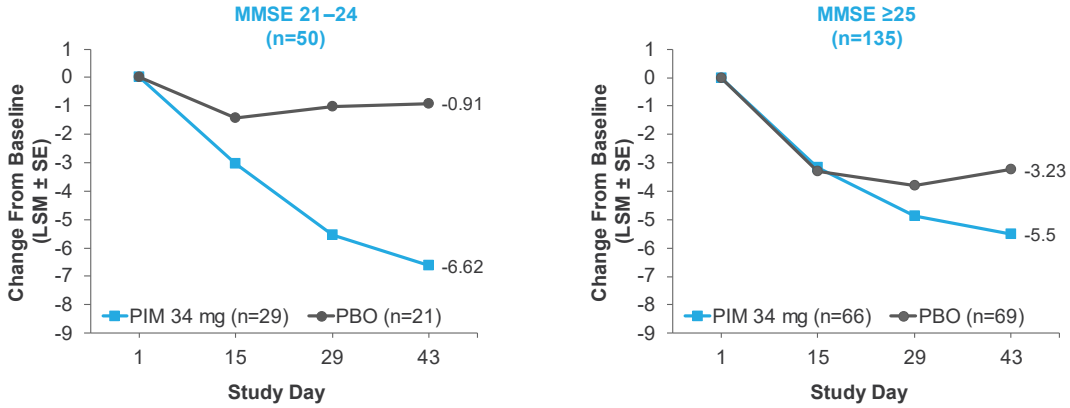
Post Hoc Analysis by Screening MMSE Score

SAPS-PD Score

Study 020 was not powered to show a statistically significant difference between pimavanserin and placebo groups based on screening MMSE score.[5] However, in a post hoc analysis, the change from baseline to Week 6 in SAPS-PD score in the pimavanserin group was similar

between participants with a screening MMSE score 21–24 and those with a screening MMSE score ≥25 (**Figure 4**).[2,3]

Figure 4. SAPS-PD Score Change from Baseline (LSM ± SE) Over Time Stratified by Screening MMSE Score (MMRM; OC; ITT Analysis Set; Study 020)[3]



For the pimavanserin group, LSM change from baseline for SAPS-PD at Week 6 was similar between subgroups. For the placebo group, participants with screening MMSE 21–24 showed a worse response vs participants with screening MMSE ≥25. Abbreviations: ITT=intent to treat; LSM=least squares mean; MMSE=Mini-Mental State Examination; PBO=placebo; PIM=pimavanserin; SAPS-PD=Scale for Assessment of Positive Symptoms for Parkinson's disease; SE=standard error.

Adverse Events

The incidence of TEAEs by MMSE score at screening is summarized in **Table 6**. TEAEs occurring in >5% of pimavanserin-treated participants overall were urinary tract infection, fall, peripheral edema, hallucinations, nausea, and confusional state.[3] In the pimavanserin group, 1 death each occurred in the MMSE 21–24 and MMSE ≥25 subgroups; in the placebo group, 1 death occurred in the MMSE 21–24 subgroup. All deaths were regarded as unrelated to study drug.

Table 6. Incidence of TEAEs by Screening MMSE Score (Safety Analysis Set; Study 020)[3]

