Pimavanserin Treatment of Hallucinations and Delusions in Patients With Parkinson's Disease Dementia: Post Hoc Analysis of the HARMONY Trial

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INTRODUCTION

- Pimavanserin is a selective serotonin-receptor modulator with inverse agonist/antagonist activity at the $5HT_{2A}$ receptor, and to a lesser extent at the $5HT_{2C}$ receptor.[1]
- Pimavanserin 34 mg is approved in the United States to treat hallucinations and delusions associated with Parkinson's disease (PD) psychosis[2] and was investigated for the treatment of dementia-related psychosis, including a subgroup of patients with PD dementia (PDD) and psychosis, in the HARMONY study.[3]
- HARMONY was stopped early when a prespecified interim analysis met stopping criteria for efficacy. 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; 2-sided *P* value=0.005).[3]
- A post hoc subgroup analysis of data from patients with PDD with psychosis treated with pimavanserin 34 mg can expand on the established efficacy and safety of pimavanserin in patients receiving pimavanserin in line with its currently approved indication.

OBJECTIVE

- To describe the efficacy and safety of pimavanserin 34 mg for the treatment of hallucinations and delusions in a subgroup of patients with PDD with psychosis in HARMONY.

METHODS

Study Design

- HARMONY (NCT03325556) was a phase 3, placebo-controlled, randomized discontinuation study. Study design and primary results in the overall dementia-related psychosis population have been published.[3]
- Patients (MMSE 6-24) with a clinical diagnosis of dementia and moderate-to-severe psychosis were enrolled.
- Eligible patients received pimavanserin once daily for 12 weeks during the open-label period.
  - All patients initiated pimavanserin at a dose of 34 mg once daily; dose reduction to 20 mg daily based on tolerability was permitted from weeks 1–4, after which the dose remained fixed for the remainder of the open-label period.
- Patients meeting prespecified criteria for treatment response (defined as ≥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 much improved [2]/very much improved [1]) at weeks 8 and 12, relative to baseline, in the open-label period were randomized 1:1 to continue pimavanserin or receive placebo for up to 26 weeks in the double-blind period.
  - Randomization was stratified by dementia subtype, which included the strata for Parkinson's disease dementia or dementia with Lewy bodies.
- An interim analysis of the primary efficacy endpoint by an independent Data Safety Monitoring Board (DSMB) was prespecified.

Assessments

- At screening, investigators reported on the duration of cognitive impairment and rated the severity of dementia (mild, moderate, or severe) for each patient.
- The primary endpoint was time to psychosis relapse during the double-blind period. Relapse criteria were defined as one or more of the following:
  - ≥30% increase (worsening) from week 12 (ie, double-blind baseline) on the SAPS–H+D total score AND CGI-I score of much worse (6) or very much worse (7) relative to the double-blind baseline; OR
  - Treatment with an antipsychotic (other than pimavanserin) for dementia-related delusions and/or hallucinations; OR
  - Stopping study drug or withdrawing from study for lack of efficacy (as reported by the patient or study partner/caregiver) or the investigator discontinued study drug due to lack of efficacy; OR
  - Hospitalization for worsening dementia-related psychosis.
- Treatment-emergent adverse events (TEAEs) were collected throughout the duration of the study.
- Motor-related function was evaluated using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A), with higher scores indicating worsened motor function (range, 0–120).[4]
- Cognitive abilities were evaluated using the Mini-Mental State Examination (MMSE), with lower scores indicating greater cognitive impairment (range, 0–30).[5]

Statistical Analysis

- Time from randomization to relapse of psychosis was analyzed using a Cox regression model in those patients who were stabilized on 34 mg prior to randomization and then randomized to stay on pimavanserin 34 mg or placebo.
- Baseline characteristics and safety data were analyzed using descriptive statistics.

RESULTS

Baseline Characteristics

- HARMONY enrolled 392 patients into the open-label period, 59 of whom had PDD and psychosis.
  - Of these 59 patients, the pimavanserin dose was reduced to 20 mg in 10 patients, who were excluded from this analysis. The remaining 49 patients received pimavanserin 34 mg only in the open-label period and were analyzed here.
- At open-label baseline, the mean age was 72.6 years (**Table 1**). 32.7% (n=16) of patients exhibited mild dementia, 57.1% (n=28) exhibited moderate dementia, and 10.2% (n=5) exhibited severe dementia.

