Efficacy and safety of pimavanserin in patients with Alzheimer's dementia psychosis in the HARMONY phase 3, randomized discontinuation study: post hoc subgroup analysis

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INTRODUCTION

- Pimavanserin is a selective serotonin-receptor with inverse agonist/antagonist at the $5HT_{2A}$ receptor, and to a lesser extent at the $5HT_{2C}$ receptor[1]
- Pimavanserin 34 mg once daily (QD) is approved in the United States to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP)[2]
- There are no pharmacological treatments approved to treat psychosis in patients with Alzheimer's disease in the United States[3]
- Pimavanserin was evaluated for the treatment of dementia-related psychosis, including the largest disease subtype of patients with Alzheimer's disease (AD) and psychosis (ADP), in the phase 3 randomized withdrawal HARMONY trial (NCT03325556)[4]
- A post hoc analysis of patients with ADP was conducted to explore the efficacy of pimavanserin in this subgroup of patients

OBJECTIVE

- We evaluated the consistency of efficacy of pimavanserin 34mg QD for reducing the risk of relapse in a subgroup of patients with ADP

METHODS

Study Design

- The HARMONY study design and primary results in the overall dementia-related psychosis (DRP) population have been previously published[4]
- Patients with dementia and moderate-to-severe psychosis were eligible
- Patients meeting prespecified response criteria at weeks 8 and 12 were randomized to continue pimavanserin at the stabilized dose level or receive corresponding placebo for up to 26 weeks in the double-blind (DB) period

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 from randomization to relapse during the double-blind period; relapse criteria were centrally assessed and were defined as meeting ≥1 of 4 criteria (**Figure 1**)
- Treatment-emergent adverse events (TEAEs; defined as an AE with an onset after the first study dose or ≤30 days after the last study dose) were recorded throughout the duration of the study
- Cognitive abilities were evaluated using the Mini-Mental State Examination (MMSE), with lower scores indicating greater cognitive impairment (range, 0–30); new onset or worsening of extrapyramidal symptoms were evaluated using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)[5]

Statistical Analysis

- The study was powered to evaluate efficacy in the overall DRP population as a unitary construct; it was not powered to demonstrate statistical significance in subgroups such as ADP
- Time from randomization to relapse of psychosis was analyzed using a Cox regression model in those ADP patients who were stabilized on 34 mg prior to randomization and then randomized to stay on pimavanserin 34 mg or placebo
- Efficacy analyses included patients at the interim analysis (IA); safety analyses included all treated patients
- Baseline characteristics and safety data were analyzed using descriptive statistics

RESULTS

Baseline Characteristics

- In total, 260 ADP patients enrolled in the HARMONY trial
- At baseline, mean age in the pimavanserin 34 mg group was 75.7 years; mean MMSE score was 16.0 (**Table 1**)

Efficacy

- Twenty-nine patients were discontinued from the study by the sponsor; of the remaining 214 ADP patients, 130 (60.7%) met response criteria at weeks 8 and 12 and were randomized (**Figure 2**)
- At the interim analysis (IA), 116 ADP patients were randomized to pimavanserin 34 mg (N=57) or placebo (N=59) (**Table 2**)
- The hazard ratio for psychosis relapse risk was 0.466 (95% CI: 0.179, 1.214) for pimavanserin 34 mg versus placebo and demonstrated a relapse risk reduction of 53%; 6/57 (10.5%) pimavanserin-treated and 14/59 (23.7%) placebo-treated patients met relapse criteria (**Figure 3**)

Safety

- TEAE incidence rates: DB-pimavanserin 34 mg, 39.7% (25/63); DB-placebo, 34.3% (23/67) (**Table 3**)
- Pimavanserin was not associated with extrapyramidal symptoms as assessed by Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) score (**Figure 4**) or have a negative effect on Mini-Mental State Examination (**Figure 5**) change from baseline versus placebo in the DB period, suggesting no worsening of motor or cognitive function.

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Figure 1. Relapse Criteria

≥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

Discontinuation of study treatment or withdrawal from study due to lack of efficacy according to patient, partner/caregiver, or study investigator

OR

Hospitalization for worsening dementia-related psychosis

SAPS-HD, Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions subscales; CGI-S, Clinical Global Impression-Severity

Table 1. Baseline Demographics and Characteristics

	Open-Label Period Pimavanserin 34 mg[a] (N=243)
Age at screening, years (mean)	75.7
Age range, years (min, max)	53, 90
Female, n (%)	162 (66.7)
White race, n (%)	232 (96.7)
Hispanic/Latino, n (%)	66 (27.5)
Living at home, n (%)	230 (94.7)
Dementia severity, n (%)	
Mild	26 (10.7)
Moderate	176 (72.4)
Severe	41 (16.9)
MMSE total score, mean (SE)	16.0 (0.30)
CGI-S score, mean (SE)	4.8 (0.04)
SAPS-H+D, mean (SE)	23.9 (0.56)

Number of patients with non-missing values is used as the denominator for calculating percentages within each group; Data reflect open-label safety analysis sets, which included all patients who received at least one dose of study drug.
[a]17 patients received pimavanserin 20mg beyond OL week 4 and were not included in these results.
CGI-S, Clinical Global Impression-Severity; MMSE, Mini-Mental State Examination; SAPS-H+D, Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions subscales; SE, standard error.

