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NUPLAZID® (pimavanserin): Clinical Trial and Post-Marketing Mortality Events in Psychosis in Parkinson's Disease

This letter is provided in response to your specific request for information regarding clinical trial and post-marketing mortality events in psychosis in Parkinson's disease (PD).

Relevant Labeling Information
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.[1]

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia who experience psychosis unless their hallucinations and delusions are related to Parkinson's disease.**

Summary

- In the **6-week, placebo-controlled trials**, 3 deaths occurred in the pimavanserin 34 mg groups (n=202) and 1 death occurred in the placebo groups (n=232) during treatment or within 30 days of the last dose.[2]
- In the **open-label extension study** of long-term treatment with pimavanserin 34 mg daily, 59 (12.9%) deaths reported by investigators occurred during treatment or within 30 days of the last dose of pimavanserin.[3]
- The mortality rate observed in **post-marketing assessments** of patients receiving pimavanserin has remained consistent over time. The estimated overall cumulative reported post-marketing mortality rate is 15.40/100 patient-years.[4]
    - Overall, the reported causes of death reflect common comorbidities and underlying conditions of an elderly, frail PD population treated for psychosis.[4]
- Mortality data with pimavanserin are available from **several retrospective studies**, the interpretation of which is limited by their observational nature and because most, but not all, did not study mortality as a primary objective.
- Acadia continues to monitor the safety profile of NUPLAZID (pimavanserin), and the benefit/risk profile has not changed since its launch in 2016.

Clinical Development Experience

The safety and efficacy of pimavanserin in participants with Parkinson's disease psychosis (PDP) were evaluated in 4 short-term placebo-controlled trials and 2 long-term open-label studies comprised of over 1,200 participants receiving pimavanserin (including 616 participants with PDP and over 250 participants treated for >1 year).[2]

Placebo-controlled Trials

In the 6-week, placebo-controlled trials, 3 deaths occurred in the pimavanserin 34 mg groups (n=202) and 1 death occurred in the placebo groups (n=232) during treatment or within 30 days of the last dose (**Table 1**).[2]

Table 1. Crude Mortality Rate in 6-week ACP-103-012 (Study 012; Phase 2b/3) and ACP-103-020 (Study 020; Phase 3)[2]

	Placebo (n=231)	Pimavanserin 34 mg (n=202)
PDP placebo-controlled trials at approval		
Number of deaths*	1	3
Crude death rate	0.4%	1.5%

**Participants who died during treatment or within 30 days after the last dose of study drug.*
Abbreviation: PDP=Parkinson's disease psychosis.

Open-label Extension Study

Participants who completed the 6-week placebo-controlled trials were eligible to enroll in an open-label extension (OLE) study and receive pimavanserin 34 mg.[3] Of the 459 participants treated in this OLE study (mean age 71.2 years), the median duration of treatment was 454 days, with the longest duration being approximately 9 years. Over the entire study period (approximately 11 years) 61 participants died, 59 (12.9%) during treatment or within 30 days of the last dose of the study drug; 43 deaths occurred at ≥1 year of treatment. The observed mortality rate was 6.45 per 100 patient years of exposure. **Table 2** describes the most common adverse events (AEs) with fatal outcomes reported.

Table 2. Most Common Adverse Events with Fatal Outcomes in the OLE[3]

Adverse Event		Percentage of Participants (n=459)
System	Cardiac disorders	3.7
	Respiratory disorders	2.6
Preferred term	Pneumonia	1.1
	Parkinson's disease	1.1
	Acute respiratory failure	0.9
	Acute myocardial infarction	0.7
	Dementia	0.7
	Cardiac arrest	0.7

Abbreviations: AE=adverse event; OLE=open-label extension.

Post-marketing Mortality Experience

Acadia continues to monitor all reported fatal cases.[4] The estimated overall cumulative reported mortality rate is 15.40/100 patient-years (**Table 3**). A review of cases with fatal outcomes did not indicate a particular etiology that would suggest a causal relationship to pimavanserin. Overall, the reported causes of death reflect common comorbidities and underlying conditions of an elderly, frail PD population treated for psychosis such as PD, disease progression, dementia, pneumonias, respiratory and cardiac events.

