Safety Profile of Pimavanserin Therapy in Elderly Patients With Neurodegenerative Disease-Related Neuropsychiatric Symptoms: a Phase 3b Study

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Poster Number: 76487

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INTRODUCTION

- Pimavanserin, a 5-HT2A receptor inverse agonist/antagonist,[1,2] is approved by the US Food and Drug Administration to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP)[3]
- Most patients with a neurodegenerative disease (NDD), such as Parkinson's disease (PD), will experience neuropsychiatric symptoms, such as hallucinations and delusions, apathy, and agitation, at some point over the course of their disease[4,5]
- NDD patients include frail, older adults and the elderly who are highly sensitive to adverse effects associated with antipsychotic use[6,7]; therefore, these patients represent an important population for evaluating the safety profile of pimavanserin to further inform its use in patients with PDP
- This phase 3b, 8-week (duration of up to 16 weeks), multicenter, randomized, double-blind, parallel-group study evaluated the safety and tolerability profile of pimavanserin using a placebo-controlled design in a large population of frail older adults and elderly patients with neuropsychiatric symptoms related to NDD, including PDP

OBJECTIVE

To assess the safety profile and efficacy of pimavanserin compared with placebo in frail older adults and elderly patients with neuropsychiatric symptoms related to NDDs

METHODS

- Eligibility criteria included male or females aged ≥60 years with a NDD who require some form of assistance with activities of daily living and who are able to provide written informed consent
- The study design is summarized in **Figure 1**
- The primary endpoint of the study was safety assessed by treatment-emergent adverse events (TEAEs); a TEAE was defined as an adverse event that started on or after the first dose of the study drug and no later than 30 days after the last dose of the study drug
- Secondary and exploratory endpoints are summarized in **Table 1**
  - Assessments were scheduled at weeks 1, 2, 4, 6, and 8 (end of treatment)
- Safety and efficacy endpoints were summarized using descriptive statistics, and TEAE percentages were summarized
- Changes from baseline scores were analyzed using a mixed-effects model repeated measures (MMRM) approach, with the exception of data collected from the EQ-5D-5L visual analog scale, which was analyzed using an ANCOVA; between-group differences in least squares mean (LSM) and corresponding 95% CI, *p*-value, and effect size were reported as changes from baseline values

RESULTS

- Overall, 1440 patients were screened; of the 784 in the randomized analysis set, 730 patients completed the study (93.1%), and 54 (6.9%) terminated the study early (**Figure 2**)
  - The most common reasons for study termination were AEs (n = 16; 2.0%); patients also terminated due to other reasons (n = 12; 1.5%), or the patient or legally acceptable representative withdrew consent (n = 11; 1.4%)
- Baseline demographics and clinical characteristics were similar between groups (**Table 2**)
  - The mean (range) age was 72.4 years (60-96), most patients were female (57.8%), most were White (93.8%), and approximately one-third were Hispanic or Latino (31.1%)
  - Dementia subtypes in this patient population include Alzheimer's disease (AD) (68.4%), vascular dementia (19.3%), Parkinson's disease (9.2%; patients with PD and dementia: 5.1%; patients without dementia: 3.7%; patients with PDD and PDP: 7.8% [3 patients had PD and dementia, but the primary cause of dementia was AD in patients treated with pimavanserin, and, therefore, values do not sum to the total]), Frontotemporal dementia (2.2%), and Dementia with Lewy Bodies (1.4%)
  - The baseline mean (SE) Clinical Global Impression-Severity (CGI-S) scale score of all patients was 4.6 (0.02), and most patients were considered either moderately (49.4%) or markedly (45.8%) ill
  - Before baseline was measured, 1.7% of patients had suicidal ideation or behavior measured using either the Columbia-Suicide Severity Rating Scale or Global Clinician Assessment of Suicidality scale
- About a third of patients (29.8%) total reported experiencing at least 1 TEAE (pimavanserin: 30.4%; placebo: 29.3%) (**Table 3**)
  - Serious TEAEs were reported in 14 patients (overall: 1.8%; pimavanserin: 2.0%; and placebo: 1.5%), and TEAEs leading to discontinuation or study termination were reported in 19 patients (overall: 2.4%; pimavanserin: 2.6%; and placebo: 2.3%)
  - The most frequently reported TEAEs included urinary tract infection (pimavanserin: 6.4%; placebo: 4.1%) and headache (pimavanserin: 2.0%; placebo: 3.8%)
  - Mortality was reported in 4 patients (0.5% in each group)
- No significant differences were observed between groups in the change from baseline to week 8 in either extrapyramidal symptoms measured using the Extrapyramidal Symptom Rating Scale-Abbreviated, cognition measured using the Mini-Mental State Examination, or efficacy measured using the CGI-S (**Table 4**)
- Additionally, no significant differences were found in health outcomes measured using the EQ-5D-5L visual analog scale (ANCOVA LSM: pimavanserin 7.6; placebo 6.4; $p = 0.19$)
- At week 8, a significant improvement was observed in the pimavanserin group compared with placebo in the Clinical Global Impression-Improvement scale (MMRM LSM difference [SE]: -0.2 [0.07]; $p = 0.0140$; **Figure 3**)
- An improvement was also observed from baseline to week 8 in the Sleep Disturbances Inventory (SDI) MMRM LSM difference (SE) (-0.3 [0.06]; $p < 0.0001$; **Figure 4**)

