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NUPLAZID® (pimavanserin): Clinical Trials in Dementia-related Psychosis

This letter is provided in response to your specific request for information regarding clinical trials with pimavanserin in patients with dementia-related psychosis.

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

- The efficacy and safety of pimavanserin in treating hallucinations and delusions associated with dementia-related psychosis was evaluated in **HARMONY (ACP-103-045)**, a Phase 3 double-blind, placebo-controlled, randomized withdrawal (relapse prevention) study.[2]
- The **primary endpoint** was met, and the study was stopped at the pre-planned interim analysis based on pre-specified stopping criteria requiring a one-sided p-value <0.0033 on the study's primary endpoint, time from randomization to relapse. Risk of relapse was reduced by 2.8-fold compared to placebo (hazard ratio [HR]=0.35; 95% confidence interval [CI] 0.17, 0.73; one-sided p=0.0023).[2,3]
- Pimavanserin met the **key secondary endpoint** by significantly reducing risk of discontinuation for any reason by 2.2-fold (HR=0.45; 95% CI 0.26, 0.79; one-sided p=0.0024).[2,3]
- In the double-blind period, **treatment-emergent adverse events** (TEAEs) were observed in 41.0% of patients on pimavanserin and 36.6% on placebo.[2]

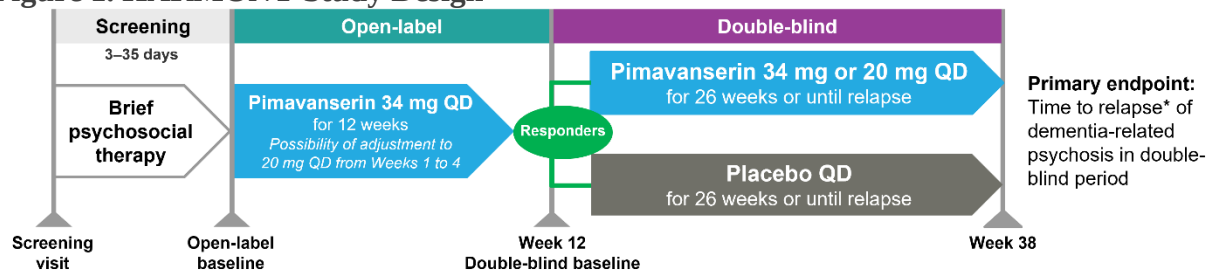
Phase 3 HARMONY Study (ACP-103-045)

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] 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 or placebo once daily, for up to 26 weeks, or until relapse.

Discontinuations in the double-blind period were adjudicated by an independent committee to determine whether the criteria for protocol-defined relapse were met. Participants who did not

show a response to pimavanserin at Week 8 of the open-label period or a achieved response criteria at Week 12 were discontinued from the study and entered the safety follow-up period.[2]

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

- ≥30% increase (worsening) from Week 12 (double-blind baseline) on the SAPS-H+D Total Score and a CGI-I score of 6 (much worse) or 7 (very much worse) - relative to the double-blind baseline.
- Treated with an antipsychotic (other than pimavanserin) for dementia-related delusions and/or hallucinations.
- Stops study drug or withdraws from study for lack of efficacy (as reported by the subject or study partner/caregiver) or Investigator discontinues study drug due to lack of efficacy
- Hospitalized for worsening dementia-related psychosis.

The secondary endpoint in the study was time to discontinuation for any reason in the double-blind period as represented by the hazard ratio. In prespecified safety analyses, cognitive and motor function were measured using Mini-Mental State Examination (MMSE) and Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) Total Score, respectively.[2]

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

Table 1. Selected Inclusion and Exclusion Criteria[2]

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 one of the following disorders: dementia associated with Parkinson's disease dementia, dementia with Lewy bodies, possible or probable Alzheimer's disease, possible or probable frontotemporal degeneration spectrum disorders or vascular dementia
• 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 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

