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

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- 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 brain¹
- 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 receptors²⁻⁴
- Pimavanserin was investigated for the treatment of patients with dementia-related psychosis, including PDD or DLB, in the HARMONY study⁵
- 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

D→ □ METHODS

- HARMONY (NCT03325556) was a phase 3, placebo-controlled, randomized discontinuation study of patients with dementia and moderate to severe psychosis⁵
- The study design, eligibility criteria, and results for the full population have been published⁵ - The full study population included patients with PDD, DLB, possible or probable Alzheimer's disease, frontotemporal dementia, or vascular dementia⁵
- 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 (doubleblind) 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: \geq 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

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

Relative to week 12 (double-blind baseline), 🍄 **+** 🚺

- SAPS-H+D total score: \geq 30% increase (worsening) AND • CGI-I score: much worse (6) or very much worse (7)
- \bigcirc

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)

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

Pimavanser n=2	
n=1	9

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. ^aTreatment response was defined as \geq 30% reduction in the SAPS-H+D total score and a CGI-I score of much improved (2) or very much improved (1). ^bPatient 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)

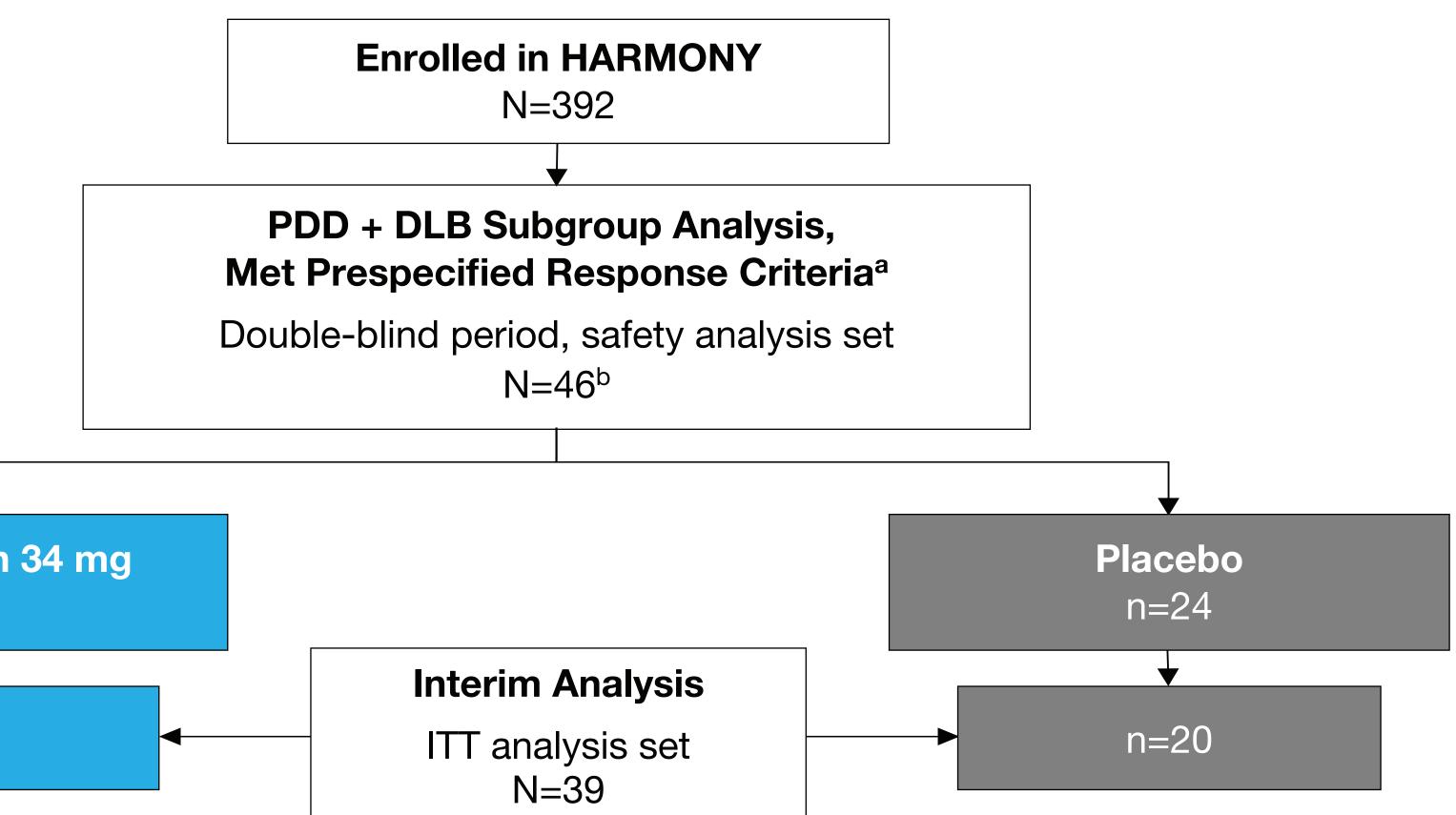
haracteristic

- Age, mean (SE), y
- Female, n (%)
- Race/ethnicity, n (%)^a
- White race Hispanic/Latino
- Dementia subtype, r
- PDD
- DLB Dementia severity, n (%
- Mild
- Moderate
- Severe
- Age at cognitive impair
- Duration of cognitive in Symptoms after onset
- Visual hallucinations Auditory hallucination
- Delusions Previous treatment for
- SAPS-H+D score, mea
- CGI-S score, mean (SI
- MMSE total score, mea ESRS-A, mean (SE)

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 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**)



	Open-label baseline	Double-blind baseline	
	Pimavanserin 34 mg n=76	Placebo n=24	Pimavanserin 34 mg n=22
	72.8 (0.87)	73.2 (1.78)	70.1 (1.39)
	29 (38.2)	11 (45.8)	8 (36.4)
	n=72	n=22	n=22
	69 (95.8)	22 (100)	20 (90.9)
	10 (13.9)	1 (4.5)	4 (18.2)
(%)			
	49 (64.5)	20 (83.3)	16 (72.7)
	27 (35.5)	4 (16.7)	6 (27.3)
%)			
	20 (26.3)	7 (29.2)	8 (36.4)
	49 (64.5)	14 (58.3)	14 (63.6)
	7 (9.2)	3 (12.5)	-
irment onset, mean (SE), y	69 (0.93)	70 (1.79)	66.5 (1.50)
impairment, mean (SE), y	4.2 (0.33)	3.6 (0.51)	4.2 (0.49)
t of cognitive impairment, n (%) ^a	n=75	n=24	n=21
	71 (94.7)	24 (100.0)	18 (85.7)
ons	53 (70.7)	20 (83.3)	15 (71.4)
	53 (70.7)	20 (83.3)	11 (52.4)
r dementia-related psychosis, n (%)	34 (44.7)	9 (37.5)	10 (45.5)
an (SE)	24.2 (1.11)	4.1 (0.93)	4.0 (1.19)
E)	4.7 (0.08)	2.1 (0.21)	2.0 (0.19)
ean (SE)	18.4 (0.55)	19.5 (1.16)	18.9 (1.10)
	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. ^aNumber of patients with nonmissing values is used as the denominator for calculating percentages within each group.

