HARMONY Study: Pimavanserin Significantly Reduces Risk of Relapse of Dementia-Related Psychosis

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BACKGROUND

- Dementia-related psychosis is common among dementia patients[1-5] and is associated with adverse outcomes for patients and increased burden for their caregivers.[6,7]
- No therapies are currently approved by the United States (US) Food and Drug Administration to treat dementia-related psychosis, and published studies on available typical and atypical antipsychotics suggest no to modest efficacy and significant side effects in patients with dementia-related psychosis.[8,9]
- Pimavanserin is a selective $5HT_{2A}$ inverse agonist/antagonist approved in the US to treat hallucinations and delusions associated with Parkinson's disease psychosis.[10] Pimavanserin is being investigated for the treatment of hallucinations and delusions associated with dementia-related psychosis.

OBJECTIVE

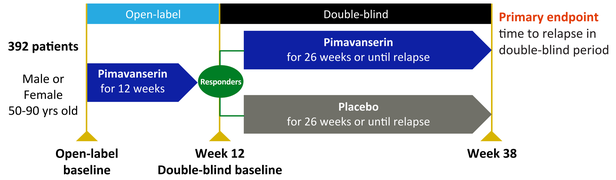
- To evaluate relapse prevention in patients with dementia-related psychosis treated with pimavanserin or placebo in the HARMONY study.

METHODS

Study Design

- HARMONY (NCT03325556) was an international, placebo-controlled, phase 3 randomized withdrawal study of the efficacy and safety of pimavanserin for treating hallucinations and delusions associated with dementia-related psychosis.
- Eligible patients enrolled into the study and received open-label pimavanserin for 12 weeks. Patients with sustained response at weeks 8 and 12 were randomized 1:1 to continue pimavanserin or receive placebo for up to 26 weeks in the double-blind period (Figure 1). Patients who did not show response to pimavanserin at week 8 of the open-label period or sustained response at week 12 were discontinued from the study.
  - Response was defined as: ≥30% reduction in total Scale for the Assessment of Positive Symptoms – Hallucinations + Delusions (SAPS-H+D) score AND Clinical Global Impressions – Improvement (CGI-I) score of much improved (2) or very much improved (1) relative to the open-label baseline.
- All terminations from the double-blind portion of the trial were adjudicated by an independent adjudication committee.
- A prespecified interim efficacy analysis of the primary efficacy endpoint was performed after 40 adjudicated relapses.

Figure 1. Study Design



Inclusion Criteria

- Eligible patients had a likely diagnosis of Alzheimer's disease (AD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), or vascular dementia (VaD). Patients with suspected or known mixed dementia were permitted, though investigators were asked to choose the most likely primary cause of the dementia.
- Patients were required to have a Mini-Mental State Examination (MMSE) score ≥6 and ≤24.
- Patients were required to have moderate-to-severe psychosis, defined as: SAPS-H+D total score ≥10; AND SAPS-H+D global item (H7 or D13) score ≥4; AND Clinical Global Impressions – Severity (CGI-S) score ≥4.

Outcomes

- The primary endpoint was time from randomization to relapse during the double-blind period. Relapse criteria for dementia-related psychosis 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.
- The primary endpoint was assessed using Cox regression model with effects for treatment group, dementia subtype, and region. The *P* value, hazard ratio (HR), and 95% confidence interval (CI) were reported.
- The key secondary efficacy endpoint was the time from randomization to discontinuation in the double-blind period for any reason (other than termination of the study by the sponsor).
- Safety endpoints included treatment-emergent adverse events (TEAEs) and assessment of cognition (MMSE score).

Characteristics of the Overall Population

- HARMONY enrolled 392 patients into the open-label period, with a mean age of 74.5 years (Table 1).
- Most patients had moderate (70.2%) dementia, and the mean duration of cognitive impairment was 4.3 years. At open-label baseline, mean (SE) SAPS-H+D was 24.4 (0.47), mean CGI-S score was 4.7 (0.03), and mean MMSE score was 16.7 (0.24).
- Characteristics of patients randomized in the double-blind period were generally similar for pimavanserin and placebo groups (Table 1).

