Safety and Efficacy of Pimavanserin in Patients With Parkinson's Disease Dementia or Dementia With Lewy Bodies Experiencing Dementia-Related Psychosis in the HARMONY Study

Poster 142

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INTRODUCTION

- Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are types of Lewy body dementia characterized by the presence of abnormal deposits of α-synuclein in the brain[1]
- Pimavanserin, the only US Food and Drug Administration–approved medication indicated to treat hallucinations and delusions associated with Parkinson's disease psychosis, is an inverse agonist/antagonist of the serotonin 2A receptor (and to a lesser extent 5-HT_{2C}), with negligible binding at dopaminergic, adrenergic, histaminergic, and muscarinic receptors[2-4]
- Pimavanserin was investigated for the treatment of patients with dementia-related psychosis, including PDD or DLB, in the HARMONY study[5]
- The objective of this post hoc subgroup analysis was to evaluate the safety and efficacy of pimavanserin in patients with psychosis and Lewy body dementia (PDD and DLB) in HARMONY

METHODS

- HARMONY (NCT03325556) was a phase 3, placebo-controlled, randomized discontinuation study of patients with dementia and moderate to severe psychosis[5]
  - The study design, eligibility criteria, and results for the full population have been published[5]
  - The full study population included patients with PDD, DLB, possible or probable Alzheimer's disease, frontotemporal dementia, or vascular dementia[5]
- Patients included in this post hoc subgroup analysis met the clinical criteria for PDD or DLB
- In HARMONY, patients received open-label pimavanserin (34 mg/d) for 12 weeks
  - Based on tolerability, dose reduction to 20 mg daily was permitted during weeks 1 through 4
- Those who met the prespecified criteria for treatment response (as defined below) at weeks 8 and 12 vs baseline were randomized 1:1 to continue pimavanserin or receive placebo (double-blind) for ≤26 weeks
  - Randomization was stratified by dementia subtype, including PDD and DLB

Prespecified criteria for **treatment response** included **BOTH** of the following:

- SAPS-H+D total score: ≥30% reduction (improvement)
- CGI-I score: much improved (2) or very much improved (1)

CGI-I, Clinical Global Impression–Improvement; SAPS-H+D, Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

- The primary efficacy endpoint was time from randomization to psychosis relapse (as defined below) during double-blind treatment, analyzed via Cox regression model
- The study met the prespecified stopping boundary at interim analysis and was stopped early for efficacy[5]

Relapse of psychosis was defined as **≥1** of the following:

- Relative to week 12 (double-blind baseline),
  - SAPS-H+D total score: ≥30% increase (worsening) AND
  - CGI-I score: much worse (6) or very much worse (7)
- Treatment with an antipsychotic (other than pimavanserin) for dementia-related delusions and/or hallucinations
- Cessation of the study drug or withdrawing due to lack of efficacy
- Hospitalization for worsening dementia-related psychosis

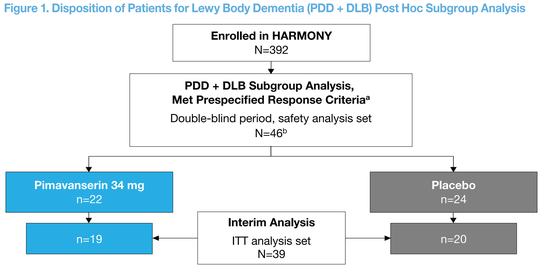
CGI-I, Clinical Global Impression–Improvement; SAPS-H+D, Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.

- Safety endpoints were summarized using descriptive statistics and included the following:
  - Motor-related function, assessed using the Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A), where higher scores indicate reduced motor function;
  - Cognitive function, measured via the Mini-Mental State Examination (MMSE), where lower scores indicate reduced cognitive function; and
  - Treatment-emergent adverse events (TEAEs)

RESULTS

- Among 392 patients enrolled in HARMONY, 76 had Lewy body dementia (PDD, n=49; DLB, n=27) and remained on 34-mg pimavanserin during the open-label period
  - Of these, 46 (60.5%) met the prespecified response criteria and were randomized (placebo, n=24; pimavanserin, n=22) (**Figure 1**)

Figure 1. Disposition of Patients for Lewy Body Dementia (PDD + DLB) Post Hoc Subgroup Analysis



CGI-I, Clinical Global Impression–Improvement; DLB, dementia with Lewy bodies; ITT, intent-to-treat; PDD, Parkinson's disease dementia; SAPS-H+D, Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions.
[a]Treatment response was defined as ≥30% reduction in the SAPS-H+D total score and a CGI-I score of much improved (2) or very much improved (1).
[b]Patient met the response criteria at both weeks 8 and 12.