n (%)	Overall Population		MMSE 21–24		MMSE ≥25	
	PIM 34 mg (n=104)	PBO (n=94)	PIM 34 mg (n=32)	PBO (n=23)	PIM 34 mg (n=71)	PBO (n=71)
Most common AEs[a]						
UTI	14 (13.5)	11 (11.7)	2 (6.3)	2 (8.7)	12 (16.9)	9 (12.7)
Fall	11 (10.6)	8 (8.5)	4 (12.5)	2 (8.7)	7 (9.9)	6 (8.5)
Peripheral edema	7 (6.7)	3 (3.2)	2 (6.3)	--	5 (7.0)	3 (4.2)
Hallucination	7 (6.7)	1 (1.1)	1 (3.1)	--	6 (8.5)	1 (1.4)
Nausea	6 (5.8)	6 (6.4)	3 (9.4)	4 (17.4)	3 (4.2)	2 (2.8)
Confusional state	6 (5.8)	3 (3.2)	2 (6.3)	--	4 (5.6)	3 (4.2)
Insomnia	5 (4.8)	4 (4.3)	2 (6.3)	1 (4.3)	3 (4.2)	3 (4.2)
Constipation	4 (3.8)	2 (2.1)	1 (3.1)	--	3 (4.2)	2 (2.8)
Arthralgia	3 (2.9)	2 (2.1)	--	1 (4.3)	3 (4.2)	1 (1.4)
Psychotic disorder	3 (2.9)	2 (2.1)	2 (6.3)	2 (8.7)	1 (1.4)	--
Back pain	3 (2.9)	1 (1.1)	--	--	3 (4.2)	1 (1.4)
Contusion	3 (2.9)	1 (1.1)	3 (9.4)	1 (4.3)	--	--
Diarrhea	3 (2.9)	1 (1.1)	1 (3.1)	--	2 (2.8)	1 (1.4)
Dehydration	3 (2.9)	--	1 (3.1)	--	2 (2.8)	--

n (%)	Overall Population		MMSE 21–24		MMSE ≥25	
	PIM 34 mg (n=104)	PBO (n=94)	PIM 34 mg (n=32)	PBO (n=23)	PIM 34 mg (n=71)	PBO (n=71)
Any AE	74 (71.2)	59 (62.8)	22 (68.8)	12 (52.2)	52 (73.2)	47 (66.2)
Any serious AE	11 (10.6)	4 (4.3)	3 (9.4)	2 (8.7)	8 (11.3)	2 (2.8)
AE leading to discontinuation	10 (9.6)	3 (3.2)	3 (9.4)	2 (8.7)	7 (9.9)	1 (1.4)
Fatal AE	2 (1.9)	1 (1.1)	1 (3.1)	1 (4.3)	1 (1.4)	--

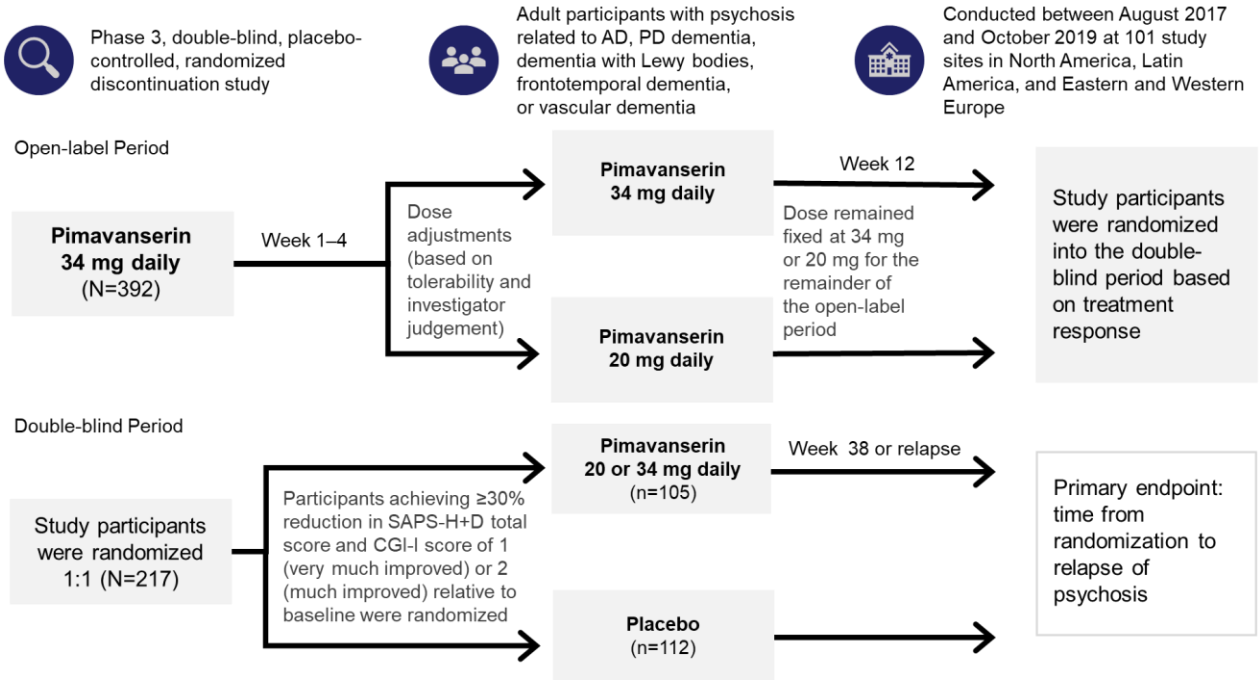
[a]*AEs occurring in >2 of the PIM-treated participants in the overall safety analysis group (1 participant did not have an MMSE score so could not be categorized for the MMSE analysis).*
Abbreviations: AE=adverse event; MMSE=Mini-Mental State Examination; PBO=placebo; PIM=pimavanserin; TEAE=treatment-emergent adverse event; UTI=urinary tract infection.