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 patients were enrolled in HARMONY. Baseline characteristics and disease characteristics of the overall population in the open-label phase and double-blind phase are shown in **Table 2**.[2] At open-label baseline, the mean (standard deviation [SD]) age of the study population was 74.5 ± 8.3 years. The mean (SD) MMSE score was 16.7 ± 4.7; 70.2% of participants had dementia of moderate severity as defined by the investigator using functional classification. The mean (SD) SAPS-H+D total score was 24.4 ± 9.2, and the mean (SD) Clinical Global Impression – Severity (CGI-S) score was 4.7 ± 0.7, consistent with the category of 'moderately ill'. Overall, 69.6% (273 of 392) of participants were taking antidementia medication (cholinesterase inhibitor and/or memantine) at open-label baseline.[2,4]

Table 2. Baseline Demographics and Clinical Characteristics (Safety Analysis Set)[2,5]

	Open-label phase	Double-blind phase	
	Pimavanserin N=392	Pimavanserin N=105	Placebo N=112
Age, years			
Mean	74.5 ± 8.3	73.8 ± 8.4	74.9 ± 8.6
Range	52-90	53-89	52-90
Female sex, n (%)	229 (58.4)	62 (59.0)	69 (61.6)
White race, n/N (%)[a]	371/384 (96.6)	103/105 (98.1)	107/109 (98.2)
Black or African American race, n/N (%)[a]	10/384 (2.6)	2/105 (1.9)	2/109 (1.8)
Hispanic or Latino ethnic group, n/N (%)[a]	86/384 (22.4)	25/105 (23.8)	26/109 (23.9)
Living at home, n (%)	373 (95.2)	94 (89.5)	109 (97.3)
Age at cognitive impairment onset, years	70.6 ± 8.9	70.1 ± 9.1	71.2 ± 9.2
Duration of cognitive impairment, years	4.3 ± 2.8	4.2 ± 2.2	4.2 ± 3.1
History of psychotic symptoms, n/N (%)			
Auditory hallucinations	287/382 (75.1)	81/101 (80.2)	92/111 (82.9)

	Open-label phase	Double-blind phase	
	Pimavanserin N=392	Pimavanserin N=105	Placebo N=112
Visual hallucinations	302/382 (79.1)	77/101 (76.2)	92/111 (82.9)
Delusions	319/382 (83.5)	77/101 (76.2)	96/111 (86.5)
Primary dementia subtype, n (%)			
Alzheimer's disease	260 (66.3)	67 (63.8)	70 (62.5)
Dementia with Lewy bodies	28 (7.1)	6 (5.7)	4 (3.6)
Frontotemporal dementia	7 (1.8)	1 (1.0)	2 (1.8)
Parkinson's disease dementia	59 (15.1)	19 (18.1)	23 (20.5)
Vascular dementia	38 (9.7)	12 (11.4)	13 (11.6)
Antidementia drug use, n (%)[b]			
Any	273 (69.6)	81 (77.1)	72 (64.3)
Acetylcholinesterase inhibitor	172 (43.9)	49 (46.7)	42 (37.5)
Antidepressant use, n (%)	81 (20.7)	14 (13.3)	23 (20.5)
MMSE score	16.7 ± 4.7	18.3 ± 5.4	17.9 ± 5.9
SAPS H+D total score	24.4 ± 9.2	5.0 ± 5.3	5.2 ± 5.4
CGI-S score	4.7 ± 0.7	2.3 ± 1.0	2.3 ± 1.0

Plus–minus values are means ± standard deviation. Percentages may not total 100 because of rounding.
[a] Race and ethnic group were determined by site staff or by the patient or care partner.
[b] Antidementia drugs included acetylcholinesterase inhibitors, memantine, or both. The use of an acetylcholinesterase inhibitor alone or in a combination pill is noted as a subcategory.
Abbreviations: CGI-S=Clinical Global Impressions – Severity; MMSE=Mini-Mental State Examination; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

Efficacy Results

A prespecified efficacy Interim Analysis was triggered after 40 relapse events occurred. Pimavanserin met its primary endpoint at the Interim Analysis, demonstrating a statistically significant reduction in risk of relapse of psychosis with pimavanserin compared to placebo.[2] Upon the recommendation of HARMONY's independent data monitoring committee, which met to review the data from the prespecified efficacy Interim Analysis, the study was stopped early based on pre-specified stopping criteria requiring a one-sided p-value less than 0.0033 on the study's primary endpoint.[3]