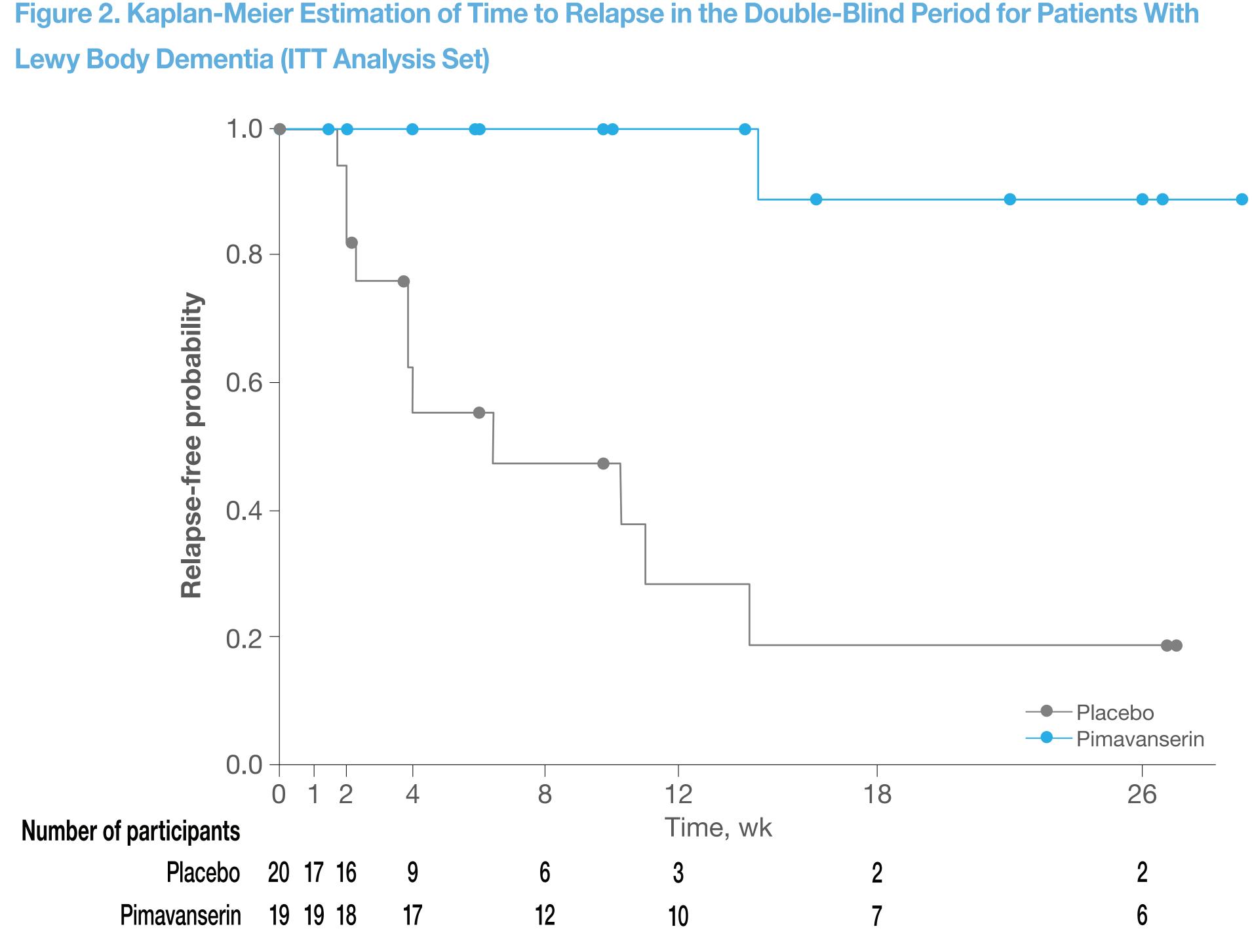
relapse criteria (**Table 2**)

Body Dementia (ITT Analysis Set)

Characteristic Patients with a relapse event, n (%) Patients with censored data, n (%) Completed week 26 without a relapse Prematurely discontinued prior to week 2 Ongoing at time of data cutoff

ITT intent-to-treat

0.10; 2-sided nominal *P*<0.0001; **Figure 2**)



ITT, intent-to-treat.

• When the trial was stopped early for efficacy, 1 (5.3%) pimavanserin and 11 (55.0%) placebo patients met Figure 3. ESRS-A Total Change From Double-Blind Baseline for Patients With Lewy Body Dementia

Table 2. Primary Endpoint: Time to Relapse in the Double-Blind Period for Patients With Lewy

