Pimavanserin Safety in Adult and Elderly Patients With Neuropsychiatric Symptoms Related to Neurodegenerative Disease: An Open-Label Extension Study

Poster 760

Wiesław J. Cubała,[1] Ana Berrio,[2,*] Katherine Chi-Burris,[2] Gustavo Alva,[3] Lambros Chrones,[4] Sanjeev Pathak[4]

[1]Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland; [2]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [3]ATP Clinical Research, Department of Psychiatry and Neuroscience, University of California at Riverside, Riverside, CA, USA; [4]Acadia Pharmaceuticals Inc., Princeton, NJ, USA

*Presenting author

INTRODUCTION

- Psychosis, which is characterized by hallucinations or delusions, is a common neuropsychiatric symptom in elderly patients with neurodegenerative diseases (NDDs) such as Parkinson's disease (PD).[1,2]
- There are few treatment options available for NDDs, and elderly patients are highly sensitive to the limiting adverse events (AEs) of atypical antipsychotics, including somnolence, extrapyramidal symptoms, tremor, and falls.[3] These patients also tend to have high rates of polypharmacy, which increases the potential for AEs.[4]
- Pimavanserin, a selective serotonin 2A (5-HT_{2A}) inverse agonist and, to a lesser extent, 5-HT_{2C} inverse agonist/antagonist, is the only US Food and Drug Administration–approved treatment for hallucinations and delusions associated with PD with or without dementia.[5,6]
- In an 8-week, multicenter, phase 3b, double-blind (DB) randomized controlled trial (NCT03575052) of frail older adults and elderly patients with neuropsychiatric symptoms related to an NDD, pimavanserin was well tolerated and not associated with motor or cognitive impairment.[5]
- Here, we report results from a 52-week, open-label extension (OLE) (NCT03623321) of the predecessor 8-week, phase 3b trial; the objective of this OLE was to assess the long-term safety and tolerability of pimavanserin.

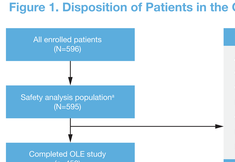
METHODS

- The OLE study enrolled patients from the predecessor placebo-controlled trial. Patients satisfied all eligibility criteria for the predecessor trial, which included the presence of neuropsychiatric symptoms related to an NDD and an assessment by the study investigator that longer-term treatment with pimavanserin could be beneficial.
- All patients received oral pimavanserin 34 mg once daily for 52 weeks.
  - Clinic visits occurred at baseline and weeks 2, 4, 8, 12, 16, 28, 40, and 52.
  - Dose adjustments down to 20 mg (and back up to 34 mg) were permitted at any clinic visit (scheduled or unscheduled) after baseline at investigator discretion.
- The primary endpoint was treatment-emergent AEs (TEAEs); AEs were defined as a TEAE if they began on or after the OLE first dose of pimavanserin and ≤30 days after the last dose of pimavanserin.
- Exploratory endpoints included the Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A) for movement disorders, Mini-Mental State Examination (MMSE), and change from baseline in Clinical Global Impression–Severity (CGI-S) score for neuropsychiatric symptoms, EuroQoL 5-Dimension 5-Level (EQ-5D-5L) for health-related quality of life, Sleep Disorders Inventory (SDI) score, and Columbia-Suicide Severity Rating Scale (C-SSRS) or Global Clinician Assessment of Suicidality (GCAS).
  - ESRS-A, MMSE, CGI-S, and C-SSRS or GCAS were performed at all scheduled study visits. EQ-5D-5L and SDI were performed at baseline and weeks 12, 28, and 52.
- The safety analysis population included all enrolled patients who received ≥1 dose of pimavanserin. Results were analyzed using descriptive statistics.

RESULTS

- A total of 596 patients enrolled at 86 sites, and 595 received pimavanserin treatment. Of these, 452 (76.0%) patients completed the study (**Figure 1**).

Figure 1. Disposition of Patients in the OLE Study of Pimavanserin



Early termination reason	n	Early termination reason	n
AE	32	Lost to follow-up	6
Consent withdrawn	29	Noncompliance with study drug	6
COVID-19 public health emergency	16	Physician decision	5
Living situation changed	11	Noncompliance with study activities	4
Geopolitical conflict	10	Use of prohibited medication	3
Lack of efficacy	9	Medical decision	2
Death	9	Protocol deviation	1
Total			143

AE, adverse event; OLE, open-label extension.
[a]Patients who received ≥1 dose of pimavanserin during the OLE period.

- Patients were a mean age of 72.2 years (range, 60-96 y), predominantly White (94.3%), and mostly (58.5%) female; nearly all patients (95.3%) had dementia, 68.7% of whom had Alzheimer's disease, 18.5% of whom had vascular dementia, and 4.7% of whom had PD (**Table 1**).

