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Efficacy results of pimavanserin from a multi-center, open-label extension study in Parkinson's disease psychosis patients

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A B S T R A C T

Introduction: Pimavanserin, a selective 5-HT_{2A} inverse agonist/antagonist, was approved for hallucinations and delusions associated with Parkinson's disease psychosis (PDP). We present durability of response with pimavanserin in patients with PDP for an additional 4 weeks of treatment.

Methods: This was an open-label extension (OLE) study in patients previously completing one of three double-blind, placebo-controlled (Core) studies. All patients received pimavanserin 34 mg once daily. Efficacy assessments included the Scale for the Assessment of Positive Symptoms (SAPS) PD and H + D scales, Clinical Global Impression (CGI) Improvement and Severity scales and Caregiver Burden Scale (CBS), through 4 weeks in the OLE. Safety assessments were conducted at each visit.

Results: Of 459 patients, 424 (92.4%) had a Week 4 efficacy assessment. At Week 4 (10 weeks total treatment), SAPS-PD mean (standard deviation) change from OLE baseline was −1.8 (5.5) and for SAPS-H + D was −2.1 (6.2) with pimavanserin 34 mg. Patients receiving placebo during the Core studies had greater improvements (SAPS-PD -2.9 [5.6]; SAPS-H + D −3.5 [6.3]) during the OLE. For participants treated with pimavanserin 8.5 or 17 mg during the Core studies, further improvement was observed during the OLE with pimavanserin 34 mg. The mean change from Core Study baseline for SAPS-PD score was similar among prior pimavanserin 34 mg and prior placebo-treated participants (−7.1 vs. −7.0). The CGI-I response rate (score of 1 or 2) at Week 4 was 51.4%. Adverse events were reported by 215 (46.8%) patients during the first 4 weeks of OLE. The most common AEs were fall (5.9%), hallucination (3.7%), urinary tract infection (2.8%), insomnia (2.4%), and peripheral edema (2.2%)

Conclusions: Patients previously on pimavanserin 34 mg during three blinded core studies had durability of efficacy during the subsequent 4 week OLE SAPS-PD assessment. Patients previously on blinded placebo improved after 4 weeks of OL pimavanserin treatment. These results in over 400 patients from 14 countries support the efficacy of pimavanserin for treating PDP.

1. Introduction

Psychotic symptoms are a common occurrence for patients with Parkinson's disease (PD), which develop in approximately 50% of patients over the course of their disease [1,2]. The onset and progression of these symptoms complicate PD management and are linked to increased co-morbidity [1]. Parkinson's disease psychosis (PDP) is itself a major risk factor for hospitalization, nursing home placement, and mortality [3–7]. Prior to the approval of pimavanserin, the only pharmacological treatment options for PDP in the U.S. were off-label use of antipsychotics or acetylcholinesterase inhibitors [8]. However, these drugs lack proven efficacy, may worsen motor symptoms, have limiting side effects, and/or require blood monitoring for significant risks [9–16].

The selective 5-HT_{2A} receptor inverse agonist/antagonist pimavanserin is devoid of dopaminergic, histaminergic, adrenergic, or muscarinic activity in animal models [17]. In the Phase 3, placebo-controlled pivotal study (Study 020), pimavanserin 34 mg once daily (equivalent to 40 mg pimavanserin tartrate) exhibited significant

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antipsychotic effects (improvement in hallucinations and delusions) with secondary endpoints demonstrating improved sleep and a reduction in caregiver burden over the 6-week blinded treatment period, was well tolerated, and did not worsen motor function [18]. Pimavanserin was approved in the U.S. for the treatment of hallucinations and delusions associated with PDP in April 2016. The long term evaluation of the safety and tolerability of the entire OLE population has been separately reported [19]. In this analysis of the Phase 3 open-label extension (OLE) study, the efficacy of pimavanserin 34 mg once daily was evaluated in >400 patients worldwide with PDP who continued treatment from three Core double-blind, placebo-controlled studies or a previous extension study using the prespecified efficacy endpoint SAPS-PD (the Core study primary endpoint) after 4 weeks of OLE treatment.

2. Methods

The study was conducted according to the ethical principles of Good Clinical Practices, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; United States Code of Federal Regulations; and World Medical Association-Declaration of Helsinki. Institutional Review Board or Ethics Committee approval for the protocol and the Informed Consent Form was obtained at each clinical site. Written approval of these documents was obtained from each patient and caregiver before any study procedures were performed. This study was registered at clinicaltrials.gov: NCT00550238.