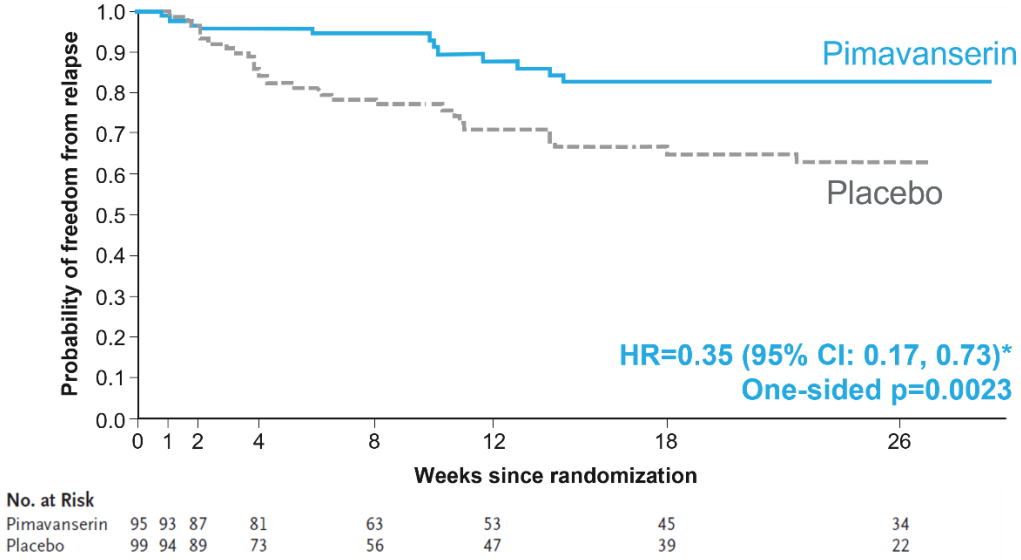
Open-label Results

In the open-label treatment period, 392 participants were enrolled, and 61.8% of eligible participants (217/351) met sustained response criteria and entered the double-blind phase (41 participants remained in the open-label period at the time of study discontinuation and were administratively discontinued).[2] Eighty-eight percent of participants who responded at Week 8 had sustained response at the enriched Week 12 population. Week 12 is an enriched population because it only includes participants who met response criteria at Week 8 and were subsequently assessed at Week 12.

Double-blind Results

The primary endpoint was met, and the study was stopped at the prespecified Interim Analysis based on pre-specified stopping criteria requiring a one-sided p-value <0.0033 on the study's primary endpoint. Risk of relapse was reduced by 2.8-fold compared to placebo (HR=0.35; 95% CI 0.17, 0.73; one-sided p=0.0023; two-sided p=0.005; **Figure 2**). In addition, pimavanserin met the key secondary endpoint by significantly reducing risk of discontinuation for any reason by 2.2-fold (HR=0.45; 95% CI 0.26, 0.79; one-sided p=0.0024; two-sided p=0.005).[2,3]

Figure 2. Time from Randomization to Relapse of Psychosis in the Double-Blind Period (ITT Analysis Set at Interim Analysis)[2,3]



**The Cox regression model includes effects for treatment group, dementia type, and region.*
Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=Intent-to-treat.

Safety Results

In the double-blind period, TEAEs were observed in 41.0% of participants on pimavanserin and 36.6% on placebo.[2] Discontinuations due to TEAEs were 2.9% for pimavanserin and 3.6% for placebo. Serious TEAEs were 4.8% in the pimavanserin group and 3.6% in the placebo group. One death was reported in the open-label period and one death was reported in the pimavanserin group during the double-blind period. According to Investigators, neither death was considered related to the study drug. The incidence of TEAEs by study period is shown in **Table 3**.[2]

Table 3. Incidence of TEAEs and TEAEs Occurring in ≥2% of Participants (Safety Analysis Set)[2]