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

	Placebo (N=59)	Pimavanserin 34 mg (N=57)
Patients with a relapse event, n (%)	14 (23.7)	6 (10.5)
Patients censored from survival analysis, n (%)	45 (76.3)	51 (89.5)
Completed week 26 without a relapse, n (%)	18 (30.5)	22 (38.6)
Prematurely discontinued prior to week 26, n (%)	6 (10.2)	5 (8.8)
Ongoing at the time of database cutoff, n (%)	21 (35.6)	24 (42.1)

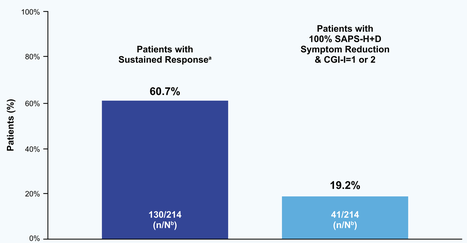
Efficacy data reflect the interim-to-treat analysis set at the time of the interim analysis (N=116). Twenty-nine patients were terminated, based on recommendation by the Data Safety Monitoring Board for positive efficacy. These 29 patients were not part of the efficacy analysis.

Table 3. Overall Summary of Treatment-Emergent Adverse Events

	Open-Label Period	Double-Blind Period	
TEAEs, n (%)	Pimavanserin 34 mg (N=243)	Placebo (N=67)	Pimavanserin 34 mg (N=63)
Any TEAE	72 (29.6)	23 (34.3)	25 (39.7)
Serious TEAE	12 (4.9)	2 (3.0)	3 (4.8)
Related TEAE[a]	17 (7.0)	6 (9.0)	6 (9.5)
Related serious TEAE[a]	–	–	–
TEAE leading to discontinuation or study termination	17 (7.0)	2 (3.0)	2 (3.2)
TEAE resulting in death	–	–	1 (1.6)

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

Figure 2. Patients Meeting Response Criteria to Pimavanserin



[a]Sustained response is defined as >=30% SAPS-H+D improvement and CFI-1 "very much" or "much improved" at both Weeks 8 and 12.
[b]The denominator excluded 41 patients who were ongoing at the time of study discontinuation.
OL, open-label period; DB, double-blind period; SAPS-H+D, Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions subscales; CGI-S, Clinical Global Impression-Severity.

Figure 3. Psychosis Relapse Risk with Pimavanserin vs Placebo

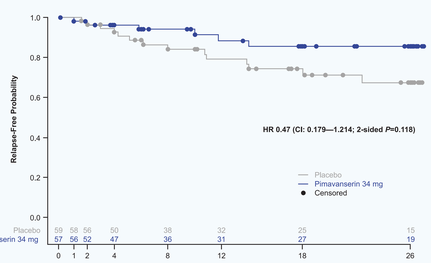
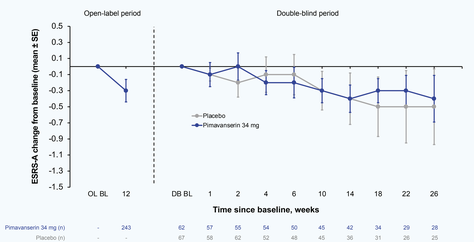


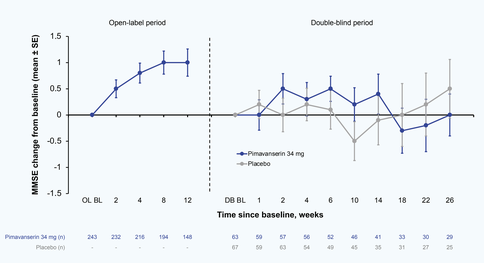
Figure 4. ESRS-A Mean (SE) Score Change From Baseline in OL and DB



	OL BL	12	DB BL	1	2	4	6	10	14	18	22	26
Pimavanserin 34 mg (n)	-	243		62	57	55	54	50	45	42	34	29	28
Placebo (n)	-	-		67	58	62	52	48	45	36	31	26	25

Open-label baseline is the latest non-missing value prior to OL first dose of study drug.
OL, open-label; DB, double-blind; SE, standard error; ESRS, Extrapyramidal Symptom Rating Scale

Figure 5. MMSE Mean (SE) Score Change From Baseline in OL and DB



	OL BL	2	4	8	12	DB BL	1	2	4	6	10	14	18	22	26
Pimavanserin 34 mg (n)	243	232	216	194	148		63	59	57	56	52	46	41	33	30	29
Placebo (n)	-	-	-	-	-		67	59	63	54	49	45	35	31	27	25

Open-label baseline is the latest non-missing value prior to OL first dose of study drug.
OL, open-label; DB, double-blind; SE, standard error; MMSE, mini-mental status exam.

CONCLUSIONS

- In this post hoc subgroup analysis, a robust reduction in the risk of relapse was observed in patients treated with pimavanserin 34 mg versus placebo
- Nominal statistical significance was not achieved in the context of a study that was powered for the overall DRP population and not for the ADP subgroup
- Pimavanserin was not associated with an adverse impact on cognition or motor function

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