2.1. Study design

This is an analysis of the efficacy results of a long-term, single arm, OLE of previous placebo-controlled studies or previous OLE studies. This paper describes the efficacy assessments completed during three 6 week, placebo-controlled (Core) studies through the initial 4 weeks of the OLE. Clinical sites in North America, Europe, and India enrolled patients after completion of treatment with pimavanserin or placebo for 6 weeks in one of three, Core double-blind, randomized, placebo-controlled Phase 3 clinical studies (ACP-103-012, NCT00477672; ACP-103-014, NCT00658567; or ACP-103-020, NCT01174004). Three additional patients who were enrolled did not participate in one of these studies, one from a previous OLE (Study 010; NCT01518309) (Fig. 1).

For patients who enrolled within 1 week of completing a double-blind study (Core Study), assessments performed at the final double-blind visit of the Core studies (Week 6 for studies 012, 014, and 020) or the previous OLE study (Study 010) served as baseline for this 4-week OLE. Thus, no additional baseline evaluations were required except for a medical history and completion of a baseline Resource Utilization in Dementia [RUD]-Lite assessment [20]. For patients who were not enrolled within 1 week of completing a Core, all baseline assessments were required before study entry. A caregiver was required to accompany the patient to all visits to provide information to study staff regarding the patient's symptoms, and to complete a questionnaire to assess caregivers' quality of life (Zarit Caregiver Burden Scale) [21]. Following baseline assessments, pimavanserin 34 mg was taken orally by the patient once daily. During the OLE, patients remained blinded to the original treatment allocation from the double-blind Core studies.

2.2. Patient selection

Men or women who had completed a previous Core double-blind study with pimavanserin within the past 28 days were eligible if the Investigator determined they could benefit from continued treatment with pimavanserin. Patients previously had satisfied eligibility criteria from the Core studies. Patients were required to be oriented to time, person, and place. All patients were required to be willing and able to provide informed consent and to have a caregiver who could provide informed consent. The caregiver had to agree to accompany the patient

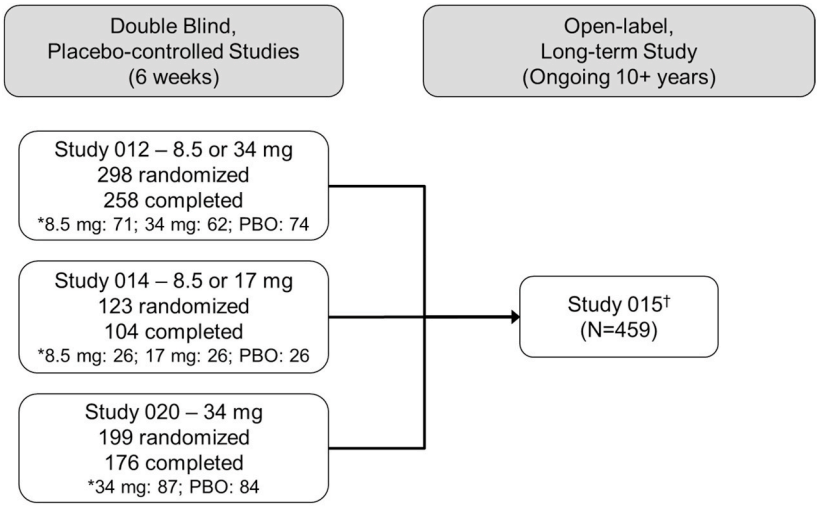


Fig. 1. Disposition of patients from Core double-blind, placebo-controlled studies eligible for open-label (OLE) study.
* Represents number of patients from each Core Study who entered the 015 OLE study.
† Two patients were in screening for Study 020 when enrollment was closed and were offered open-label treatment in Study 015, and one patient entered the open-label 015 study from Study 010 (NCT01518309)
PBO = placebo.

* Represents number of patients from each Core Study who entered the 015 OLE study.

† Two patients were in screening for Study 020 when enrollment was closed and were offered open-label treatment in Study 015, and one patient entered the open-label 015 study from Study 010 (NCT01518309)

PBO = placebo

to all study visits. Women had to be of non-childbearing potential during the study or agree to use a clinically acceptable method of contraception during the study. Patients were required to have psychotic symptoms of at least moderate severity consistent with established diagnostic criteria for PDP [22], which occurred at least weekly in the month prior to the start of blinded therapy. Improvement of symptoms during the previous double-blind Core studies of pimavanserin was not required for entry into the OLE study. Doses of dopaminergic drugs were maintained at a stable level throughout the Core study and during the 4 week efficacy assessment.