Table 3. Cumulative Post-marketing Mortality Rate per 100 Patient-years[4]

Time Period	Deaths	Minimum Patients[a] Exposed (Patient-years)	Mortality Rate/100 Patient-years	Exact 95% CI of Mortality Rate/100 Patient-years
Launch to April 28, 2021 (cumulative)	4687[b]	41,218 (30,426)	15.40	(14.97–15.85)

[a]Based on unique patients tracked through Acadia's reimbursement HUB and specialty pharmacy distribution channel plus a limited number of long-term care pharmacy partners.
[b]Case processing was completed on May 03, 2021. Cumulative death count is through data retrieval date of May 10, 2021.
Abbreviation: CI=confidence interval.

NUPLAZID is distributed via a specialty pharmacy model, as opposed to a retail pharmacy. This model allows for more frequent contact with each patient or caregiver by staff from Specialty Pharmacies, as well as the reimbursement HUB and a limited number of long-term care pharmacy partners. These frequent contacts generate solicited AE reports but enable Acadia to collect information on the safety of pimavanserin much more completely compared to retail distribution. During the last reporting period, 96% (5443/5652) were considered solicited resulting from the described outgoing contacts.[4] Any AEs mentioned during these regular calls are reported to the United States Food and Drug Administration (FDA) as part of Acadia's pharmacovigilance process.[5]

On September 20, 2018, the FDA released a statement which described their recently completed review of all post-marketing reports of deaths and serious AEs reported with the use of NUPLAZID which highlighted: no new or unexpected safety findings, NUPLAZID and other antipsychotics have a Boxed Warning regarding the increased risk of death in elderly patients with dementia-related psychosis associated with the use of these drugs, reports of death are consistent with PDP patients, as they "have a higher mortality (death) rate due to their older age, advanced Parkinson's disease, and other medical conditions," "the drug's benefits outweigh its risks for patients with hallucinations and delusions of Parkinson's disease psychosis," and a reminder of the warning in the NUPLAZID prescribing information around coadministration with drugs that increase the QT interval.[6]

Available Literature Regarding Mortality Rate in Parkinson's Disease Psychosis

Retrospective cohort analyses have examined the mortality rate of patients with PD vs PDP, the mortality rate associated with antipsychotics in PD, and the mortality rate associated with concomitant antipsychotic use vs monotherapy in individuals with PDP.[7-10] Direct comparisons cannot be made between studies. An overview of retrospective studies evaluating mortality rate in PDP is shown in **Table 4**.

Table 4. Retrospective Studies Evaluating Mortality Rate in Parkinson's Disease Psychosis

Study	Design	Active Comparator	Number of Patients	Primary Objective
Wetmore et al.[8]	Retrospective Medicare data extraction of PDP patients (2007–2015)	No	PDP: 1699 Non-PDP: 6796	Evaluate the association of death in patients with PDP vs direct matched PD patients without psychosis

Study	Design	Active Comparator	Number of Patients	Primary Objective
Weintraub et al.[7]	Medicare claims database study of PD and PDP patients	No	PD: 68,821 PDP: 38,072	Age-standardized mortality in PDP vs PD with no psychosis
Weintraub et al.[9]	Retrospective matched cohort study of PD patients	No	7,877 in each cohort: patients who initiated AP therapy and those who did not	Examine the risk of mortality associated with AP use in patients with PD
Ballard et al.[10]	Post-hoc analysis from multicenter, OLE study of PIM in patients with PDP	No	PIM + APs: 66 PIM alone: 357	Risk of mortality in patients with PIM + APs vs PIM alone

Abbreviations: AP=antipsychotic; PD=Parkinson's disease; PDP=Parkinson's disease psychosis; PIM=pimavanserin.

Wetmore et al.

A retrospective study was published by Wetmore et al. using Medicare data (20% random sample; 2007–2015) which evaluated the association of death in patients with PDP.[8] To compare the association of PDP with death, PDP patients were direct matched to PD patients without psychosis. The matched patients were followed until death, admission to custodial care, or end of study period. First, the cumulative incidence of death was significantly different between the matched groups (p<0.0001). Within 1 year of PDP diagnosis, 16.4% of PDP patients experienced death vs 13.8% of patients with PD only. Secondly, PDP was associated with a greater risk of death (hazard ratio [HR]: 1.34, confidence interval (CI) [1.23–1.45], p<0.0001) using a Cox model regression analysis. Factors such as older age were associated with death, as would be expected, but female sex was associated with a lower HR for death (0.76, 0.70–0.82, p<0.0001). In conclusion, PD patients with incident psychosis were associated with nearly one-third increased risk of death.