RESULTS

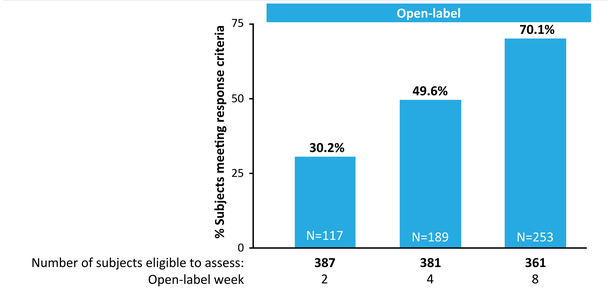
Table 1. Patient Demographics and Disease Characteristics at Open-Label Baseline

Patient Characteristics	Open-Label	Double-Blind	
	Pimavanserin	Placebo	Pimavanserin
Sex (N)	392	112	105
Female, n (%)	229 (58.4)	69 (61.6)	62 (59.0)
Age (years) (N)	392	112	105
Mean (SE)	74.5 (0.42)	74.9 (0.81)	73.8 (0.82)
Race (N)	384	109	105
White, n (%)	371 (96.6)	107 (98.2)	103 (98.1)
Living situation (N)	392	112	105
At home, n (%)	373 (95.2)	109 (97.3)	94 (89.5)
In a facility, n (%)	17 (4.3)	2 (1.8)	10 (9.5)
Other, n (%)	2 (0.5)	1 (0.9)	1 (1.0)
Dementia-related psychosis symptoms (N)	382	111	101
Visual hallucinations, n (%)	302 (79.1)	92 (82.9)	77 (76.2)
Delusions, n (%)	319 (83.5)	96 (86.5)	77 (76.2)

Open-Label Period

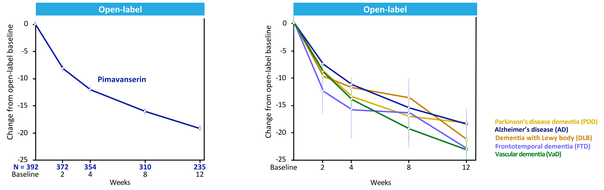
- 61.8% of eligible patients demonstrated a sustained response to pimavanserin and were randomized.
- Escalating treatment response was observed over the duration of the open-label period (Figure 2).
- 88.0% of patients who responded at week 8 also exhibited a sustained response at the enriched week 12.

Figure 2. Open-Label Responder Analysis



- Patients in the open-label period exhibited a 63.0% improvement in the total SAPS-H+D score at week 8 and a 75.2% improvement in the total SAPS-H+D score at the enriched week 12 (Figure 3).
- Reduction of psychosis symptoms was similar across enrolled dementia subtypes (Figure 3).

Figure 3. Change from Open-Label Baseline in Total SAPS-H+D



SAPS-H+D, Scale for the Assessment of Positive Symptoms – Hallucinations + Delusions.

Double-Blind Period

- Pimavanserin statistically significantly reduced the risk of relapse of symptoms by >2.8-fold. Thus, the study was stopped early for superior efficacy (HR: 0.353; 95% CI: 0.172, 0.727; one-sided *P*=0.0023) (Table 2; Figure 4).

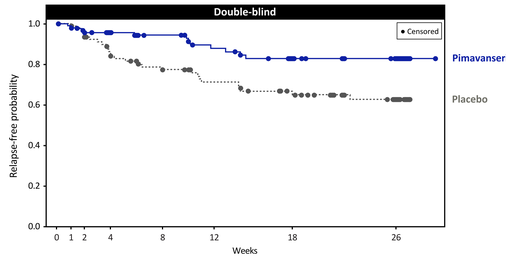
RESULTS (CONT)

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

	Placebo N=99	Pimavanserin N=95
Number of subjects having a relapse event, n (%)	28 (28.3)	12 (12.6)
Number of subjects censored, n (%)	71 (71.7)	83 (87.4)
Completed week 26 without a relapse	28 (28.3)	37 (38.9)
Prematurely discontinued prior to week 26	10 (10.1)	9 (9.5)
Ongoing at time of database cutoff	33 (33.3)	37 (38.9)
Cox regression analysis		
Hazard ratio (pimavanserin/placebo) (95% confidence interval)		0.353 (0.172, 0.727)
One-sided *P* value		0.0023
O'Brien-Fleming stopping boundary (P value scale one-sided)		0.0033

Study stopped at interim analysis for positive efficacy.