Patients were excluded for any clinically significant medical illness that might interfere with the conduct of the study; use of any prohibited or restricted medications; current use of medications known to prolong the QT interval; a baseline electrocardiogram (ECG) with Bazett's corrected QT > 460 msec for males or >470 msec for females; or allergy or sensitivity to pimavanserin or other drugs of the same class.

2.3. Study assessments

Symptoms of psychosis were measured on subscales of the Scale for the Assessment of Positive Symptoms (SAPS) in North America by central, blinded, independent raters (MedAvante, Inc.) and outside North America by qualified raters at each site trained and certified to administer the SAPS in their native language. The SAPS-PD (modified 9-item SAPS hallucinations and delusions subscales) and the SAPS-H + D (combined 20-item SAPS hallucinations and delusions subscales) [23, 24], were evaluated at Week 4 of the OLE. The Clinical Global Impression-Severity and -Improvement (CGI-S and CGI-I) scales [25] and the Caregiver Burden Scale (CBS) were scheduled after 2 and 4 weeks of the OLE. Unscheduled study visits were allowed at any time. Patients who terminated the study at any time other than a planned study visit were required to have an end-of-study evaluation (early termination visit). At each study visit, physical and neurological examinations, vital signs (blood pressure and heart rate), standard clinical laboratory tests (chemistry, hematology, urinalysis), 12-lead ECG, and adverse events (AEs) were assessed.

2.4. Statistical Analysis

SAPS-H + D and -PD, and CGI-S, CGI-I, and CBS assessments were summarized through Week 4 of the OLE. Mean changes in efficacy parameters were evaluated from Core study baseline and from OLE baseline. Change from OLE baseline to OLE Week 4 was analyzed with a paired *t*-test with the null hypothesis of no change. Changes from double-blind baseline to OLE Week 4 were analyzed with t-tests comparing group means for placebo vs. pimavanserin <34 mg, placebo vs. pimavanserin 34 mg, and pimavanserin <34 mg vs. pimavanserin 34 mg. Descriptive statistics were used to summarize the data, including number of patients, mean, median, standard deviation (SD), standard error of the mean (SE), minimum and maximum for continuous measurements and number and percentage of patients in each level of a categorical measurement. CGI-I responders were defined as having a score of 1 or 2 (very much improved or much improved). Adverse events (AEs) were summarized through the first 4 weeks of the OLE.

3. Results

Patient data were collected between July 2007 and May 2018 from 114 clinical sites in 14 countries. This report summarizes all efficacy endpoints for a total of 10 weeks which includes the 6 week placebo controlled phase (Core Study) plus the first 4 weeks of the OLE. Of 538 patients who were eligible to enroll, 459 entered the OLE study (Fig. 1); 39 subjects terminated the study in the first 4 weeks with 424 (92.4%) patients having a Week 4 OLE efficacy assessment. Withdrawals were primarily due to adverse events (14, 3.1%) or withdrawal of consent (17, 3.7%). The mean (median) time from completion of the Core Studies to enrollment in the OLE was 5.2 (1.0) days.

Baseline demographics and disease characteristics are shown for all patients combined, regardless of treatment arm, from previous studies. At baseline, the mean (SD) age was 71.2 (8.2) years, 92.2% were white, and 61.7% were male (Supplemental Table 1). Over 80% of patients were at least 65 years and 31% were over 75 years of age. Over two-thirds of patients were from North America. At baseline, mean (SD) SAPS-PD, SAPS-H + D, and CGI-S scores for all patients were 9.2 (6.8), 10.3 (8.0), and 3.3 (1.3), respectively. At baseline, 458 (99.8%) patients had a medical history of a psychiatric disorder including visual hallucinations (88.0%), delusions (65.4%), and auditory hallucinations (46.2%).