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ACKNOWLEDGMENTS

Funding was provided by Acadia Pharmaceuticals, Inc. Medical writing support was provided by CiTRUS Health Group (United States) in accordance with Good Publication Practice (GPP 2022) guidelines.

DISCLOSURES

G. Alva: research support from Accera, Allergan, Axovant, Eisai, Genentech, Intra Cellular, Janssen, Lundbeck, Neurim, Neurotrope, Novartis, Otsuka, Roche, Suven, and Trans Tech; speakers bureau and consultancy for Acadia, Alkermes, Allergan, Avanir, Janssen, Lundbeck, Merck, Nestle, Otsuka, Sunovion, Takeda, and Vanda. **W.J. Cubała:** received grants from Acadia, Alkermes, Allergan, Angelini, Auspex Pharmaceuticals, BMS, Celon, Cephalon, Cortexyme, Ferrier, Forest Laboratories, Gedeon Richter, GW Pharmaceuticals, HMNC Brain Health, IntraCellular Therapies, Janssen, KCR, Lilly, Lundbeck, Minerva, MSD, NIH, Novartis, Orion, Otsuka, Sanofi, and Servier; received honoraria from Adamed, Angelini, AstraZeneca, Bristol Myers Squibb, Celon, GSK, Janssen, KRKA, Lekam, Lundbeck, Minerva, NeuroCog, Novartis, Orion, Pfizer, Polfa Tarchomin, Sanofi, Servier, and Zentiva; served on advisory boards for Angelini, Celon (terminated), Douglas Pharmaceuticals, Janssen, MSD, Novartis, and Sanofi. **A. Berrio, B. Coate, V. Abler,** and **S. Pathak:** employees of Acadia Pharmaceuticals, Inc. (San Diego, CA, USA) at the time of the study.

Table 1. Study endpoints

Primary endpoint	Secondary endpoints	Exploratory endpoints
Safety assessed by TEAEs	Assessment of extrapyramidal symptoms: ESRS-A	Assessment of pimavanserin efficacy: CGI-I and CGI-S
	Assessment of cognitive function: MMSE	Assessment of sleep disturbances: SDI
		Assessment of suicidality: C-SSRS or GCAS
		Assessment of health outcomes: EQ-5D-5L visual analog scale

CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; EQ-5D-5L, 5-level version of EQ-5D-5L; GCAS, Global Clinician Assessment of Suicidality; MMSE, Mini-Mental State Examination; SDI, Sleep Disturbances Inventory; TEAE, treatment-emergent adverse event.