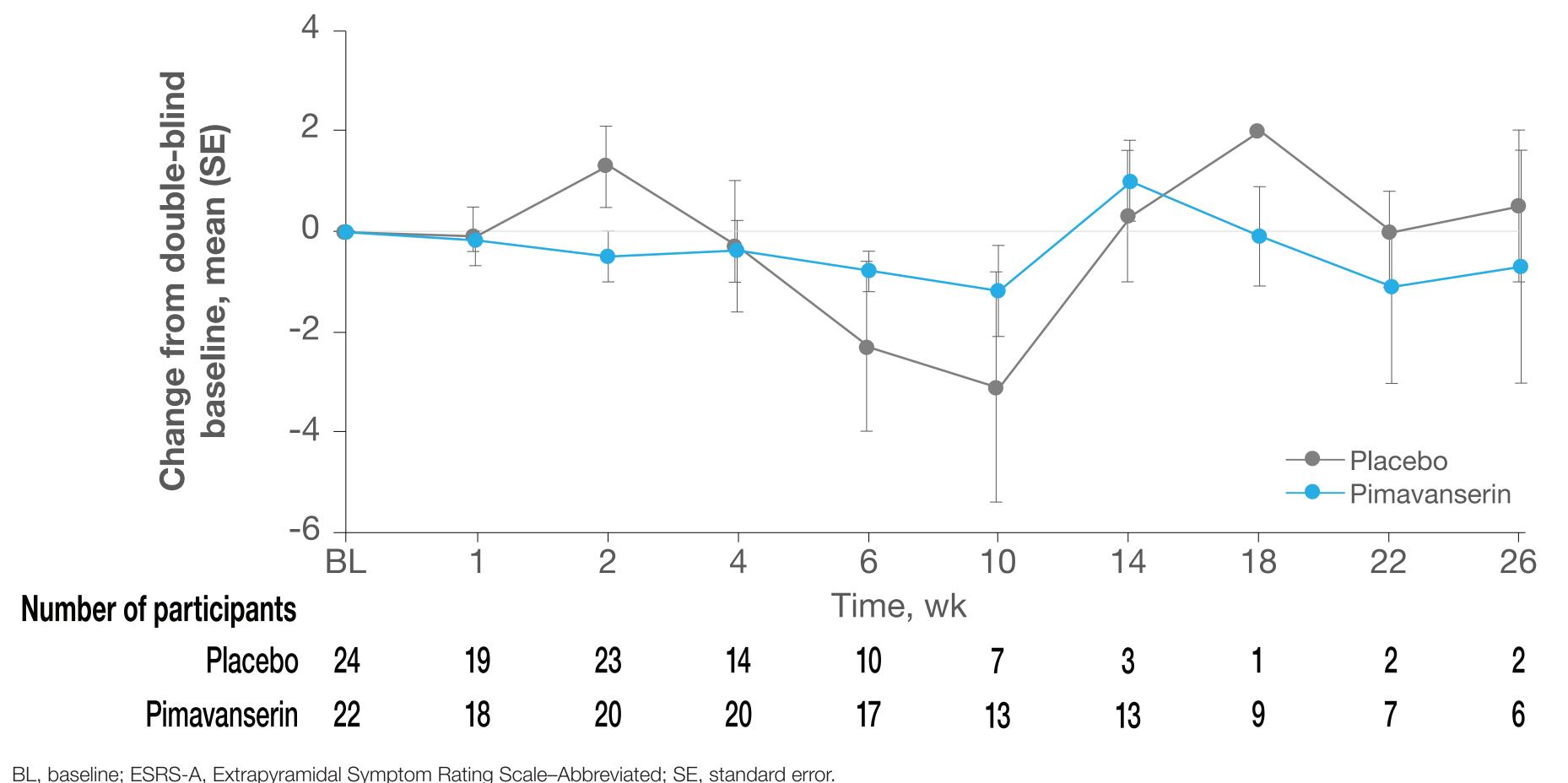
	Placebo n=20	Pimavanserin n=19
	11 (55.0)	1 (5.3)
	9 (45.0)	18 (94.7)
	2 (10.0)	6 (31.6)
26	3 (15.0)	4 (21.1)
	4 (20.0)	8 (42.1)

• The risk of psychosis relapse was significantly lower with pimavanserin vs placebo (HR, 0.03; 95% Cl, 0.01-