Table 1. Baseline Demographics and Characteristics

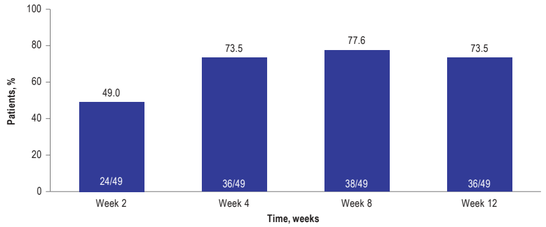
	Open-Label Period	Double-Blind Period	
	Pimavanserin 34 mg (N=49)	Placebo (N=20)	Pimavanserin 34 mg (N=16)
Age, years (mean ± SE)	72.6 ± 1.08	72.3 ± 1.93	69.6 ± 1.78
Age range, years	59–87	60–87	59–79
Female, n (%)	19 (38.8)	8 (40.0)	6 (37.5)
White race, n (%)	47 (100.0)	19 (100.0)	16 (100.0)
Hispanic/Latino, n (%)	6 (12.8)	1 (5.3)	3 (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)	0 (0.0)
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
Psychotic symptoms, 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)
Previous treatment for dementia-related psychosis, n (%)[a]	18 (36.7)	6 (30.0)	6 (37.5)
MMSE total score (mean ± SE)	18.9 ± 0.74	19.3 ± 1.29	19.6 ± 1.26
ESRS-A (mean ± SE)	26.2 (1.89)	26.3 (3.14)	27.4 (3.99)
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

Number of patients with nonmissing values is used as the denominator for calculating percentages within each group;
Data reflect open-label and double-blind safety analysis sets, which included all patients who received at least one dose of study drug.
[a]For patients 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.
CGI-S, Clinical Global Impression-Severity; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; MMSE, Mini-Mental State Examination;
SAPS–H+D, Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions subscales; SE, standard error.

Efficacy

- Majority of patients (73.5% [36 of 49]) achieved response criteria to pimavanserin at weeks 8 and 12 during the open-label period and entered the double-blind period (**Figure 1**).

Figure 1. Patients Meeting Response Criteria to Pimavanserin



Missing values imputed as nonresponders.

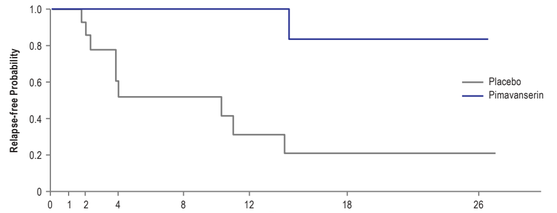
- In the double-blind period, 16 patients were randomized to pimavanserin 34 mg and 20 were randomized to placebo.
- At the time the study was stopped, 1 pimavanserin-treated patient and 9 placebo-treated patients had met relapse criteria and were adjudicated as relapses (**Table 2**).
- The risk of psychosis relapse was lower in the pimavanserin group than in the placebo group (HR: 0.052; 95% CI: 0.016–0.166; 1-sided *P*<0.0001) (**Figure 2**).

Table 2. Time to Relapse in the Double-Blind Period

	Double-Blind Period	
	Placebo (N=17)	Pimavanserin 34 mg (N=13)
Patients with a relapse event, n (%)	9 (52.9)	1 (7.7)
Patients censored from survival analysis, n (%)	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 (42.6)

Efficacy data reflect the intent-to-treat analysis set at the time of the interim analysis (N=30). Six additional patients had been randomized by the time the study was stopped, based on recommendation by the Data Safety Monitoring Board for positive efficacy. These 6 subjects were not part of the efficacy analyses.

Figure 2. Kaplan-Meier Estimation of Time to Relapse in the Double-Blind Period



Safety

- In the open-label period, 46.9% (n=23) of patients included in the subgroup analysis experienced any TEAE and 10.2% (n=5) experienced a serious TEAE (**Table 3**).

Table 3. Overall Summary of Treatment-Emergent Adverse Events

	Open-Label Period	Double-Blind Period	
TEAEs, n (%)	Pimavanserin 34 mg (N=49)	Placebo (N=20)	Pimavanserin 34 mg (N=16)
Any TEAE	23 (46.9)	9 (45.0)	5 (31.3)
Serious TEAE	5 (10.2)	-	-
Related TEAE	5 (10.2)	3 (15.0)	-
Related serious TEAE	-	-	-
TEAE leading to discontinuation or study termination	7 (14.3)	2 (10.0)	1 (6.3)
TEAE resulting in death[a]	1 (2.0)	-	-

Numbers presented represent patients. Events with a missing relationship were counted as related.
[a]One patient died during the open-label period from myocardial infarction, which was considered unrelated to trial drug by the investigator.
TEAE, treatment-emergent adverse event.