Table 2. Baseline demographics and clinical characteristics

	Placebo (N = 392)	PIM 34 mg (N = 392)	Total (N = 784)
Sex (female), n (%)[a]	213 (54.3)	240 (61.2)	453 (57.8)
Age, mean (SE)	72.1 (0.36)	72.7 (0.35)	72.4 (0.25)
Age categories at screening (years), n (%)[a]			
<65	64 (16.3)	54 (13.8)	118 (15.1)
65 to 74	187 (47.7)	169 (43.1)	356 (45.4)
75 to 84	121 (30.9)	151 (38.5)	272 (34.7)
≥85	20 (5.1)	18 (4.6)	38 (4.8)
Dementia subtype, n (%)			
Alzheimer's disease	260 (66.3)	276 (70.4)	536 (68.4)
Vascular dementia	80 (20.4)	71 (18.1)	151 (19.3)
Parkinson's disease[b,c]	37 (9.4)	35 (8.9)	72 (9.2)[d]
Without dementia	13 (3.3)	16 (4.1)	29 (3.7)
With dementia	24 (6.1)	16 (4.1)	40 (5.1)
Fronto-Temporal dementia	9 (2.3)	8 (2.0)	17 (2.2)
Dementia with Lewy Bodies	6 (1.5)	5 (1.3)	11 (1.4)
Race (White), n (%)[a]	367 (93.6)	368 (93.9)	735 (93.8)
Ethnicity, n (%)[a]			
Hispanic or Latino	124 (31.6)	120 (30.6)	244 (31.1)
Non-Hispanic or Latino	268 (68.4)	272 (69.4)	540 (68.9)
Region, n (%)[a]			
North America	123 (31.4)	123 (31.4)	246 (31.4)
Europe	250 (63.8)	250 (63.8)	500 (63.8)
Rest of the world	19 (4.8)	19 (4.8)	38 (4.8)
MMSE, mean (SE)	18.6 (0.23)	18.4 (0.24)	18.5 (0.17)
CGI-S, mean (SE)	4.5 (0.03)	4.6 (0.03)	4.6 (0.02)
EQ-5D-5L visual analog scale, mean (SE)	52.7 (0.92)	54.6 (0.94)	53.6 (0.66)
ESRS-A, mean (SE)	6.1 (0.56)	5.9 (0.53)	6.0 (0.38)
SDI, mean (SE)	1.3 (0.08)	1.2 (0.07)	1.2 (0.05)
QTcF, mean (SE)	407.9 (0.92)	409.5 (0.87)	--
Ever had suicidal ideation or behavior, assessed with C-SSRS or GCAS, Yes, n (%)[a]	6 (1.7)	6 (1.6)	12 (1.7)

[a]n was the number of subjects with non-missing data in the given treatment group and was used as the denominator for calculating percentages.
[b]Three subjects have Parkinson's disease but do not have Parkinson's disease as the primary cause of dementia.
[c]Includes Parkinson's disease subjects with and without dementia.
[d]The proportions were balanced across pimavanserin and placebo.
CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; EQ-5D-5L, 5-level version of EQ-5D-5L; GCAS, Global Clinician Assessment of Suicidality; MMSE, Mini-Mental State Examination; PIM, pimavanserin; QTcF, corrected QT interval using Fridericia's correction method; SDI, Sleep Disturbances Inventory.

Table 3. Summary of treatment-emergent adverse events

	Placebo (N = 392)		PIM 34 mg (N = 392)		Total (N = 784)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Any TEAE	115 (29.3)	205	119 (30.4)	220	234 (29.8)	425
Any related TEAE[a]	30 (7.7)	50	30 (7.7)	49	60 (7.7)	99
Any serious TEAE	6 (1.5)	9	8 (2.0)	11	14 (1.8)	20
Any related serious TEAE[a]	--	--	--	--	--	--
Any TEAE leading to study drug discontinuation or study termination	9 (2.3)	9	10 (2.6)	10	19 (2.4)	19
Any TEAE resulting in death[b]	2 (0.5)	2	2 (0.5)	2	4 (0.5)	4