Weintraub et al: Medicare Claims Database

Weintraub et al. presented data on a medical claims database study.[7] Patients identified as having a diagnosis of PD (n=68,821) and those identified as having a diagnosis of PDP (n=38,072) were evaluated. Age-standardized mortality in the PDP cohort was significantly higher than in those with PD and no psychosis (28.2 vs 7.3 deaths per 100 patient-years; p<0.0001).

Weintraub et al: Veterans' Health Administration Database

Weintraub et al. published a retrospective matched-cohort study which examined the risk of mortality associated with antipsychotic use in a cohort of patients with PD.[9] The rates of 180-day mortality were compared in matching cohorts of 7,877 patients in each of two groups: patients initiating antipsychotic therapy and patients who did not initiate therapy. There was an increased risk of mortality in patients taking antipsychotics vs those not taking antipsychotics (HR 2.35, 95% CI 2.08–2.66, p<0.001). The mortality rates per 100 person-years in those patients taking antipsychotics are described in **Table 5**.

Table 5. Unadjusted Mortality Rates by Antipsychotic Exposure[9]

Antipsychotic	No. Patients Died/ Total (%)	Total Person-years	Mortality Rate per 100 Person-years (95% CI)
Haloperidol	60/282 (21.3)	122.5	49.0 (37.4–63.0)
Other typical AP	20/140 (14.3)	64.0	31.3 (19.1–48.3)
Olanzapine	113/837 (13.5)	386.3	29.3 (24.1–35.2)
Quetiapine	462/5270 (8.8)	2488.8	18.6 (16.9–20.3)
Risperidone	164/1155 (14.2)	529.5	31.0 (26.4–36.1)
Other atypical AP	13/193 (6.7)	91.3	14.2 (7.6–24.3)

Abbreviations: AP=antipsychotic; CI=confidence interval.

Ballard et al.

In a post-hoc analysis of data from a multicenter, OLE study of pimavanserin (n=423), patients with PDP on concomitant antipsychotics (n=66) were found to be at increased risk for mortality vs pimavanserin alone (n=357): incidence rate ratio (IRR) (4.20, 95% CI 2.13–7.96).[10]

Retrospective Studies of Pimavanserin Mortality in Patients with PDP

An overview of retrospective studies evaluating mortality in patients with PDP receiving pimavanserin is shown in **Table 6**. The evaluation of mortality with pimavanserin in these studies is limited by their observational nature and because most, but not all, did not study mortality as a primary objective. In addition, the use of the FDA AE reporting system (FAERS) in Brown et al. is limited by potential confounders with the use of this database including duplicative reports, lack of certainty establishing causation, and lack of verification of reports. The methodology of each study should be reviewed and considered when interpreting the respective results.

Table 6. Retrospective Studies in Pimavanserin Mortality in Patients with PDP

Study	Design	Active Comparator	Number of Patients	Primary Objective
Layton et al.[11]*	Retrospective new-user cohort study of PDP patients in Medicare; April 2016–Dec 2019	Yes	Matched PIM initiators: 2,891 Matched atypical AP initiators: 2,891	All-cause mortality with PIM vs atypical APs
Rao et al.[12]*	Retrospective new user cohort study of PDP patients aged ≥65 years in Medicare; April 2016–Dec 2021	Yes	Matched PIM initiators: 4,381 Matched atypical AP initiators: 4,381	All-cause mortality with PIM vs atypical APs
Longardner et al.[13]	Retrospective EMR data extraction of PDP patients (UCSD Health System); April 2016–April 2019	Yes	Untreated controls: 66 PIM: 34 Quetiapine: 147 Both agents: 68	Review of clinical, iatrogenic and demographic factors associated with increased mortality in PDP patients
Alipour-Haris et al.[14]	Retrospective new user cohort study of PDP patients aged ≥65 years in Medicare; May 2016–Dec 2018	Yes	PIM: 844 Quetiapine: 2,505	All-cause hospitalization and mortality with PIM vs quetiapine
Nguyen et al.[15]	Retrospective new-user cohort study of PD patients aged ≥40 years in Optum; May 2016–Mar 2021	Yes	PIM: 775 Preferred DRB atypical AP: 4,563	All-cause mortality with PIM vs preferred or non-