HARMONY: Post Hoc Subgroup Analysis

Background and Study Design

HARMONY was a Phase 3 study evaluating the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis (**Figure 5**).[7] 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.[4]

Figure 5. HARMONY Trial Design[4]



Abbreviations: AD=Alzheimer's disease; CGI-I=Clinical Global Impression–Improvement; PD=Parkinson's disease; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

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 <0.0033 on the study's primary endpoint).[8] 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).[7,8]

The intent to treat (ITT) population for the double-blind phase comprised patients randomized to continue pimavanserin or treatment with placebo.[4] 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).
The primary endpoint in the study was time from randomization to relapse of psychosis in the double-blind period. Relapse was defined as 1 or more of the following:[4]

- 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.[4] Cognitive function was evaluated using the MMSE and extrapyramidal symptoms were evaluated using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A).
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.[4] Participants included here met clinical criteria for (1) dementia, and (2) PD dementia.[9,10] Patients with dementia with Lewy bodies were also enrolled in the HARMONY study but were not included in this subgroup analysis.[11] Selected inclusion and exclusion criteria are shown in **Table 7**.

Table 7. Selected Inclusion and Exclusion Criteria (HARMONY Post Hoc)[4,7]

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 PD
• Had a MMSE score ≥6 and ≤24
• Had psychotic symptoms for ≥2 months
• Had all 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 participant 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 participant was taking an antipsychotic 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; CNS=central nervous system; MMSE=Mini-Mental State Examination; NIA-AA=National Institute on Aging Alzheimer's Association; PD=Parkinson's disease; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

Post Hoc 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.[4] Baseline characteristics and disease characteristics of the subgroup population in the open-label period and double-blind period are shown in **Table 8**.

Table 8. Baseline Demographics and Clinical Characteristics (HARMONY Post Hoc; Open-label and Double-blind Safety Analysis Sets)[4,12]

	Open-label Period	Double-blind Period	
	PIM 34 mg N=49	Placebo n=20	PIM 34 mg n=16
Age, years (mean ± SE)	72.6±1.08	72.3±1.93	69.6±1.78
Age range, years	59–87	60–87	59–79
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)
Living at home, n (%)	48 (98.0)	20 (100.0)	15 (93.8)
Dementia severity, n (%)			
Mild	16 (32.7)	6 (30.0)	7 (43.8)
Moderate	28 (57.1)	11 (55.0)	9 (56.3)
Severe	5 (10.2)	3 (15.0)	--
Age at cognitive impairment onset, years (mean ± SE)	69.3±1.13	69.0±1.96	66.4±1.71
Duration of cognitive impairment, years (mean ± SE)	3.8±0.33	3.8±0.59	3.8±0.33
Symptoms of psychosis, historical n/N (%)			
Auditory hallucinations	37/48 (77.1)	17/20 (85.0)	12/15 (80.0)
Visual hallucinations	45/48 (93.8)	20/20 (100.0)	12/15 (80.0)
Delusions	32/48 (66.7)	16/20 (80.0)	6/15 (40.0)
SAPS-H+D score (mean ± SE)	23.5±1.45	3.8±0.99	3.4±1.02
CGI-S score (mean ± SE)	4.7±0.11	2.1±0.23	2.1±0.23
ESRS-A score (mean ± SE)	26.2±1.89	26.3±3.14	27.4±3.99
MMSE total score (mean ± SE)	18.9±0.74	19.3±1.29	19.6±1.26
Previous treatment for psychosis	18 (36.7)	6 (30.0)	6 (37.5)
Antidementia medications, n (%)	22 (44.9)	8 (40.0)	10 (62.5)
Memantine HCL	7 (14.3)	1 (5.0)	4 (25.0)
Rivastigmine/rivastigmine hydrogen tartrate	10 (20.4)	4 (20.0)	3 (18.8)
Memantine	5 (10.2)	1 (5.0)	3 (18.8)
Donepezil/donepezil HCL	2 (4.1)	2 (10.0)	--