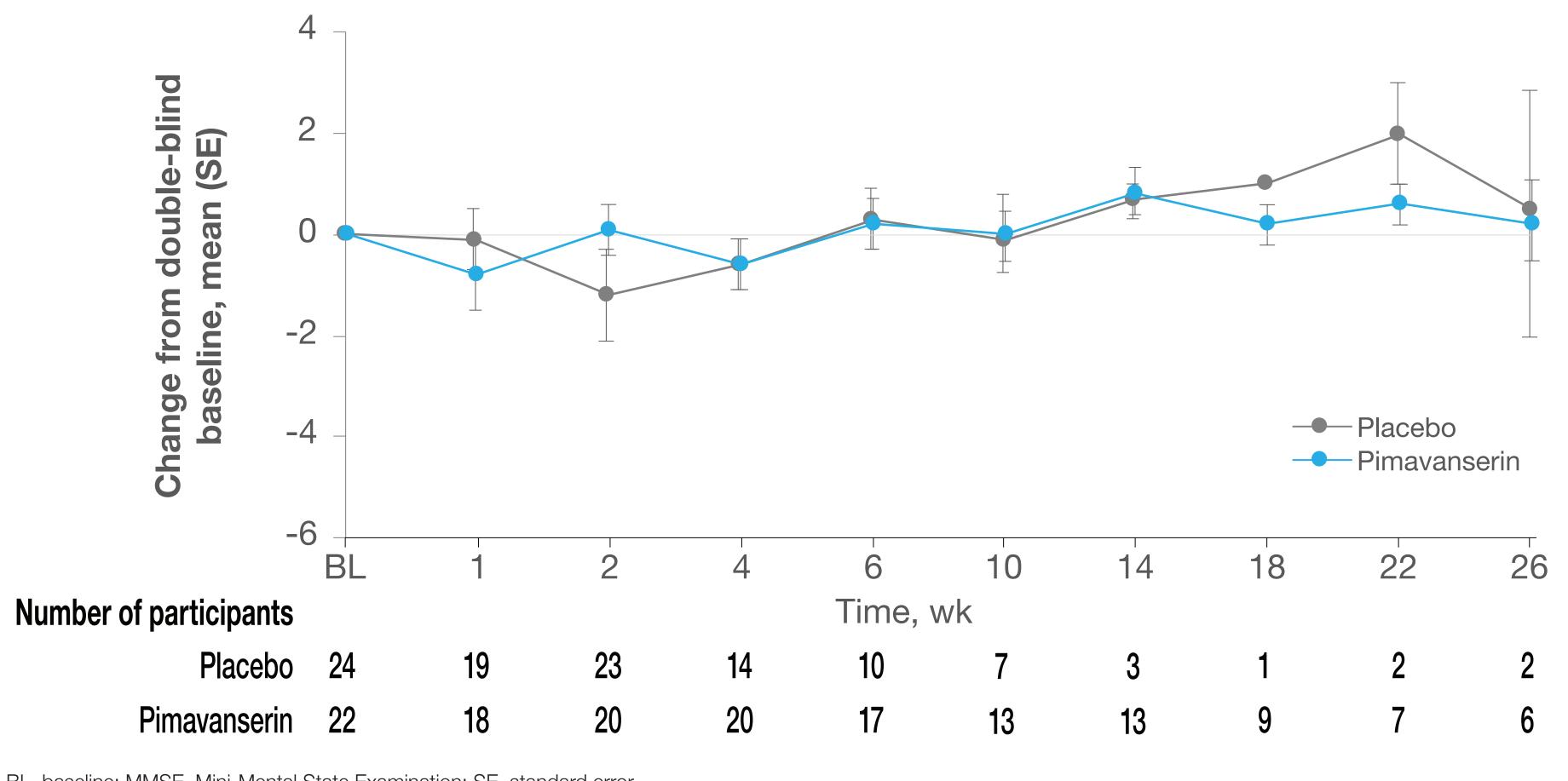
 In the open-label pimavanserin treatment period (n=76), mean ESRS-A and MMSE changes from open-label baseline to week 12 were -1.6 (SE, 0.60) and 0.6 (SE, 0.55), respectively

• 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









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)

	Open-label baseline	Double-blind baseline	
TEAE category, n (%)	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. ^aOne patient died during the open-label period from myocardial infarction that was considered unrelated to trial drug by the investigator.



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

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

YT-Y is a speaker and consultant for Abbott, AbbVie, Acadia, Acorda, Amneal, Kyowa Kirin, Sunovion, and Teva. **GB**, **LC**, and **VA** are employees of Acadia Pharmaceuticals.