Study	Design	Active Comparator	Number of Patients	Primary Objective
			Non-preferred DRB atypical AP: 1,297	preferred DRB atypical APs
Mosholder et al.[16]	Retrospective new-user cohort study of PD patients in Medicare; April 2016–March 2019	Yes	PIM: 3,227 Atypical APs (weighted): 3,251	All-cause mortality with PIM vs atypical APs
Hwang et al.[17]	Retrospective study of LTC residents aged ≥65 years with PD (Minimum Data Set 3.0); Nov 2015–Dec 2018	No	PIM users (weighted): 2,089 Nonusers (weighted): 18,248	Risk of hospitalization and death up to 1 year
Brown et al.[18]	Retrospective analysis of AE case reports submitted to the FAERS; 2016–Q3/2019	Yes	Not applicable	Proportional reporting ratio lower 95% confidence limit for all-cause death in PIM-treated patients
Horn et al.[19]	Retrospective cohort study of patients with PDP or DLB (PDMDC)	Yes	PIM: 45 Quetiapine: 47	Time to discontinuation of PIM or quetiapine
Gupta et al.[20]	Retrospective chart review of PDP patients (KUMC); June 2016–Sept 2018	No	PIM: 107	Safety and efficacy of PIM in PDP patients
Sellers et al.[21]	Retrospective chart review of PDP patients (VUMC); May 2016–July 2018	No	71/91 PD 11/91 DLB	Clinical experience with PIM
Moreno et al.[22]	Retrospective study of PD patients (UCSD Health System); April 2016–April 2018	Yes	PIM: 113 Quetiapine: 505 Both agents: 58	Experience with PIM for treatment of PDP
Mahajan et al.[23]	Retrospective chart review (Henry Ford PD and Movement Disorders Clinic); up to July 2017	No	PDP: 16 DLB: 1	Descriptive analysis of efficacy, tolerability, and clinical outcomes

**Rao et al.[12] was a follow-up study to the analysis conducted by Layton et al. [11]*
Abbreviations: AE=adverse event; AP=antipsychotic; CI=confidence interval; DLB=dementia with Lewy bodies; DRB=dopamine receptor blocking; EMR=electronic medical record; FAERS=US Food & Drug Administration's Adverse Event Reporting System; HR=hazard ratio; KUMC=University of Kansas Medical Center; LTC=long-term care; PD=Parkinson's disease; PDMDC=University of Pennsylvania Parkinson's Disease and Movement Disorders Center; PIM=pimavanserin; UCSD=University of California San Diego; VUMC=Vanderbilt University Medical Center.

Layton et al.

A retrospective new-user cohort study was conducted in Medicare beneficiaries (100% sample) with PD-related psychosis initiating pimavanserin (n=2,892) or comparator antipsychotics (n=19,083) from April 1, 2016 to December 31, 2019 to assess all-cause mortality.[11] Patients were excluded if they had a diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or major depressive disorder with symptoms of psychosis. Comparator antipsychotics were clozapine, quetiapine, risperidone, olanzapine, aripiprazole, and brexpiprazole. Follow-up for each patient started at the index date and ended on the date of death or censoring at the earliest occurrence of one of the following events: end of study period, disenrollment from Medicare, discontinuation of the index study drug, or use of a different study medication.

Propensity score matching was used to balance pimavanserin initiators (n=2,891) and comparator initiators (n=2,891) on treatment group characteristics.

After propensity score matching, the two groups were well balanced on all covariates, including demographic characteristics, psychiatric diagnoses, comorbidities, comedication use, and healthcare utilization.[11] All-cause mortality in the primary PDP cohort was 22% lower in patients treated with pimavanserin vs other atypical antipsychotics. No difference in HR was seen in the matched long-term care/skilled nursing facility (LTC/SNF) subcohort (**Table 7**). Of the matched comparator initiators, 85.7% were quetiapine users. In sensitivity analysis not requiring a recorded psychosis diagnosis, the HR was 0.76 (95% CI, 0.68–0.85). In sensitivity analysis with extended follow-up after treatment discontinuation, the HR was 0.78 (95% CI, 0.70–0.86).