	Open-label Period	Double-blind Period	
	PIM 34 mg N=49	Placebo n=20	PIM 34 mg n=16
Dopaminergic medication, n (%)			
Levodopa	49 (100)	19 (95.0)	16 (100)
Dopamine agonists	21 (42.9)	4 (20.0)	5 (31.3)
MAO-B inhibitors	6 (12.2)	0	2 (12.5)
Amantadine	4 (8.1)	2 (10.0)	1 (6.3)
≥1 LEDDs at baseline, n (%)	46 (93.9)	19 (95.0)	14 (87.5)
LEDD, mg (mean ± SE)	860.80±65.07	861.20±100.62	1019.60±109.14
Antidepressants, overall n (%)	6 (12.2)	4 (20.0)	1 (6.3)

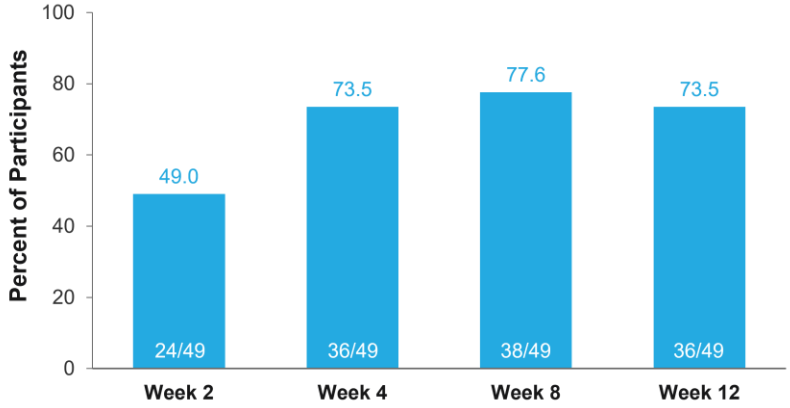
Abbreviations: CGI-S=Clinical Global Impression–Severity; LEDD=levodopa equivalent daily dose; MMSE=Mini-Mental State Examination; PD=Parkinson's disease, PIM=pimavanserin; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions; SE=standard error.

At open-label baseline, the mean (standard error [SE]) age of the subgroup population was 72.6 ± 1.08 years. The mean (SE) MMSE total score was 18.9±0.74; 57.1% of participants had dementia of moderate severity as defined by the investigator using functional classification. Mean (SE) SAPS-H+D was 23.5±1.45 and mean (SE) CGI-S was 4.7±0.11, consistent with the category of 'moderately ill'. Overall, 48.9 % were on concomitant cognitive-enhancing medications (memantine, memantine hydrochloride, rivastigmine, or donepezil).[4]

Outcomes

In the post hoc subgroup analysis, 73.5% (36/49) of eligible participants achieved response criteria to pimavanserin at Week 12 in the open-label treatment period (**Figure 6**), and were randomized to pimavanserin (n=16) or placebo (n=20) in the double-blind period.[4] Thirteen (13; 26.5%) participants were terminated early; reasons for early termination were: lack of response in open-label (n=6), AE (n=4), death (n=1), non-compliance with study drug (n=1), and participant withdrew consent (n=1).

