Duration of Illness and Complete Response to Pimavanserin in Parkinson's Disease Psychosis: Analysis of Pooled Clinical Trial Data

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Khashayar Dashtipour,[1] Alberto J. Espay,[2] Michele Tagliati,[3] Gregory Brunson,[4] Katherine Chi-Burris,[4] Nazia Rashid,[4] Lambros Chrones[5]

[1]Department of Neurology, Loma Linda University School of Medicine, Loma Linda, CA, USA; [2]University of Cincinnati Gardner Neuroscience Institute, Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA; [3]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [5]Acadia Pharmaceuticals Inc., Princeton, NJ, USA

INTRODUCTION

- Parkinson's disease psychosis (PDP) affects ≥50% of patients with Parkinson's disease[1]; if left untreated, the symptoms tend to worsen over time[2]
- Despite its progressive nature, some clinicians delay treatment of PDP when symptoms are perceived as less severe[3]
- Earlier treatment of mild PDP symptoms has been suggested to lower the risk of later deterioration; however, evidence for the potential benefit of early treatment is limited[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 PDP[5]
- In a pivotal trial, nearly 14% of patients treated with pimavanserin reported complete response (CR; no hallucinations or delusions) at the end of the 6-week study[5]
- We conducted a post hoc analysis to explore the relationship between the time since PDP diagnosis and the initiation of pimavanserin in patients who achieved CR

METHODS

- Data were pooled from patients with PDP treated with pimavanserin (34 mg/d) in two 6-week, randomized, placebo-controlled, double-blind clinical trials in North America
- The Scale for the Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) and Clinical Global Impression–Severity (CGI-S) scales were used at baseline and at scheduled visits to assess disease severity; CGI-S patient data were collected from the open-label extension period
  - The SAPS-PD is a modified version of the original SAPS scale, focusing on hallucinations and delusions; it consists of 9 items, and each item uses a range of responses from 0 (none) through 5 (severe)[6]
  - The CGI-S assesses patient illness severity from a global perspective on a scale from 1 (not at all ill) to 7 (among the most extremely ill)[7]
- CR was defined as a reduction of SAPS-PD score to 0 at week 6 of the double-blind period. The probability of achieving CR and its association with the timing of treatment initiation (PDP duration) was assessed using logistic regression

RESULTS

- Of the 135 patients evaluated, 21 achieved CR with pimavanserin. Baseline demographics and clinical characteristics are summarized in **Table 1**

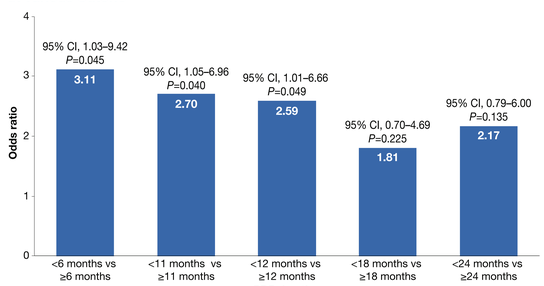
Table 1. Baseline Demographics and Clinical Characteristics

	SAPS-PD complete responders (n=21)	All patients (N=135)
Cardinal features of PD, n (%)		
Rest tremor Rigidity Bradykinesia Akinesia Postural and gait instability	15 (71.4) 19 (90.5) 20 (95.2) 7 (33.3) 20 (95.2)	106 (78.5) 122 (90.4) 123 (91.1) 37 (27.4) 113 (83.7)
Stereotaxic surgery, n (%)	2 (9.5)	11 (8.1)
Time since first PDP symptom, mean (SD), mo	26.2 (33.82)	29.9 (30.39)
Time since PD diagnosis, mean (SD), mo	98.0 (64.01)	108.8 (74.79)
Age, mean (SD), yr	71.3 (8.53)	71.8 (6.86)
Age category, n (%), yr <65 65-75 >75	 5 (23.8) 9 (42.9) 7 (33.3)	 19 (14.1) 75 (55.6) 41 (30.4)
Sex, n (%), male	16 (76.2)	94 (69.6)
Race, n (%) Asian Black Other White	 0 0 2 (9.5) 19 (90.5)	 0 2 (1.5) 4 (3.0) 129 (95.6)
SAPS-PD, mean (SD)	11.1 (4.30)	15.1 (6.52)
SAPS-D, mean (SD)	3.9 (3.30)	5.2 (4.41)
SAPS-H, mean (SD)	8.1 (3.79)	11.5 (5.29)
MMSE total score, mean (SD)	26.6 (2.64)	26.2 (2.57)
Antidementia drugs[a]	4 (19.0)	48 (35.6)
Dopaminergic agents[b]	21 (100)	132 (97.8)

MMSE, Mini Mental State Examination; PD, Parkinson's disease; PDP, psychosis associated with Parkinson's disease; SAPS-D, Scale for the Assessment of Positive Symptoms-Delusions; SAPS-H, SAPS-Hallucinations; SAPS-PD, SAPS-Parkinson's disease; SD, standard deviation.
[a]Including donepezil, galantamine, memantine, or rivastigmine.
[b]Including amantadine, apomorphine, carbidopa, entacapone, levodopa, pramipexole, rasagiline, ropinirole, selegiline, Sinemet®, Stalevo®, or tolcapone.