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Safety analysis population (N=595)
Age, mean (SE), years	72.2 (0.3)
Sex, female, n (%)	348 (58.5)
Body mass index, mean (SE), kg/m^2	26.80 (0.2)
Geographic region, n (%)	
Europe	362 (60.8)
North America	206 (34.6)
Rest of world	27 (4.5)
Race, n (%)	
White	561 (94.3)
Mixed	20 (3.4)
Black or African American	13 (2.2)
Asian	1 (0.2)
Treated with an antipsychotic for neuropsychiatric symptoms related to NDD and psychosis, n (%)	116 (19.5)
Dementia, n (%)	
Any type	567 (95.3)
Alzheimer's disease	409 (68.7)
Vascular dementia	110 (18.5)
PD[a,b]	58 (9.7)
Without dementia	28 (4.7)
With dementia	28 (4.7)
Frontotemporal dementia	12 (2.0)
Dementia with Lewy bodies	8 (1.3)
MMSE, mean (SE)	20.0 (0.21)
CGI-S, mean (SE)	4.0 (0.03)
EQ-5D-5L visual analog scale, mean (SE)	61.5 (0.73)
ESRS-A, mean (SE)	4.8 (0.36)
SDI, mean (SE)	0.6 (0.04)
QTcF, ms	
≤450	587 (98.8)
451–480	7 (1.2)
Suicidal ideation or behavior since last visit,[c] assessed with C-SSRS or GCAS, n (%)	2 (1.8)

CGI-S, Clinical Global Impression–Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ESRS-A, Extrapyramidal Symptom Rating Scale–Abbreviated; EQ-5D-5L, EuroQol, 5-Dimension, 5-Level; GCAS, Global Clinician Assessment of Suicidality; MMSE, Mini-Mental State Examination; NDD, neurodegenerative disease; PD, Parkinson's disease; QTcF, corrected QT interval using Fridericia's correction method; SDI, Sleep Disorders Inventory.
[a]Two patients had PD that was not the primary cause of dementia.
[b]Includes PD with or without dementia.
[c]End-of-study visit for predecessor randomized controlled trial.

- The overall mean duration of exposure to pimavanserin was 312.4 days.
- A total of 420 (70.6%) patients were concomitantly treated with antidementia drugs, the most common of which was donepezil (n=146; 24.5%).
- Forty percent of patients (n=238) experienced a TEAE, serious TEAEs occurred in 6.2% of patients, TEAEs leading to treatment discontinuation or study termination occurred in 6.6% of patients, and 11 (1.8%) patients experienced a TEAE leading to death. No fatalities were related to pimavanserin treatment (**Table 2**).

Table 2. Summary of TEAEs[a]

TEAE, n (%)	Safety analysis population (N=595)
Any TEAE	238 (40.0)
Serious TEAE	37 (6.2)
Drug-related TEAE[b]	61 (10.3)
Drug-related serious TEAE[c]	1 (0.2)
TEAE leading to treatment discontinuation or study termination	39 (6.6)
Fatal TEAE[b]	11 (1.8)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]Defined as an AE with an onset on or after the first dose of study drug and no later than 30 days after the last study drug dose date. Patients with >1 TEAE per event category were counted only once per category.
[b]Events with missing relationship to study drug were considered as related.
[c]Included deaths that occurred within 30 days of the last dose of study drug.

- TEAEs that occurred in ≥2% of patients are summarized in **Table 3**.

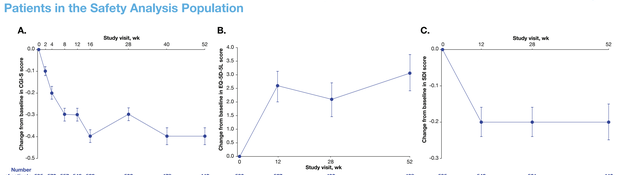
Table 3. TEAEs Reported in ≥2% of Patients and Serious TEAEs Reported in >1 Patient

TEAE, n (%)	Safety analysis population (N=595)
Any TEAE reported in ≥2% of patients	
Urinary tract infection	29 (4.9)
Headache	22 (3.7)
Dizziness	20 (3.4)
Anxiety	13 (2.2)
Insomnia	13 (2.2)
Fall	13 (2.2)
Electrocardiogram QT prolonged	13 (2.2)
Weight decreased	12 (2.0)
Arthralgia	12 (2.0)
Serious TEAE	
Cerebrovascular accident	3 (0.5)
Cardiac failure	2 (0.3)
Cardiac failure congestive	2 (0.3)
Pneumonia	2 (0.3)
Femur fracture	2 (0.3)
Brain edema	2 (0.3)
Agitation	2 (0.3)

TEAE, treatment-emergent adverse event.

- The mean (SE) change from OLE baseline to week 52 in CGI-S, EQ-5D-5L, and SDI scores were –0.4 (0.04), +3.1 (0.68), and –0.2 (0.05), respectively (**Figure 2**). Lower CGI-S and SDI scores indicate less impairment from neuropsychiatric symptoms and decreased severity of sleep disturbance, respectively. Higher EQ-5D-5L scores indicate improved health-related quality of life.