	Number (%) of participants		
	Open-label phase	Double-blind phase	
	Pimavanserin N=392	Pimavanserin N=105	Placebo N=112
Any TEAE	142 (36.2)	43 (41.0)	41 (36.6)
Serious TEAE[a]	20 (5.1)	5 (4.8)	4 (3.6)
Treatment-related TEAE[b]	45 (11.5)	9 (8.6)	10 (8.9)
TEAE leading to discontinuation	30 (7.7)	3 (2.9)	4 (3.6)
TEAE resulting in death[c]	1 (0.3)	1 (1.0)	0
Individual TEAEs[d]			
Anxiety	6 (1.5)	3 (2.9)	0
Asthenia	3 (0.8)	3 (2.9)	1 (0.9)
Confusional state	8 (2.0)	1 (1.0)	0
Constipation	10 (2.6)	2 (1.9)	1 (0.9)
Diarrhea	5 (1.3)	0	3 (2.7)
Dizziness	6 (1.5)	3 (2.9)	0
Headache	6 (1.5)	10 (9.5)	5 (4.5)

	Number (%) of participants		
	Open-label phase	Double-blind phase	
	Pimavanserin N=392	Pimavanserin N=105	Placebo N=112
Hypertension	9 (2.3)	2 (1.9)	2 (1.8)
Nasopharyngitis	7 (1.8)	1 (1.0)	4 (3.6)
Nausea	8 (2.0)	0	2 (1.8)
Prolonged QT interval[e]	2 (0.5)	3 (2.9)	0
Urinary tract infection	20 (5.1)	7 (6.7)	4 (3.6)
Weight decreased	5 (1.3)	1 (1.0)	3 (2.7)

TEAEs that occurred in at least 2% of the participants in the open-label phase or in either trial group in the double-blind phase are shown.
A TEAE is an adverse event with an onset on or after the date of the first trial dose and no later than the date of the last trial dose plus 30 days. For participants who underwent randomization in the double-blind phase, if the onset of the adverse event was on or after the date of first dose in the double-blind phase, the adverse event was assigned to the double-blind phase.
[a] A serious adverse event was an adverse event that met one or more of the following criteria: was fatal or life-threatening, resulted in disability or permanent damage, led to hospitalization, prolonged existing hospitalization, was a congenital anomaly or birth defect, or was medically significant. The classification of an adverse event as serious was made by the investigator.
[b] An adverse event was considered to be related to pimavanserin or placebo by the investigator if there was a reasonable possibility that the event may have been caused by the trial treatment under investigation. Events with a missing relationship were classified as being related.
[c] A 75-year-old White man died during the open-label phase from suspected myocardial infarction, which was considered to be unrelated to the trial drug by the investigator. An 81-year-old White man who was assigned to receive pimavanserin in the double-blind phase died from septic and metabolic encephalopathy caused by a dental abscess, which was considered to be unrelated to drug therapy by the investigator.
[d] No significant between-group differences in adverse events were observed when tested at the 5% level.
[e] The adverse events involving prolongation of the corrected QT interval, calculated with the use of Fridericia's formula, involved maximum changes from baseline of 12 msec and 51 msec in two participants in the open-label phase (the former was in a participant who discontinued the trial owing to lack of response, and the latter resolved with dose reduction) and 6 msec, 22 msec, and 77 msec in three participants in the double-blind phase (the first two resolved without intervention, and the third remained stable until the participant discontinued the trial). All events were detected on electrocardiography and were asymptomatic.
Abbreviation: TEAE=treatment-emergent adverse event.