3.1. Durability of antipsychotic response

SAPS data are based on the Core study period and the first 4 weeks of the OLE, and are presented as either the change from Core or OLE baseline (up to 10 weeks total treatment duration). In the overall population, the mean (SD) change from OLE baseline to OLE Week 4 for the SAPS-PD score was −1.8 (5.5), denoting improvement (Table 1). Significant improvements were observed from OLE baseline to OLE Week 4 for most comparisons (Supplemental Table 2). No significant changes from double-blind baseline to OLE Week 4 were observed (Supplemental Table 3). Among participants entering the OLE study having received placebo in the Core Study Period, the mean change from OLE baseline to OLE Week 4 in the SAPS-PD was −2.9 (5.6). For participants previously dosed with pimavanserin 34 mg, the mean change from OLE baseline to OLE Week 4 for the SAPS-PD was −0.8 (5.6). The mean (SD) change from Core Study baseline for SAPS-PD scores were similar among prior pimavanserin 34 mg and prior placebo-treated participants (−7.1 vs. −7.0). A similar pattern of improvement was also noted in patients switched from prior pimavanserin doses <34 mg–34 mg (Fig. 2A). No notable differences were observed for mean change from OLE baseline to OLE Week 4 in the SAPS-PD between patients treated in North America [-1.6 (6.0)] vs. outside North America [-2.0 (4.3)]. Mean (SD) SAPS-H + D scores decreased from OLE baseline to OLE Week 4 in the overall population [-2.1 (6.2)], in those receiving prior placebo [-3.5 (6.3)], and in those receiving prior pimavanserin 34 mg [-1.2 (6.3)]. At OLE week 4, mean (SD) change from core baseline was similar among prior pimavanserin 34 mg and prior placebo-treatment participants (−8.3 vs. −8.2) (Fig. 2B). At baseline, the mean Global SAPS-H + D (GSAPS-H + D) score was 3.9 (2.6), and at OLE Week 4, a mean change from OLE baseline of −0.7 (2.2) points was observed.

Patients dosed with placebo in Core double-blind studies

Table 1
Baseline and mean (standard deviation) change from OLE baseline for SAPS-PD, SAPS-H + D, SAPS-H, SAPS-D, CGI-S, and Caregiver Burden Scale (Safety analysis set).

	N	Mean (SD)	N	Mean (SD) Change
SAPS-PD				
OLE Baseline	454	9.2 (6.8)		
Week 4	390	7.1 (6.2)	389	−1.8 (5.5)
SAPS-H + D				
OLE Baseline	454	10.3 (8.0)		
Week 4	390	7.8 (6.9)	389	−2.1 (6.2)
SAPS-H				
OLE Baseline	454	6.8 (5.0)		
Week 4	392	5.4 (4.9)	391	−1.2 (4.4)
SAPS-D				
OLE Baseline	455	3.4 (4.4)		
Week 4	390	2.4 (3.4)	390	−0.9 (3.2)
CGI-S				
OLE Baseline	456	3.3 (1.3)		
Week 4	424	2.8 (1.2)	423	−0.4 (1.0)
Caregiver Burden				
OLE Baseline	453	28.2 (17.3)		
Week 4	414	28.0 (17.4)	412	0 (7.6)