- At open-label baseline, mean patient age was 72.8 years, and 38.2% were female (**Table 1**)

Table 1. Baseline Demographic and Clinical Characteristics in Patients With Lewy Body Dementia (Safety Analysis Set)

Characteristic	Open-label baseline	Double-blind baseline	
	Pimavanserin 34 mg n=76	Placebo n=24	Pimavanserin 34 mg n=22
Age, mean (SE), y	72.8 (0.87)	73.2 (1.78)	70.1 (1.39)
Female, n (%)	29 (38.2)	11 (45.8)	8 (36.4)
Race/ethnicity, n (%)[a]	n=72	n=22	n=22
White race	69 (95.8)	22 (100)	20 (90.9)
Hispanic/Latino	10 (13.9)	1 (4.5)	4 (18.2)
Dementia subtype, n (%)			
PDD	49 (64.5)	20 (83.3)	16 (72.7)
DLB	27 (35.5)	4 (16.7)	6 (27.3)
Dementia severity, n (%)			
Mild	20 (26.3)	7 (29.2)	8 (36.4)
Moderate	49 (64.5)	14 (58.3)	14 (63.6)
Severe	7 (9.2)	3 (12.5)	-
Age at cognitive impairment onset, mean (SE), y	69 (0.93)	70 (1.79)	66.5 (1.50)
Duration of cognitive impairment, mean (SE), y	4.2 (0.33)	3.6 (0.51)	4.2 (0.49)
Symptoms after onset of cognitive impairment, n (%)[a]	n=75	n=24	n=21
Visual hallucinations	71 (94.7)	24 (100.0)	18 (85.7)
Auditory hallucinations	53 (70.7)	20 (83.3)	15 (71.4)
Delusions	53 (70.7)	20 (83.3)	11 (52.4)
Previous treatment for dementia-related psychosis, n (%)	34 (44.7)	9 (37.5)	10 (45.5)
SAPS-H+D score, mean (SE)	24.2 (1.11)	4.1 (0.93)	4.0 (1.19)
CGI-S score, mean (SE)	4.7 (0.08)	2.1 (0.21)	2.0 (0.19)
MMSE total score, mean (SE)	18.4 (0.55)	19.5 (1.16)	18.9 (1.10)
ESRS-A, mean (SE)	21.5 (1.5)	22. 8 (3.1)	23.7 (3.2)

CGI-S, Clinical Global Impression–Severity; DLB, dementia with Lewy bodies; ESRS-A, Extrapyramidal Symptom Rating Scale–Abbreviated; MMSE, Mini-Mental State Examination; PDD, Parkinson's disease dementia; SAPS-H+D, Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions; SE, standard error.
[a]Number of patients with nonmissing values is used as the denominator for calculating percentages within each group.

- When the trial was stopped early for efficacy, 1 (5.3%) pimavanserin and 11 (55.0%) placebo patients met relapse criteria (**Table 2**)

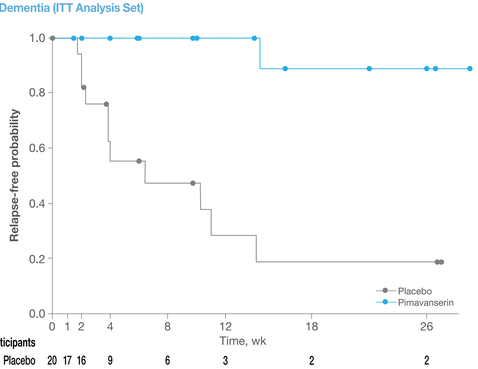
Table 2. Primary Endpoint: Time to Relapse in the Double-Blind Period for Patients With Lewy Body Dementia (ITT Analysis Set)

Characteristic	Placebo n=20	Pimavanserin n=19
Patients with a relapse event, n (%)	11 (55.0)	1 (5.3)
Patients with censored data, n (%)	9 (45.0)	18 (94.7)
Completed week 26 without a relapse	2 (10.0)	6 (31.6)
Prematurely discontinued prior to week 26	3 (15.0)	4 (21.1)
Ongoing at time of data cutoff	4 (20.0)	8 (42.1)

ITT, intent-to-treat.