Figure 4. Kaplan-Meier Estimation of Cumulative Proportion of Relapse-Free Patients

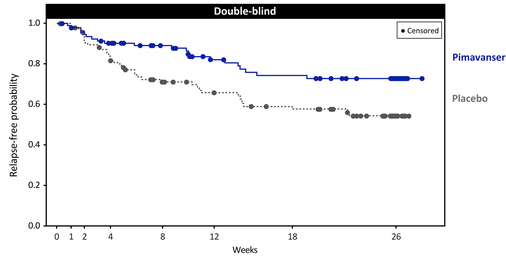


- Pimavanserin statistically significantly reduced the risk of all-cause discontinuation by 2.2-fold compared with placebo (HR=0.452, 95% CI: 0.261, 0.785; one-sided *P*=0.0024) (Table 3; Figure 5).

Table 3. Time to All-Cause Discontinuation in the Double-Blind Period

	Placebo N=99	Pimavanserin N=95
Number of subjects discontinued for any reason, n (%)	38 (38.4)	21 (22.1)
Number of subjects censored, n (%)	61 (61.6)	74 (77.9)
Completed week 26 without a relapse	28 (28.3)	37 (38.9)
Ongoing at time of database cutoff	33 (33.3)	37 (38.9)
Cox regression analysis		
Hazard ratio (pimavanserin/placebo) (95% confidence interval)		0.452 (0.261, 0.785)
One-sided P value		0.0024
O'Brien-Fleming stopping boundary (P value scale one-sided)		0.0033

Figure 5. Kaplan-Meier Estimation of Cumulative Proportion of All-Cause Discontinuation Patients



Safety Analysis

- During the open-label period, 36.2% of patients experienced any TEAE; during the double-blind period the incidence of TEAEs was comparable between placebo and pimavanserin groups (Table 4).

RESULTS (CONT)

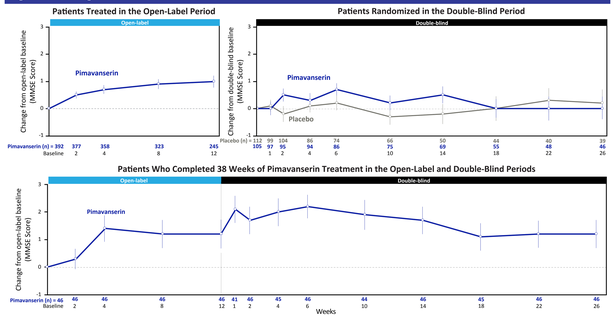
Table 4. Incidence of Adverse Events with Pimavanserin Treatment in the Open-Label and Double-Blind Safety Analysis Populations

Treatment-Emergent Adverse Event, n (%)	Open-Label	Double-Blind	
	Pimavanserin N=392	Placebo N=112	Pimavanserin N=105
Any	142 (36.2)	41 (36.6)	43 (41.0)
Any serious	20 (5.1)	4 (3.6)	5 (4.8)
Any related	45 (11.5)	10 (8.9)	9 (8.6)
Any leading to discontinuation	30 (7.7)	4 (3.6)	3 (2.9)
Any resulting in death	1 (0.3)	–	1 (1.0)

Treatment-emergent is defined as an adverse event with the onset date on or after the first dose of open-label drug (or for DB, double-blind drug) and no later than last study dose date +30. Numbers presented represent subjects. Events with a missing relationship were counted as related.

- The most common TEAEs in the open-label period were urinary tract infection (5.1%) and constipation (2.6%); the most common TEAEs in the double-blind period were headache (placebo, 4.5%; pimavanserin, 9.5%) and urinary tract infection (placebo, 3.6%; pimavanserin, 6.7%).
- No negative impact on cognition (MMSE) was observed for pimavanserin in the open-label or double-blind period. The mean change from open-label baseline (SE) for patients treated with pimavanserin for the entire duration of the study (9 months) was 1.2 (0.51) (Figure 6).

Figure 6. Change from Baseline in MMSE Score



CONCLUSIONS

- The HARMONY study demonstrated a robust decrease in hallucinations and delusions and significant maintenance of efficacy with pimavanserin treatment in dementia-related psychosis.
  - The primary endpoint was achieved in that pimavanserin statistically significantly reduced the risk of psychotic exacerbation by >2.8-fold over placebo.
  - Patients reduced the risk of all-cause discontinuation by 2.2-fold over placebo.
- Pimavanserin had no negative impact on a measure of cognition (MMSE) over 9 months of treatment.
- Pimavanserin 34 mg was well tolerated when given long term in this elderly population with significant comorbidities.

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DISCLOSURES

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