Figure 6. SAPS-H+D and CGI-I Responder Analysis by Open-label Visit Prior to the Study Discontinuation Date (Open-label Safety Analysis Set; HARMONY Post Hoc)[12]



Missing values imputed as non-responders.
Abbreviations: CGI-I=Clinical Global Impression–Improvement; PD=Parkinson's disease; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

In the double-blind treatment period at the time of prespecified IA (N=30), 1 of 13 (7.7%) pimavanserin-treated participants and 9 of 17 (52.9%) placebo-treated participants had met relapse criteria and were adjudicated as relapses by the study's independent adjudication committee (**Table 9**, **Figure 7**).[4]

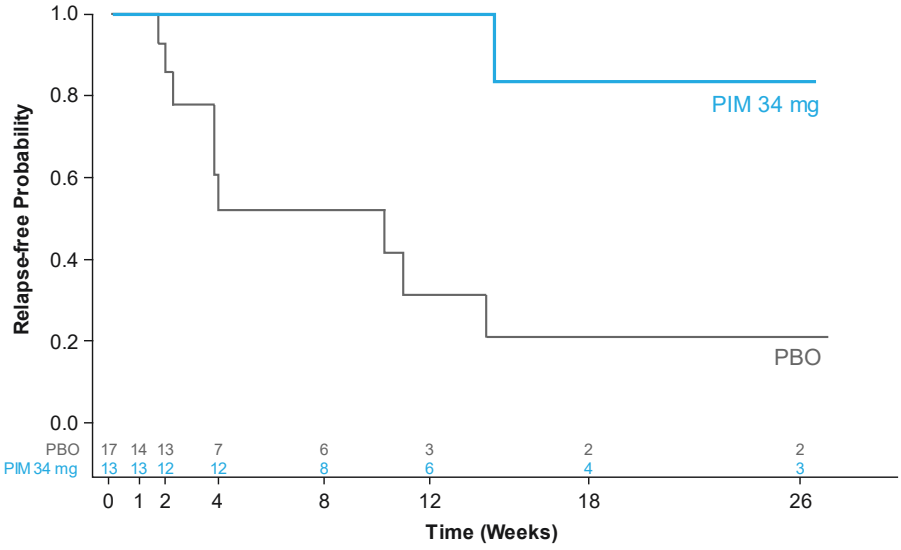
Table 9. Time from randomization to Relapse of Psychosis in the Double-blind Period (ITT Population*; HARMONY Post Hoc)[4]

n (%)	Placebo n=17	PIM 34 mg n=13
Number of participants having a relapse event	9 (52.9)	1 (7.7)
Number of participants censored from survival analysis	8 (47.1)	12 (92.3)
Completed Week 26 without a relapse	2 (11.8)	3 (23.1)
Prematurely discontinued prior to Week 26	3 (17.6)	3 (23.1)
Ongoing at time of database cutoff	3 (17.6)	6 (46.2)

**Efficacy data reflect the ITT analysis set at the time of the interim analysis (n=30). Six (6) additional patients had been randomized by the time the study was stopped based on the recommendation by the data safety monitoring board for positive efficacy. These 6 subjects were not part of the efficacy analyses.*
Abbreviations: ITT=intent to treat; PIM=pimavanserin.

Reasons for premature discontinuation prior to Week 26 included participant withdrew consent (n=2) and AE (n=1) in the pimavanserin group, and participant withdrew consent (n=1), AE (n=1), and moved to nursing home (n=1) in the placebo group.[5]

Figure 7. Kaplan-Meier Estimation of Time from Randomization to Relapse of Psychosis in the Double-Blind Period (HARMONY Post Hoc*)[12]



**Efficacy data reflect the ITT analysis set at the time of the interim analysis (n=30). Six (6) additional patients had been randomized by the time the study was stopped based on the recommendation by the data safety monitoring board for positive efficacy. These 6 subjects were not part of the efficacy analyses.*
Abbreviations: ITT=intent to treat; PBO=placebo; PIM=pimavanserin.