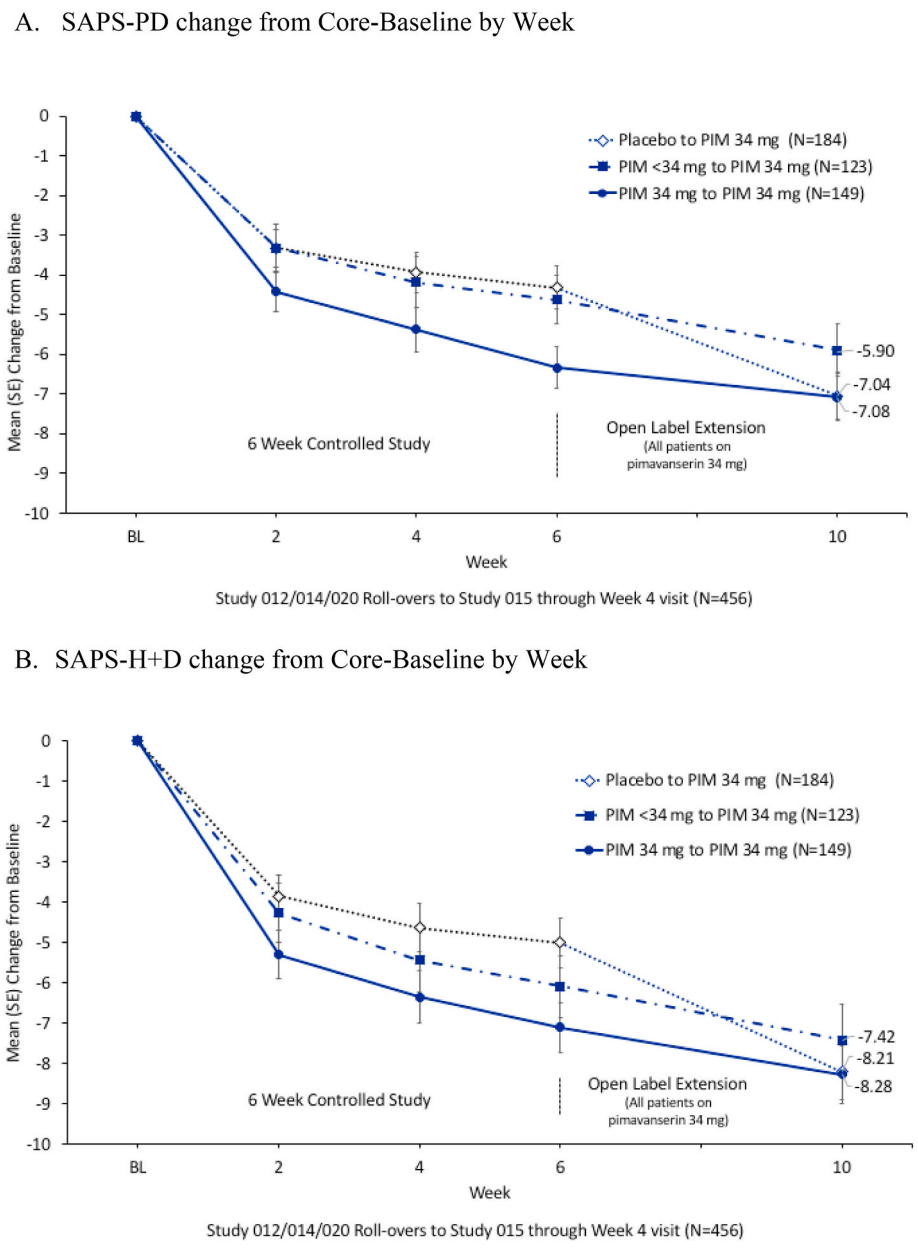


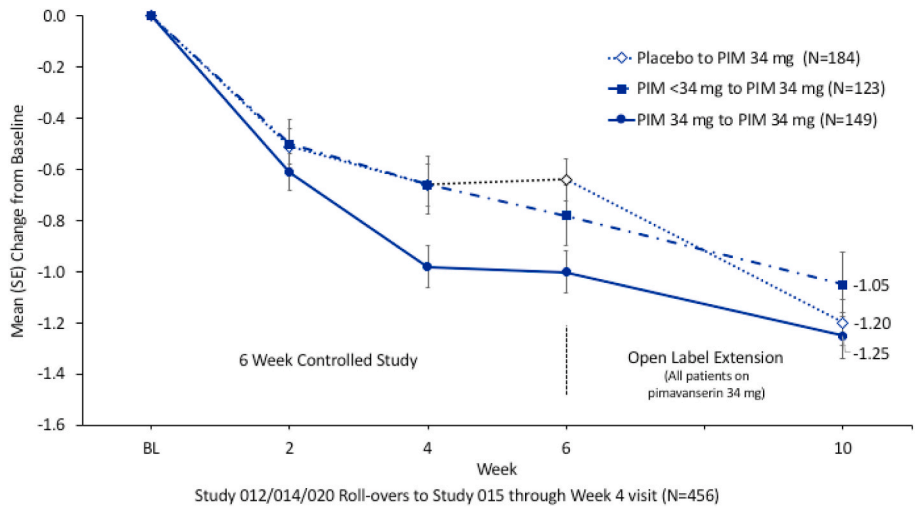
Fig. 2. Mean (SE) change from Core baseline in SAPS-PD (Panel A) and SAPS-H + D (Panel B); 6 weeks placebo controlled (Core) + 4 weeks open label extension.