- Patients with PDP durations of <6 months or <12 months at the time of pimavanserin treatment initiation had a greater probability of achieving CR compared with those who initiated ≥6 months (odds ratio [OR], 3.11; 95% CI, 1.03–9.42; *P*=0.045) or ≥12 months (OR, 2.59; 95% CI, 1.01–6.66; *P*=0.049) after PDP diagnosis
  - Later cutoffs of <18 months or <24 months did not indicate a clear advantage over ≥18 months (OR: 1.81, 95% CI: 0.70–4.69, *P*=0.225) or ≥24 months (OR: 2.17, 95% CI: 0.79–6.00, *P*=0.135) (**Figure 1**)

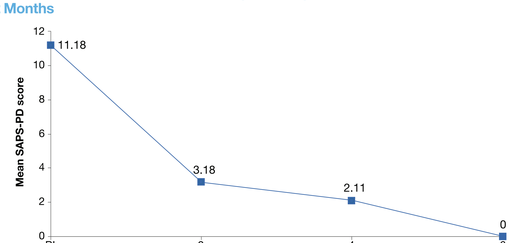
Figure 1. Odds Ratios of Achieving CR for Early Versus Late Treatment Initiation at Various Cutoffs



PDP duration is defined as the time between PDP diagnosis and treatment initiation with pimavanserin.
CR, complete response; PDP, Parkinson's disease psychosis.

- After adjusting for the baseline SAPS-PD score, the trend still favored patients who initiated treatment earlier, although not statistically significant (eg, OR of patients with PDP durations <12 months vs ≥12 months at treatment initiation was 2.27 [95% CI, 0.85–6.08; *P*=0.102])
- In patients with CR and PDP durations of <12 months, the mean change from baseline SAPS-PD score was -8.00 and -9.44 at weeks 2 and 4, respectively (**Figure 2**) and ≥33% of patients reported a complete resolution of symptoms as early as week 2 (**Figure 3**)

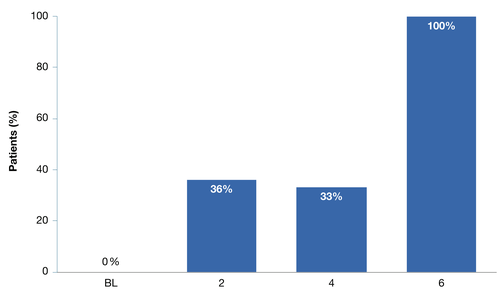
Figure 2. Mean SAPS-PD Scores in Complete Responders With PDP Duration <12 Months



No. of patients with CR and PDP <12 Months	11	11	9	11

BL, baseline; PDP, Parkinson's disease psychosis; SAPS-PD, Scale for the Assessment of Positive Symptoms-Parkinson's Disease.
PDP duration is defined as the time between PDP diagnosis and treatment initiation with pimavanserin.

Figure 3: Percentages of Patients With a SAPS-PD Score of 0 at Various Visits Among Patients With PDP Duration <12 Months who Achieved CR at Week 6

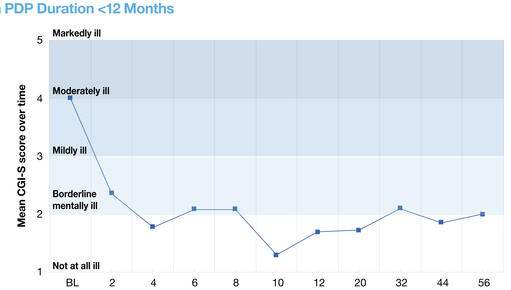


No. of patients with CR and PDP <12 Months	11	11	9	11

PDP duration is defined as the time between PDP diagnosis and treatment initiation with pimavanserin.
BL, baseline; PDP, Parkinson's disease psychosis; SAPS-PD, Scale for the Assessment of Positive Symptoms-Parkinson's Disease.

- CGI-S scores indicated that patients who achieved CR generally had most symptoms resolved by week 4, and responses were typically sustained through 56 weeks (**Figure 4**)

Figure 4. Mean CGI-S Scores Over 1 Year Follow-Up in Complete Responders with PDP Duration <12 Months



No. of patients with CR and PDP <12 Months	11	11	9	11	11	10	10	11	10	7	7

BL, baseline; CGI-S, Clinical Global Impressions Scale-Severity; CR, complete response; PDP, Parkinson's disease psychosis.

CONCLUSIONS

- Early pimavanserin treatment is associated with a higher probability of a complete resolution of PDP symptoms
- Complete responders who initiated pimavanserin within a year of PDP diagnosis maintained their response for ≥1 year
- These preliminary data warrant further investigation to help guide clinicians in their treatment of PDP

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