- The most common TEAEs during the open-label period were decreased weight (8.2%), decreased appetite (8.2%), somnolence (8.2%), and insomnia (8.2%) (**Table 4**).

Table 4. Treatment-Emergent Adverse Events Occurring in ≥3% of Patients in the Open-Label Period

	Open-Label Period
Preferred Term, n (%)	Pimavanserin 34 mg (N=49)
Decreased weight	4 (8.2)
Decreased appetite	4 (8.2)
Somnolence	4 (8.2)
Insomnia	4 (8.2)
Fall	3 (6.1)
Urinary tract infection	3 (6.1)
Constipation	2 (4.1)
Diarrhea	2 (4.1)
Nausea	2 (4.1)
Fatigue	2 (4.1)
Nasopharyngitis	2 (4.1)
Confusional state	2 (4.1)
Psychotic disorder	2 (4.1)
Orthostatic hypotension	2 (4.1)

Numbers presented represent patients. Events with a missing relationship were counted as related.
TEAE, treatment-emergent adverse event.

- During the double-blind period, 31.3% (n=5) of pimavanserin-treated and 45.0% (n=9) of placebo-treated patients experienced any TEAE (**Table 3**). No patients experienced any serious TEAEs in the double-blind period.
- Two placebo-treated and one pimavanserin-treated patient experienced a TEAE leading to discontinuation.
- AEs reported in the double-blind period are shown in **Table 5**.

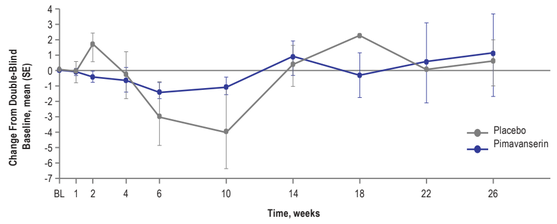
Table 5. Treatment-Emergent Adverse Events Occurring in ≥3% of Patients in Any Treatment Group and at Rates Greater Than Placebo in the Pimavanserin Group in the Double-Blind Period

Preferred Term, n (%)	Placebo (N=20)	Pimavanserin 34 mg (N=16)
Peripheral edema	-	1 (6.3)
Respiratory tract infection	-	1 (6.3)
ECG QT prolonged	-	1 (6.3)
Anxiety	-	1 (6.3)
Psychotic disorder	-	1 (6.3)

ECG, electrocardiogram.

- For ESRS-A score, the mean change from baseline to week 12 was -1.7 (N=39, standard error [SE], 0.74).
- Mean ESRS-A score change from double-blind baseline to week 26 was similar in pimavanserin- and placebo-treated patients (**Figure 3**).

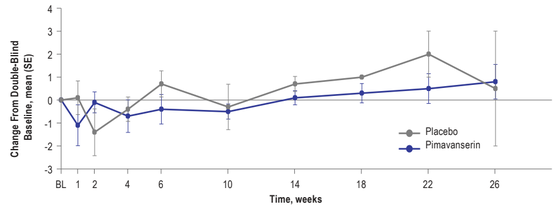
Figure 3. ESRS-A Total Score Change From Double-Blind Baseline



BL, baseline; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; SE, standard error.

- For MMSE score, the mean change from baseline to week 12 was 0.3 (N=37, SE, 0.66).
- Patients randomized to pimavanserin and placebo exhibited a similar mean MMSE score change from double-blind baseline to week 26 (**Figure 4**).

Figure 4. MMSE Score Change From Double-Blind Baseline



BL, baseline; MMSE, Mini-Mental State Examination; SE, standard error.

CONCLUSIONS

- **In this subgroup analysis of patients with PDD and psychosis in HARMONY, symptoms of psychosis were reduced during the open-label pimavanserin treatment. Efficacy was maintained during the double-blind period, as indicated by the reduced risk of psychosis relapse with pimavanserin compared with placebo.**
- **Pimavanserin was well tolerated and did not have a negative effect on motor-related function or cognitive function.**
- **These results should be interpreted with caution as HARMONY was not designed or powered to demonstrate effects by dementia subgroup.**
- **Findings from this post hoc subgroup analysis show the maintenance of antipsychotic efficacy and safety of pimavanserin in patients with PDD and psychosis.**

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