- The risk of psychosis relapse was significantly lower with pimavanserin vs placebo (HR, 0.03; 95% CI, 0.01–0.10; 2-sided nominal P<0.0001; **Figure 2**)

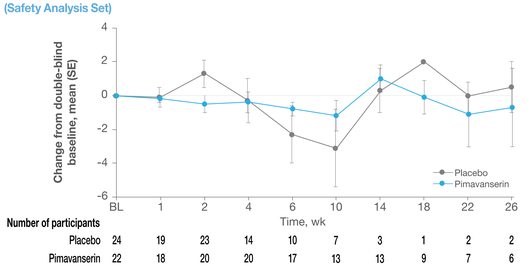
Figure 2. Kaplan-Meier Estimation of Time to Relapse in the Double-Blind Period for Patients With Lewy Body Dementia (ITT Analysis Set)



ITT, intent-to-treat.

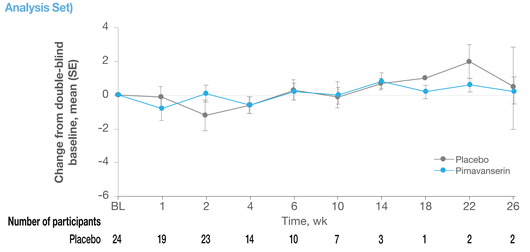
- In the open-label pimavanserin treatment period (n=76), mean ESRS-A and MMSE changes from open-label baseline to week 12 were –1.6 (SE, 0.60) and 0.6 (SE, 0.55), respectively
- In the double-blind treatment period, mean ESRS-A (**Figure 3**) and MMSE (**Figure 4**) scores remained similar from double-blind baseline through week 26 for patients randomized to pimavanserin and placebo and did not suggest worsening motor or cognitive functioning with pimavanserin

Figure 3. ESRS-A Total Change From Double-Blind Baseline for Patients With Lewy Body Dementia (Safety Analysis Set)



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

Figure 4. MMSE Change From Double-Blind Baseline for Patients With Lewy Body Dementia (Safety Analysis Set)



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

- Overall, <50% of patients experienced a TEAE in the open-label or double-blind periods (mostly mild to moderate; **Table 3**)
- TEAEs leading to discontinuation occurred in 7 (9.2%) patients during open-label and 3 (6.5%) during double-blind period (2 [8.3%] placebo; 1 [4.5%] pimavanserin)

Table 3. Summary of TEAEs for Patients With Lewy Body Dementia (Safety Analysis Set)

TEAE category, n (%)	Open-label baseline	Double-blind baseline	
	Pimavanserin 34 mg n=76	Placebo n=24	Pimavanserin 34 mg n=22
Any TEAE	35 (46.1)	10 (41.7)	9 (40.9)
Serious TEAE	6 (7.9)	-	1 (4.5)
Related TEAE	9 (11.8)	3 (12.5)	1 (4.5)
Related serious TEAE	-	-	-
TEAE leading to discontinuation	7 (9.2)	2 (8.3)	1 (4.5)
TEAE resulting in death[a]	1 (3.3)	-	-

TEAE, treatment-emergent adverse event.
[a]One patient died during the open-label period from myocardial infarction that was considered unrelated to trial drug by the investigator.

CONCLUSIONS

- In this post hoc subgroup analysis of patients with Lewy body dementia in the HARMONY trial, treatment with pimavanserin reduced the risk of psychosis relapse in patients with PDD and DLB
- Pimavanserin was well tolerated and did not worsen motor or cognitive function
- HARMONY was not designed or powered to demonstrate effects by dementia subgroup; therefore, results should be interpreted with caution

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AUTHOR DISCLOSURES

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