The mean (±SE) prolongation of the corrected QT interval, calculated with the use of Fridericia's formula (QTcF), during the open-label phase was 5.4±0.9 msec; 1 participant (0.3%) had an asymptomatic increase in the QTcF of >60 msec with pimavanserin. In the double-blind period, two participants (one in each group) had asymptomatic QTcF values >500 msec. In total, five adverse events involving an asymptomatic prolongation of the QT interval were reported with pimavanserin (two in the open-label phase and three in the double-blind phase), affecting 1.3% of the participants.[2]

The incidence of the following TEAEs were investigated in the open-label and double-blind periods: sedation; falls; cerebrovascular events; thromboembolic events; neuroleptic malignant syndrome; metabolic disorders (diabetes, dyslipidemia); hyperprolactinemia; seizures; blood dyscrasias; orthostatic hypotension; and cognitive event. No TEAEs of cerebrovascular events, thromboembolic events, neuroleptic malignant syndrome, diabetes, dyslipidemia, hyperprolactinemia, or seizure were reported in the open-label period. The observed incidence of other select TEAEs in the open-label period was ≤2.0% (**Table 4**). Select TEAEs in the double-blind phase were single reports and were more frequent in the placebo group (**Table 4**).[6]

Table 4. Incidence of Select TEAEs with Pimavanserin During Open-label and Double-blind Periods (Safety Analysis Set)[6]

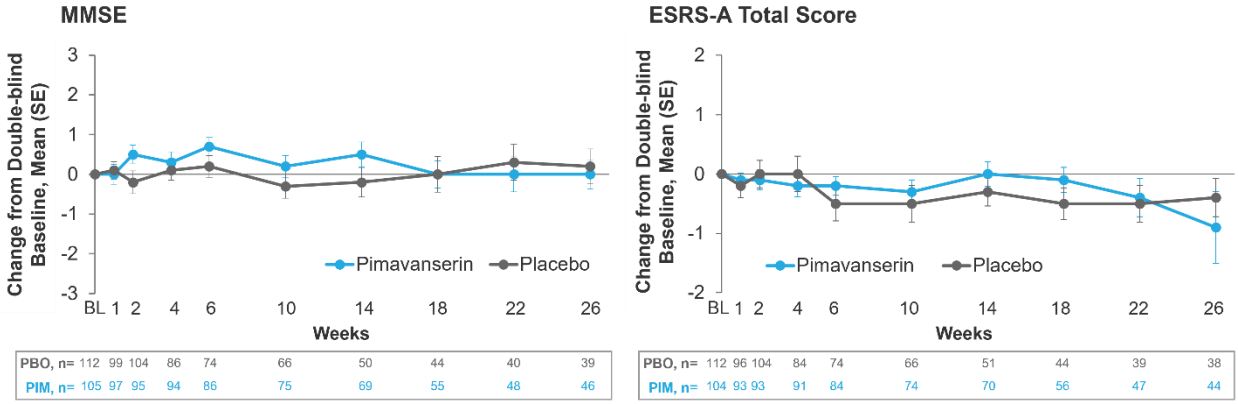
	Number (%) of participants		
	Open-label phase	Double-blind phase	
	Pimavanserin (N=392)	Pimavanserin (N=105)	Placebo (N=112)
Akathisia	1 (0.3)	0	1 (0.9)
Anemia	1 (0.3)	1 (1.0)	1 (0.9)
Ataxia	1 (0.3)	0	0
Confusional state	8 (2.0)	1 (1.0)	0
Mental status change	1 (0.3)	0	0
Fall	7 (1.8)	0	1 (0.9)
Hyperprolactinemia	0	0	2 (1.8)
Orthostatic hypotension	2 (0.5)	0	1 (0.9)
Parkinsonism	2 (0.5)	0	0
Sleep disorder	1 (0.3)	0	0
Somnolence	6 (1.5)	0	1 (0.9)
Tremor	1 (0.3)	0	1 (0.9)

Abbreviation: 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 3**).[2]

Figure 3. Prespecified Safety Analyses (Safety Analysis Set)[2,5]



Mean (SE) MMSE at double-blind BL: 18.3 (0.53) for pimavanserin 34 mg (N=105); 17.9 (0.55) for placebo (N=112).
Mean (SE) ESRS-A at double-blind BL: 7.7 (1.30) for pimavanserin 34 mg (N=104); 7.2 (1.25) for placebo (N=112).
Abbreviations: BL=baseline; ESRS-A=Extrapyramidal Symptom Rating Scale-Abbreviated; MMSE=Mini-Mental State Examination; PBO=placebo; PIM=pimavanserin; SE=standard error.

References

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