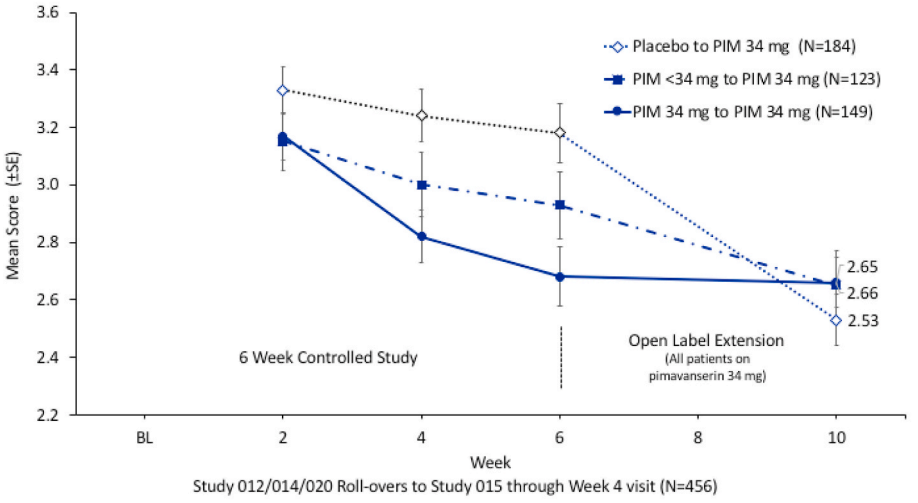
experienced a change (improvement) from OLE baseline of −2.1 (4.2) in the mean SAPS-H score at OLE Week 4. Patients previously dosed with pimavanserin 34 mg experienced a change from OLE baseline of −0.4 (4.6). Patients previously dosed with placebo had a change from OLE baseline in the mean SAPS-D score at OLE Week 4 of −1.4 (3.3), and patients previously dosed with pimavanserin 34 mg had a change from OLE baseline of −0.8 (3.0). Overall, improvement in the SAPS-H and SAPS-D scores that was observed during the Core double-blind treatment persisted through OLE Week 4 of the OLE, while scores improved among patients switched from placebo to pimavanserin.

For all patients, the mean (SD) CGI-S score at OLE baseline was 3.3 (1.3) denoting mild symptoms. The mean change from OLE baseline to OLE Week 4 for the CGI-S was −0.4 (1.0) indicating that the improvement seen in Core studies over baseline was maintained (Table 1 and Fig. 3A). For CGI-I, the mean (SD) score at Week 2 and Week 4 of the OLE was 2.8 (1.3) and 2.6 (1.2), respectively (Fig. 3B). The proportion of CGI-I responders (very much improved or much improved) was 42.5% at Week 2 and 51.4% at Week 4. The mean CBS score remained stable, with a mean (SD) change from OLE baseline through Week 4 of the OLE of 0.0 (7.6) (Fig. 3C), and the proportion of caregivers with little or no burden on the CBS of 39.3% at Week 4 of the OLE.

3.2. Tolerability

Following 4 weeks of OLE treatment, AEs were reported by 215 (46.8%) patients (Table 2). Twenty-seven (5.9%) patients had an AE that resulted in discontinuation of the study or study drug. The majority of AEs were of mild or moderate intensity, but 7 (1.5%) patients had serious AEs with the most common being pneumonia 0.4%, and presyncope, syncope, acute respiratory failure, chronic obstructive pulmonary disease, pulmonary embolism and deep vein thrombosis all at 0.2%. The most common AEs were fall (5.9%), hallucination (3.7%), urinary tract infection (2.8%), insomnia (2.4%), and peripheral edema (2.2%) (Table 2). No clinically relevant changes were observed for serum chemistry, hematology or urinalysis or for ECG findings.





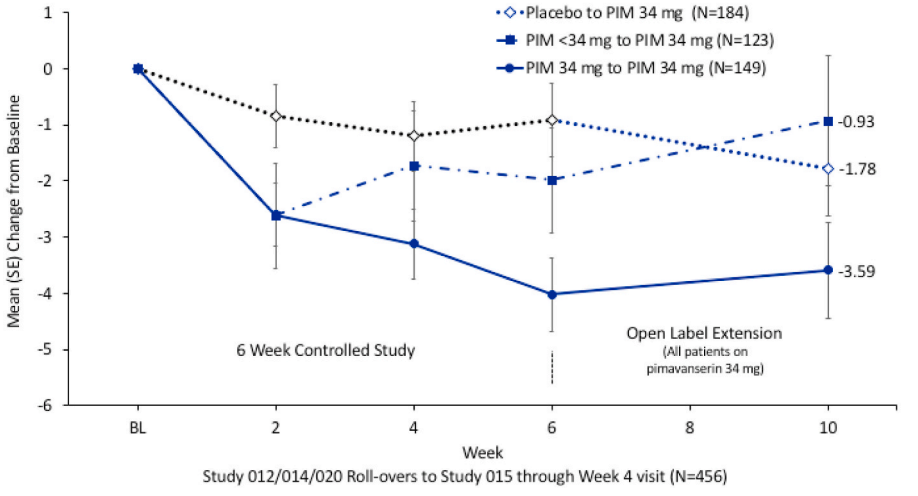


Fig. 3. Mean (SE) change from Core baseline for CGI-S (A), CGI-I (B), and Caregiver Burden Score (C).