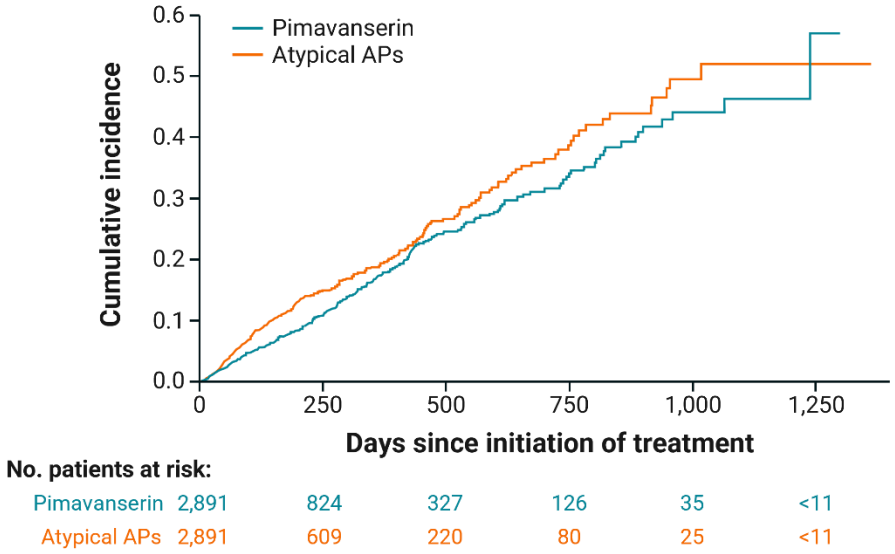
Table 7. Layton et al: Mortality in Patients with PDP Who Initiated Treatment with Atypical Antipsychotics[11]

Study Cohort and Treatment Group	Patients	Events	Person-Years	IR per 100 Person-Years (95% CI)	HR (95% CI)
Matched Primary PDP cohort					
Pimavanserin	2,891	317	1,674.70	18.93 (16.90–21.13)	0.78 (0.67–0.91)
Comparator	2,891	336	1,395.14	24.08 (21.58–26.80)	–
Matched LTC/SNF subcohort					
Pimavanserin	652	110	332.81	33.05 (27.16–39.84)	0.78 (0.60–1.01)
Comparator	652	125	290.31	43.06 (35.84–51.30)	–

Abbreviations: CI=confidence interval; HR=hazard ratio; IR=incidence rate; LTC=long-term care; PDP=Parkinson's disease psychosis; SNF=skilled nursing facility.

Cumulative incidence curves for the matched cohort demonstrated generally reduced risks of mortality in the pimavanserin group throughout follow-up (**Figure 1**); however, after 2 years, small sample sizes limit interpretation.[11]

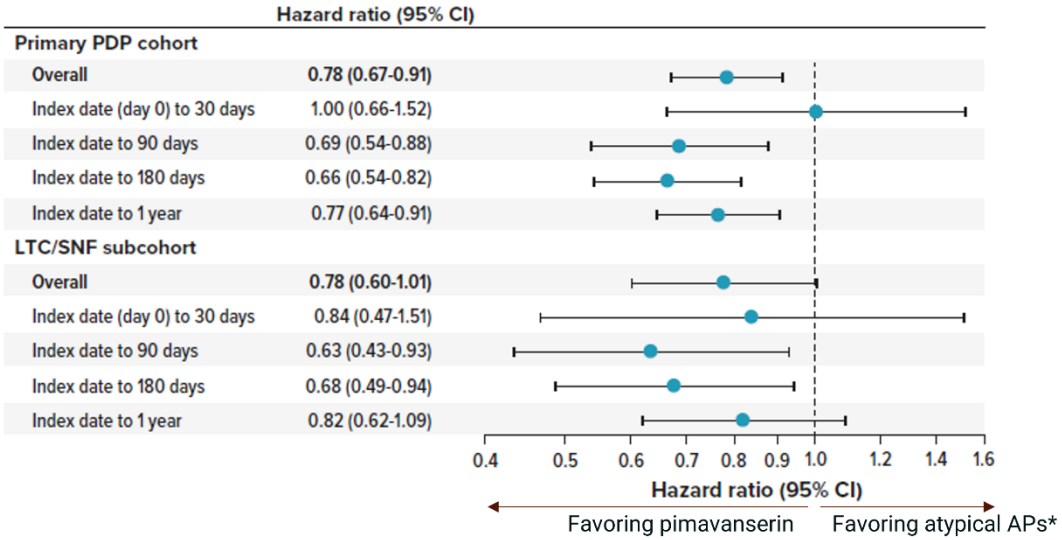
Figure 1. Layton et al: Cumulative Incidence of All-cause Mortality in the Matched Primary PDP Cohort[11]



Abbreviations: AP=antipsychotic; PDP=Parkinson's disease psychosis.