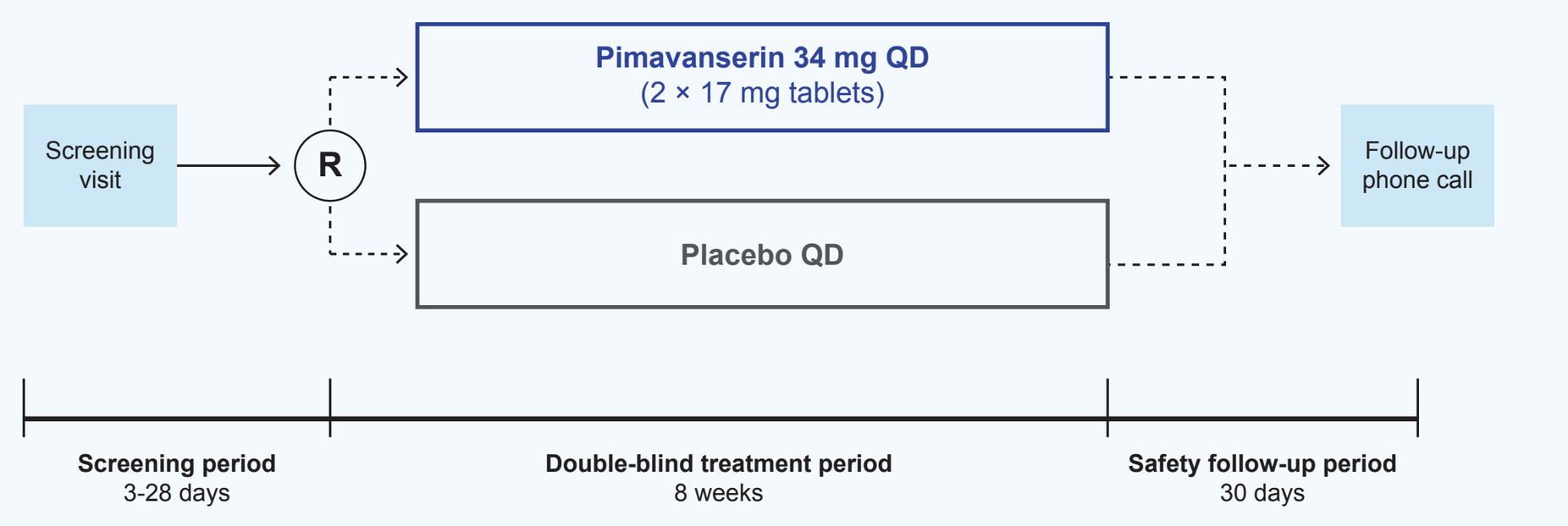
Note: N was used as the denominator for calculating percentages within each treatment group for the subject counts. A TEAE was an adverse event with onset date on or after the first study dose date and no later than the last study dose date + 30 days. Subjects may have had more than one TEAE per category. In the "Events" column, all occurrences of TEAEs were counted per category. In the "Subjects" column, subjects were counted at most once per category. In the "Events" column, all occurrences of TEAEs were counted per category.
[a]Events with missing relationship were considered related.
[b]Death occurred within 30 days of the last dose of the study drug.
PIM, pimavanserin; TEAE, treatment-emergent adverse event.

Table 4. Secondary and exploratory endpoints

Parameter	MMRM LSM (SE) result at week 8: Pimavanserin	MMRM LSM (SE) result at week 8: Placebo	MMRM LSE (SE) difference at week 8: Pimavanserin vs Placebo
ESRS-A	N = 358 -0.5 (0.19)	N = 355 -0.6 (0.19)	0.1 (0.27)
MMSE	N = 358 1.3 (0.15)	N = 354 1.2 (0.15)	0.1 (0.21)
CGI-S	N = 361 -0.5 (0.04)	N = 358 -0.5 (0.04)	0.0 (0.05)