4. Discussion

This single arm OLE study demonstrated that the effects of pimavanserin 34 mg once daily on psychotic symptoms seen in placebo controlled studies was maintained for an additional 4 weeks in >400 patients with PDP worldwide. Among those who switched from placebo to 34 mg pimavanserin in the OLE study, mean scores improved to the same level as the 34 mg pimavanserin group over the next 4 weeks of the OLE study. Those from <34 mg groups (8.5 mg and 17 mg) demonstrated a more modest improvement in the SAPS-PD score when

Table 2
Summary of adverse events, including by most frequently reported, occurring in ≥2% of patients in the first 4 weeks of the open-label study grouped by placebo controlled (Core) study treatment group (Safety analysis set).

		Number (%) of Patients					
		Adverse Events Occurring During First 4 Weeks of Open Label Extension by Core Study Treatment Group					
	Adverse Events Occurring in Core Studies (N = 456)	Placebo (n = 184)	8.5 mg (n = 96)	17 mg (n = 26)	34 mg (n = 150)	All PIM (n = 272)	All Patients (N = 459)
≥1 AE	279 (61.2)	97 (52.7)	37 (38.5)	11 (42.3)	69 (46.0)	117 (43.0)	215 (46.8)
≥1 Drug-Related AE	113 (24.8)	38 (20.7)	22 (22.9)	3 (11.5)	24 (16.0)	49 (18.0)	87 (19.0)
≥1 SAE	7 (1.5)	4 (2.2)	1 (1.0)	1 (3.8)	0	2 (0.7)	7 (1.5)
AE Leading to Study Termination or Dose Discontinuation	0 (0.0)	12 (6.5)	7 (7.3)	0	8 (5.3)	15 (5.5)	27 (5.9)
Fall	37 (8.1)	11 (6.0)	4 (4.2)	1 (3.8)	11 (7.3)	16 (5.9)	27 (5.9)
Hallucination	7 (1.5)	7 (3.8)	5 (5.2)	1 (3.8)	4 (2.7)	10 (3.7)	17 (3.7)
Urinary tract infection	25 (5.5)	9 (4.9)	0 (0.0)	0 (0.0)	4 (2.7)	4 (1.5)	13 (2.8)
Insomnia	11 (2.4)	4 (2.2)	3 (3.1)	0 (0.0)	4 (2.7)	7 (2.6)	11 (2.4)
Peripheral edema	18 (3.9)	6 (3.3)	1 (1.0)	0 (0.0)	3 (2.0)	4 (1.5)	10 (2.2)

switched to 34 mg. A durable response with 34 mg pimavanserin was observed for SAPS-PD and SAPS H + D scores at OLE Week 4 that was maintained among patients who entered the OLE study from the 6-week pimavanserin 34 mg arm in the Core blinded trials.

In this OLE study, the mean change in SAPS-PD at OLE Week 4 was −2.9 points among patients on placebo in the double-blind studies; this was comparable to the treatment effect observed for pimavanserin 34 mg over placebo in 6-week Core blinded studies of pimavanserin [19,26]. The slope of the curves for pimavanserin <34 mg–34 mg and pimavanserin 34 mg–34 mg groups during the OLE are similar, reflecting continuing improvement in SAPS-PD from the Core Studies into the OLE. The difference in mean scores between these 2 active treatment groups likely reflects the lower dose of 8.5 or 17 mg pimavanserin used in the Core studies. The more marked decrease in the placebo to pimavanserin 34 mg group during the OLE extension reflects the effects of active drug treatment during the OLE. The SAPS-PD scale retains the reliability, sensitivity to change, and effect size of the larger SAPS-H + D, with reduced score variability. Regression analyses using the SAPS-PD scale indicated that a clinically meaningful change in the CGI-I scale was associated with a 2.33-point change in the SAPS-PD score [24]. Thus, the results obtained in this OLE are consistent with a clinically meaningful improvement. Of interest, during the OLE, some baseline patients were less severely affected regarding SAPS-PD and SAPS-H + D because of previous treatment with pimavanserin.