When evaluated over time, no difference was seen in the first 30 days after treatment initiation in the matched primary PDP cohort, and the largest differences in mortality risk between treatment groups were observed in the first 180 days of follow-up (**Figure 2**).[11] In the matched LTC/SNF subcohort, no difference was seen in the first 30 days after treatment initiation or in the analysis from index date to 1 year.

Figure 2. Layton et al: Matched HRs of All-cause Mortality, Overall and in Specified Follow-up Periods[11]



Abbreviations: AP=antipsychotic; CI=confidence interval; LTC=long-term care; PDP=Parkinson's disease psychosis; SNF=skilled nursing facility.

Rao et al.

A retrospective new-user cohort study was conducted in Medicare beneficiaries (100% sample) with PD-related psychosis aged ≥65 years initiating pimavanserin (n=4,834) or comparator atypical antipsychotics (n=28,042) from April 1, 2016 to December 31, 2021 to assess all-cause mortality.[12] This was a follow up study to a previous analysis by Layton et al. with similar methodology,[11] with 2 additional years of data through the COVID-19 pandemic. Comparator antipsychotics were aripiprazole, brexpiprazole, clozapine, lumateperone, olanzapine, quetiapine, or risperidone. Among comparator atypical antipsychotic initiators, 67.2% initiated quetiapine. Propensity score matching was used to balance pimavanserin initiators (n=4,381) and comparator initiators (n=4,381) on treatment group characteristics.[12]

After propensity score matching, patient characteristics were well balanced between the two groups. All-cause mortality in the primary PDP cohort was 24% lower in patients treated with pimavanserin vs other atypical antipsychotics (HR 0.76, 95% CI 0.68–0.85). No difference in HR was seen in the matched LTC/SNF subcohort (**Table 8**). Results were consistent across sensitivity analyses based on not requiring psychosis diagnosis, disregarding treatment discontinuation, quetiapine and non-quetiapine comparator groups, requiring treatment for PD, and former use of other antipsychotics.[12]

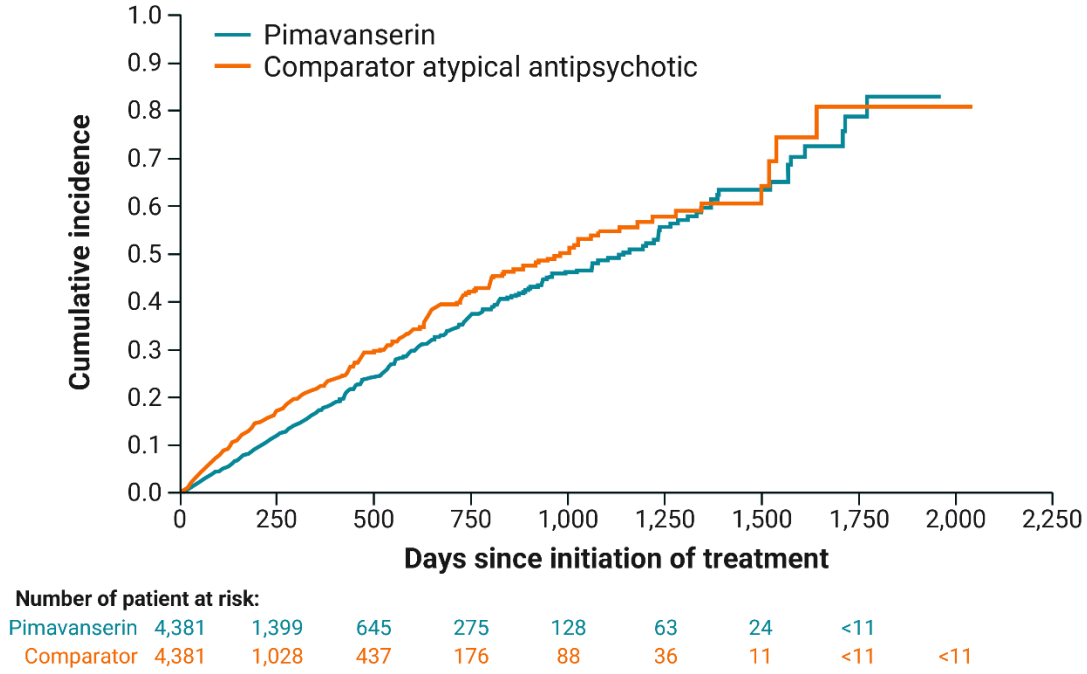
Table 8. Rao et al: Mortality in Patients with PDP Who Initiated Treatment with Atypical Antipsychotics[12]