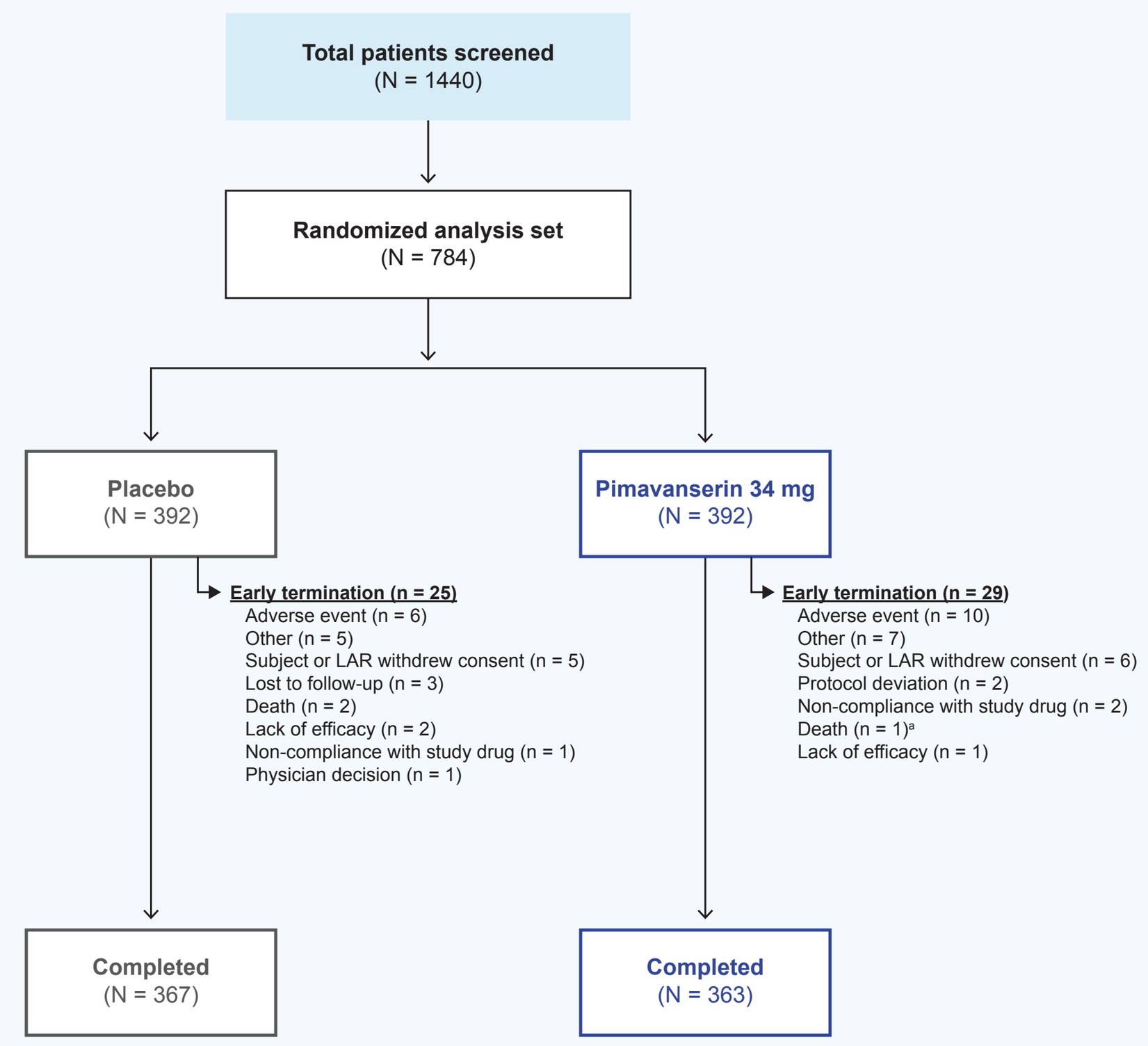
CGI-S, Clinical Global Impression-Severity; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; LSM, least square means; MMRM, mixed-effects model repeated measures; MMSE, Mini-Mental State Examination.

Figure 1. Study design[a]