Figure 2. Change From OLE Baseline in (A) CGI-S Score, (B) EQ-5D-5L Score, and (C) SDI Score Among Patients in the Safety Analysis Population



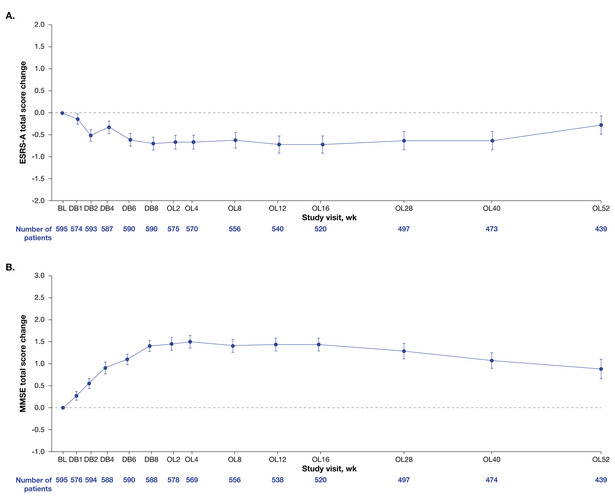
CGI-S, Clinical Global Impression–Severity; EQ-5D-5L, EuroQoL 5-Level 5-Dimension; OLE, open-label extension; SDI, Sleep Disorders Inventory.

CONCLUSIONS

- The findings from this OLE study were consistent with those from the predecessor randomized clinical trial.
- Pimavanserin was generally well tolerated, and no new safety signals were observed in frail older adults or elderly patients with neuropsychiatric symptoms related to an NDD and treated with pimavanserin. These findings inform the use of pimavanserin in patients experiencing hallucinations and delusions associated with PD.

- The mean (SE) changes from DB baseline to OLE week 52 in ESRS-A and MMSE scores were –0.3 (0.22 and 0.9 (0.21), respectively (**Figure 3**).
- No patients reported suicidal behavior as assessed by GCAS or C-SSRS.

Figure 3. Change From DB Baseline in (A) ESRS-A Score and (B) MMSE Score Among Patients in the Safety Analysis Population



BL, baseline; DB, double-blind; ESRA-A, Extrapyramidal Symptom Rating Scale–Abbreviated; MMSE, Mini-Mental State Examination; OL, open-label.

ACKNOWLEDGMENTS AND FUNDING

This study was funded by Acadia Pharmaceuticals. Medical writing support was provided by Alexander Simon of MedLogix Communications, LLC, a Citrus Health Group, Inc. company (Chicago, Illinois), and was funded by Acadia Pharmaceuticals.

DISCLOSURES

WJC: Grants: Acadia, Alkermes, Allergan, Angelini, Auspex Pharmaceuticals, Beckley Psytech, BMS, Celon, Cephalon, Cortexyme, Ferrier, Forest Laboratories, GedeonRichter, GH Research, GW Pharmaceuticals, HMNC Brain Health, IntraCellular Therapies, Janssen, KCR, Lilly, Lundbeck, Minerva, MSD, NIH, Novartis, Orion, Otsuka, Recognify Life Sciences, Sanofi, and Servier. Honoraria: Adamed, Angelini, AstraZeneca, BMS, Celon, GSK, Janssen, KRKA, Lekam, Lundbeck, Minerva, NeuroCog, Novartis, Orion, Pfizer, Polfa Tarchomin, Sanofi, Servier, and Zentiva. Advisory boards: Angelini, Celon (terminated), Douglas Pharmaceuticals, GH Research, Janssen, MSD, Novartis, and Sanofi.

GA: Research support: AbbVie, Accera, Axsome, Axovant, Biogen, Eisai, Lilly, Neurotrope, Genentech, Intra Cellular, Janssen, Lundbeck, Neurim, Novartis, Otsuka, Roche, Sage, Suven, and Trans Tech. Speakers bureau and consultant: AbbVie, Acadia, Alkermes, Axsome, Biogen, Janssen, Idorsia, Lundbeck, Myriad, Neurocrine, Nestle, Otsuka, Sage, Sunovion, Teva, and Takeda.

AB, KC-B, LC, and **SP** are employees of Acadia Pharmaceuticals.

REFERENCES

1. Cressot C, et al. *J Alzheimers Dis*. 2024;99(1):85-99.
2. Hommel ALAJ, et al. *Mov Disord Clin Pract*. 2020;7(5):531-542.
3. Mühlbauer V, et al. *Cochrane Database Syst Rev*. 2021;12(12):CD013304.
4. Pazan F and Wehling M. *Eur Geriatr Med*. 2021;12(3):443-452.
5. Alva G, et al. *J Alzheimers Dis*. 2024;99(1):265-274.
6. Vanover KE, et al. *J Pharmacol Exp Ther*. 2006;317(2):910-918.

Presented at International Congress of Parkinson's Disease and Movement Disorders 2024; September 27–October 1, 2024; Philadelphia, PA

ACADIA