Safety

In the open-label period (N=49), 46.9% (n=23) of participants included in the subgroup analysis experienced any TEAE and 10.2% (n=5) experienced a serious TEAE (8 events: 2 falls and 1 each of myocardial infarction, diarrhea, bone fissure, dehydration, agitation, and psychotic

disorder). One (1) 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]
In the double-blind period (N=36), TEAEs were observed in 31.3% (n=5) of participants on pimavanserin and 45.0% (n=9) on placebo (**Table 10**). Discontinuations due to TEAEs were 6.3% (n=1) for pimavanserin and 10.0% (n=2) for placebo; no serious TEAEs were reported.[4]
The incidence of TEAEs by study period is shown in **Table 11**.

Table 10. Incidence of TEAEs in the Open-label Period and Double-blind Period (Open-label and Double-blind Safety Analysis Sets; HARMONY Post Hoc)[4]

n (%)	Open-label Period	Double-blind Period	
	PIM 34 mg N=49	Placebo n=20	PIM 34 mg n=16
Any TEAE	23 (46.9)	9 (45.0)	5 (31.3)
Serious TEAE	5 (10.2)	0	0
Treatment-related TEAE	5 (10.2)	3 (15.0)	0
Any related serious TEAE	0	0	0
TEAE leading to discontinuation or study termination	7 (14.3)	2 (10.0)	1 (6.3)
TEAE resulting in death	1 (2.0)	0	0

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

Table 11. TEAEs Occurring in ≥3% of Participants in Either Study Period (Open-label and Double-blind Safety Analysis Sets; HARMONY Post Hoc)[4]

n (%)	Open-label Period	Double-blind Period	
	PIM 34 mg N=49	Placebo n=20	PIM 34 mg n=16
Weight decreased	4 (8.2)	0	0
Decreased appetite	4 (8.2)	0	0
Somnolence	4 (8.2)	0	0
Insomnia	4 (8.2)	0	0
Urinary tract infection	3 (6.1)	0	0
Fall	3 (6.1)	0	0
Constipation	2 (4.1)	0	0
Diarrhea	2 (4.1)	0	0
Nausea	2 (4.1)	0	0
Fatigue	2 (4.1)	0	0
Nasopharyngitis	2 (4.1)	0	0
Confusional state	2 (4.1)	0	0
Psychotic disorder	2 (4.1)	0	1 (6.3)
Orthostatic hypotension	2 (4.1)	0	0

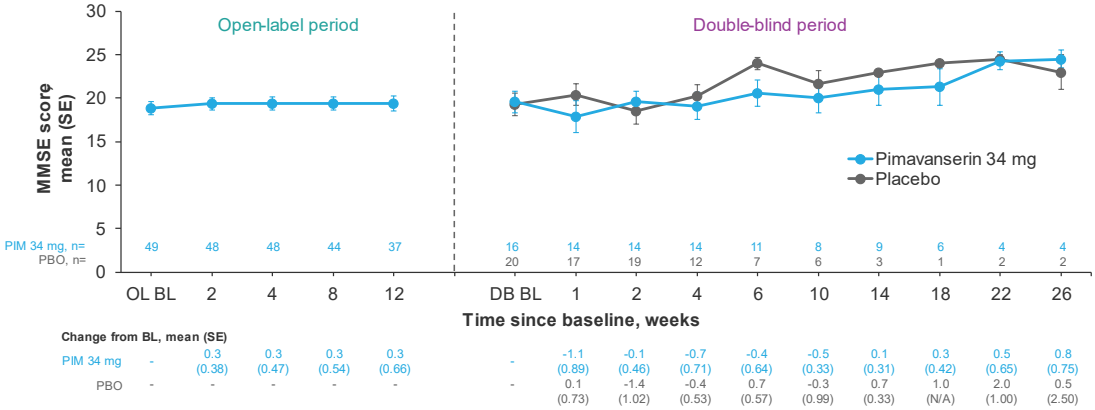
Numbers presented represent participants.
Abbreviations: PIM=pimavanserin; TEAE=treatment-emergent adverse event.