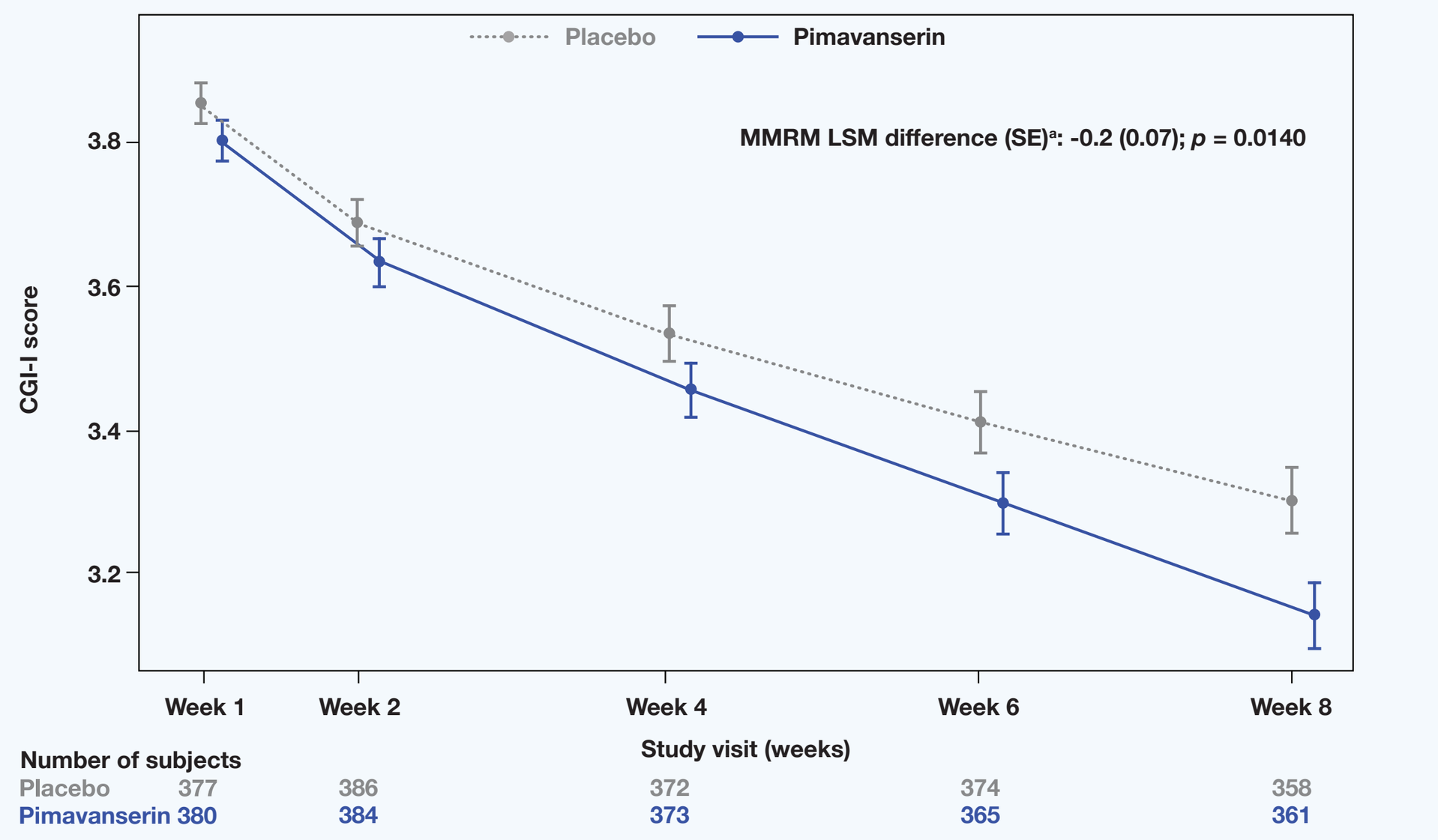
[a]Subjects who enrolled in the open-label extension study did not complete the safety follow-up period.
R, randomization; QD, once daily.

Figure 2. Patient disposition


Total patients screened
(N = 1440)
Randomized analysis set
(N = 784)
Placebo
(N = 392)
Pimavanserin 34 mg
(N = 392)
Early termination (n = 25)
Adverse event (n = 6)
Other (n = 5)
Subject or LAR withdrew consent (n = 5)
Lost to follow-up (n = 3)
Death (n = 2)
Lack of efficacy (n = 2)
Non-compliance with study drug (n = 1)
Physician decision (n = 1)
Early termination (n = 29)
Adverse event (n = 10)
Other (n = 7)
Subject or LAR withdrew consent (n = 6)
Protocol deviation (n = 2)
Non-compliance with study drug (n = 2)
Death (n = 1)a
Lack of efficacy (n = 1)
Completed
(N = 367)
Completed
(N = 363)