Prior to the availability of pimavanserin, treatment approaches for PDP have included a reduction or simplification of anti-Parkinson's medications (a strategy that may worsen motor symptoms and increase OFF time), discontinuation of non-essential CNS-active drugs, addition of cholinesterase inhibitors in cognitively impaired patients, and the addition of antipsychotics with limited parkinsonian side effects (quetiapine or clozapine medication) [27,28]. At least 30% of PD patients [29], and 50% of PDP patients will start antipsychotic drugs over an extended period [30]. However, a significant increase in mortality is reported with the use of other antipsychotics in patients with PDP [14], necessitating caution with their use [14]. In addition, with the exception of clozapine and pimavanserin, objective evidence is lacking for efficacy to improve psychotic symptoms with the use of other antipsychotics in PDP patients, and clozapine requires regular blood monitoring due to the risk of agranulocytosis [11].

Previous studies have shown that the caregiver burden increases as symptoms of psychosis become more severe in patients with PDP [31] and caregiver burden is worse in PD patients with psychosis compared with those without [32]. Among PD patients, psychosis was one of the primary determinants of caregiver burden [33]. Results from this study show that over the first 4 weeks of this study, the CBS score remained stable with no worsening.

Limitations of this study were its single arm OL design and the lack of a comparison group. Only descriptive statistics were performed, and direct comparisons between change from OLE baseline to endpoint between groups were not possible for those previously on pimavanserin versus placebo. Another limitation is selection bias that could have resulted from the non-random selection of patients for the OLE. These results provide the first efficacy data from extended treatment with pimavanserin in a population of patients with PDP, and patients remained blinded to treatment allocation in the Core studies during the 4-week OLE. The results substantiate that the treatment response as measured by the SAPS-PD during Core double-blind, randomized studies with pimavanserin 34 mg is maintained during continued OLE treatment for a total of 10 weeks.

Overall, the durability of response and sustained improvement in the severity of psychotic symptoms seen at the end of the Core studies was maintained as assessed with the SAPS-PD at Week 4 of the OLE. Improvements also were seen in CBS and CGI scales over the same time period suggesting that the effects on psychosis were clinically meaningful to caregivers as well as clinicians. Patients initially randomized to placebo and switched to pimavanserin for the OLE showed improvement that was comparable to patients receiving pimavanserin for the entire 10 weeks. In this study, the evaluation of >400 patients and the inclusion of enrolling sites worldwide provides the largest assessment of treatment of PDP to date. These findings support the efficacy of pimavanserin in treating hallucinations and delusions associated with PDP, and provide additional efficacy data up to 10 weeks.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.04.012.

Documentation of author roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.
SI: 1B, 1C, 2C, 3A, 3B.
CB, DK: 1A, 1B, 2A, 3B, 3C.

JN, GD, I-YL, SS: 1C, 2C, 3A, 3B.
BC: 1A, 2A, 2B, 2C, 3B.
HHF, TVI, J-PA, JJF, VA: 2C, 3B.

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CB: Has received grants and personal fees from ACADIA and Lundbeck, personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GlaxoSmithKline, and Pfizer.

At the time of this study, I-YL, GD, VA, JN, and SS were employees of ACADIA Pharmaceuticals Inc.

DK: Has been an investigator in clinical trials sponsored by Teva, Impax, Acadia, Pharma2b, UCB, Biotie, Lundbeck, Pfizer, served on advisory boards sponsored by Impax, Accorda, UCB, Teva, Acadia, USworld Med, Intec, and is on the following Speakers' Bureau: Teva, Lundbeck, Acadia, Impax, Adamas, UCB, USworld Meds.

SI: Honoraria for CME, consultant, research grants, and/or promotional speaker on behalf of: Abbvie, Acadia, Acorda, Adamas, Addex, Allergan, Amarantus, Axovant, Biogen, Britannia, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Intec Pharma, Kyowa, Lundbeck, Michael J. Fox Foundation, Neurocrine, Neuroderm, Parkinson Study Group, Pharma2B, Roche, Sanofi, Sunovion, Teva, UCB, US World Meds, Zambon.

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