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 8** and **Figure 9**).[4]

The mean MMSE score at open-label baseline was 18.9 (SE, 0.74), and the mean change from baseline to Week 12 was 0.3 (SE, 0.66). Participants randomized to pimavanserin and placebo had similar mean MMSE scores at double-blind baseline (pimavanserin, 19.6 [SE, 1.26]; placebo, 19.3 [SE, 1.29]) and exhibited a similar mean MMSE score change from double-blind baseline to Week 26 (**Figure 8**).[4]

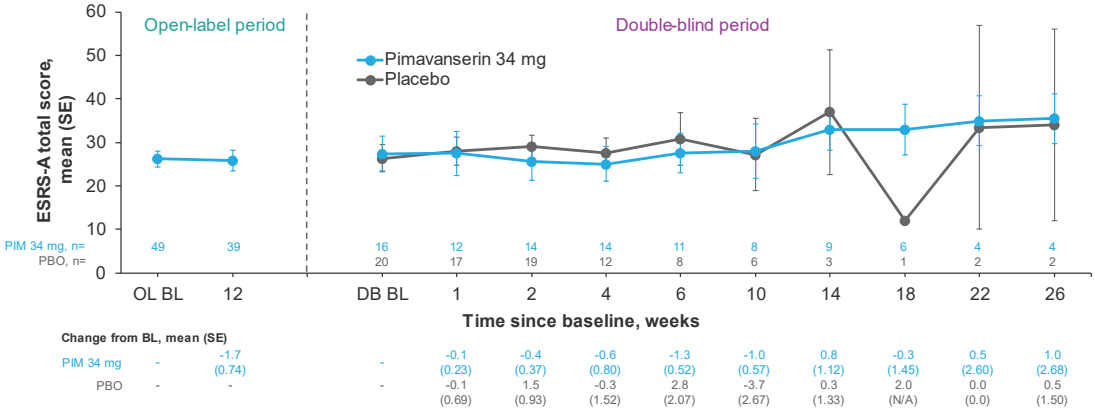
Figure 8. MMSE Score Change from Double-blind Baseline (Open-label and Double-blind Safety Analysis Sets; HARMONY Post Hoc)[4]



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

The mean ESRS-A score at open-label baseline was 26.2 (SE, 1.89), and the mean change from baseline to Week 12 was -1.7 (SE, 0.74). Mean ESRS-A scores at double-blind baseline (pimavanserin, 27.4 [SE, 3.99]; placebo, 26.3 [SE, 3.14]) and the mean changes from double-blind baseline to Week 26 were similar in pimavanserin- and placebo-treated participants (**Figure 9**).[4]

Figure 9. ESRS-A Total Score Change from Double-blind Baseline (Open-label and Double-blind Safety Analysis Sets; HARMONY Post Hoc)[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 the subgroup.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. 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]**
3. Espay AJ, Guskey MT, Norton JC, et al. Pimavanserin for Parkinson's Disease psychosis: Effects stratified by baseline cognition and use of cognitive-enhancing medications. *Mov Disord.* 2018;33(11):1769-1776. **[PubMed]**
4. Weintraub D, Espay AJ, Sharma VD, et al. Pimavanserin for psychosis in Parkinson's disease dementia: Subgroup analysis of the HARMONY Trial. *Parkinsonism Relat Disord.* 2024;119:105951. **[PubMed]**
5. Acadia Pharmaceuticals Inc. Data on File. San Diego, CA.
6. Acadia Pharmaceutical Inc. NUPLAZID® Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee on 29 March 2016.
7. Tariot PN, Cummings JL, Soto-Martin ME, et al. Trial of Pimavanserin in Dementia-Related Psychosis. *N Engl J Med.* 2021;385(4):309-319. **[PubMed]**
8. Acadia Pharmaceutical Inc. NUPLAZID® Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee on 17 June 2022.
9. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-269. **[PubMed]**
10. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord.* 2007;22(12):1689-1707; quiz 1837. **[PubMed]**
11. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005;65(12):1863-1872. **[PubMed]**
12. Weintraub D, Espay A, Sharma V, et al. Pimavanserin Treatment of Hallucinations and Delusions in Patients With Parkinson’s Disease Dementia: Post Hoc Analysis of the HARMONY Trial. Paper presented at: Clinical Trials on Alzheimer’s Disease (CTAD) 2020 Annual Meeting; November 9-12, 2021.