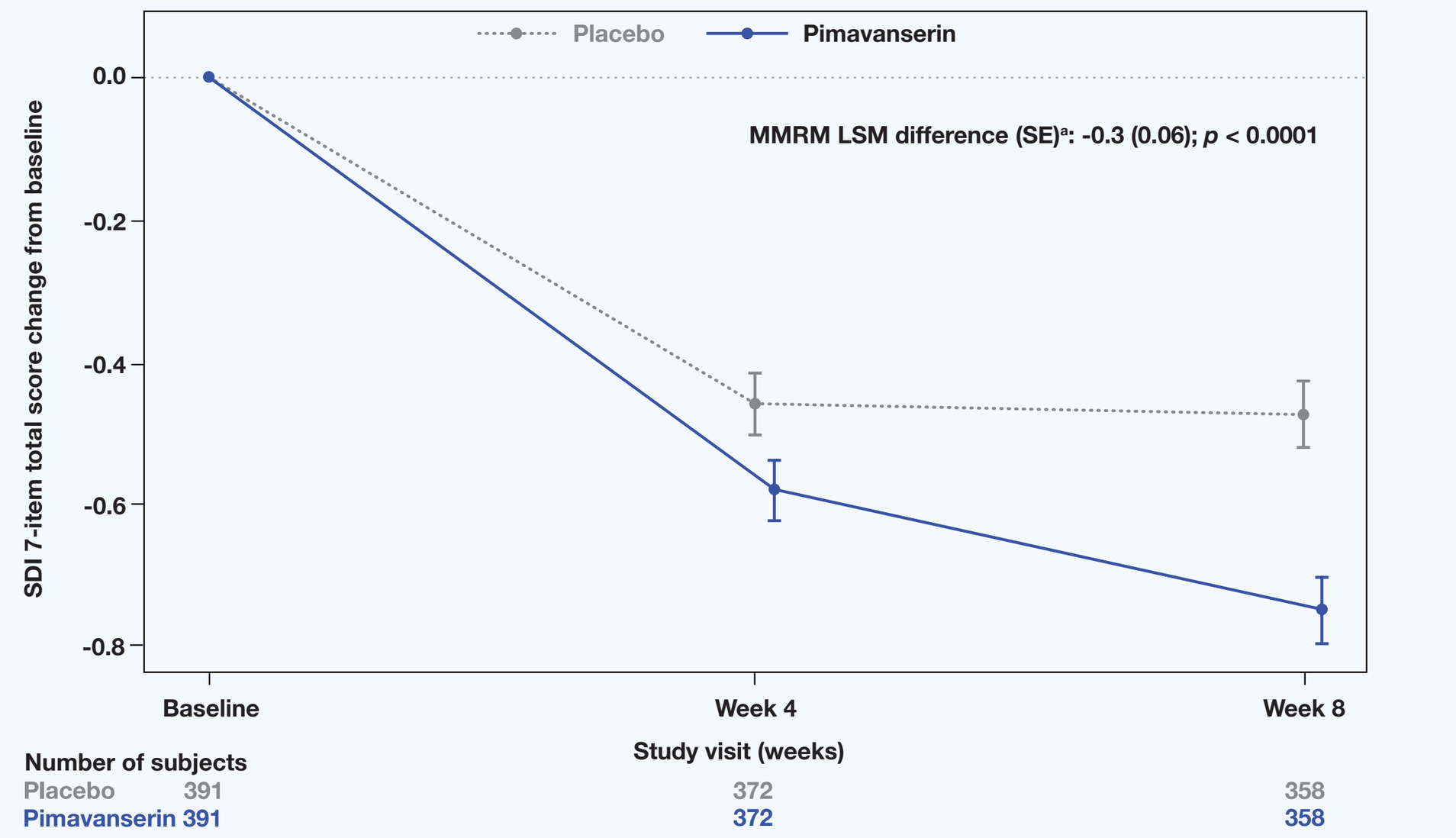
[a]One patient in the pimavanserin group was discontinued from the study due to an AE, and died 4 days after ET visit and 4 days after stopping study drug.
LAR, legally acceptable representative.

Figure 3. Total score change on the CGI-I



[a]LSM from MMRM with fixed categorical effects of region, planned treatment, visit, treatment-by-visit interaction, and fixed continuous covariates of baseline CGI-S score and baseline CGI-S score-by-visit interaction.
CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; LSM, least square means; MMRM, mixed-effects model repeated measures.

Figure 4. Total score change from baseline on the SDI



[a]LSM from MMRM with fixed categorical effects of region, planned treatment, visit, treatment-by-visit interaction, and fixed continuous covariates of baseline SDI score and baseline SDI score-by-visit interaction.
LSM, least square means; MMRM, mixed-effects model repeated measures. SDI, Sleep Disorders Inventory.

CONCLUSIONS

- Pimavanserin was well tolerated in this frail older and elderly population of patients with neuropsychiatric symptoms related to NDD, including Parkinson's disease, and suggested an improvement in neuropsychiatric symptoms
- Pimavanserin was not associated with cognitive decline or motor dysfunction, and safety data were consistent with the well-characterized safety profile of pimavanserin
- These results further add to our knowledge of the safety of pimavanserin for patients with PDP

Poster presented at the 2023 Annual Alzheimer's Association International Conference | July 16-20, 2023 | Amsterdam, Netherlands

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