Study Cohort and Treatment Group	Patients	Events	Person-Years	IR per 100 Person-Years (95% CI)	HR (95% CI)
Matched Primary PDP cohort					
Pimavanserin	4,381	603	2,925.1	20.61 (19.00-22.33)	0.76 (0.68-0.85)
Comparator	4,381	638	2,367.2	26.95 (24.90-29.13)	–
Matched LTC/SNF subcohort					
Pimavanserin	905	182	504.8	36.06 (31.01-41.69)	0.90 (0.74-1.10)
Comparator	905	194	487.1	39.83 (34.42-45.85)	–

Abbreviations: CI=confidence interval; HR=hazard ratio; IR=incidence rate; LTC=long-term care; PDP=Parkinson's disease psychosis; SNF=skilled nursing facility.

Cumulative incidence curves for the matched cohort demonstrated generally reduced risks of mortality in the pimavanserin group throughout follow-up (**Figure 3**); however, after approximately 3 years, small sample sizes limit interpretation.[12]

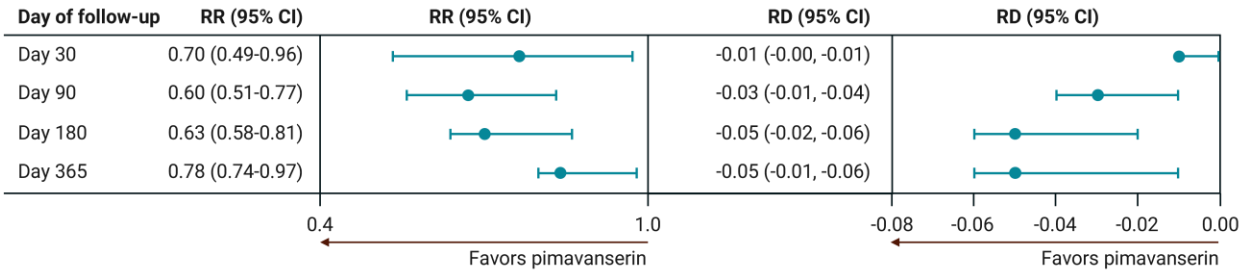
Figure 3. Rao et al: Cumulative Incidence of All-cause Mortality in the Matched Primary PDP Cohort[12]



Abbreviation: PDP=Parkinson's disease psychosis.

Time period–specific relative risk (RR) and absolute risk difference (RD) estimates demonstrated pimavanserin to be associated with a sustained lower risk of mortality; on the relative scale (RR), the largest benefit of pimavanserin was seen at day 90 and day 180; on the absolute scale (RD), the largest benefit of pimavanserin was seen from day 180 through day 365 (**Figure 4**). In the matched LTC/SNF subcohort, no difference was seen in any time-period specific analysis.[12]

Figure 4. Rao et al. Relative Risk and Risk Difference of All-cause Mortality in the Matched Primary PDP Cohort[12]



Abbreviations: CI=confidence interval; PDP=Parkinson's disease psychosis; RD=absolute risk difference; RR=relative risk.

Longardner et al.

A retrospective electronic medical record data extraction by the University of California San Diego (UCSD) investigated clinical, iatrogenic and demographic factors associated with increased mortality in PDP patients.[13] Mortality and clinical characteristics during the study period were compared between untreated patients and those receiving pimavanserin, quetiapine, or both agents. Electronic medical record data extraction included clinically diagnosed PD patients seen in the UCSD Health System between April 29, 2016, and April 29, 2019. Psychosis was diagnosed based on ICD-10 code and antipsychotic prescription. For patients prescribed antipsychotics, individual chart review was performed to ascertain that the medication was prescribed for treatment of psychosis (i.e., rather than for sleep or mood). Patients with primary psychiatric diagnoses or atypical parkinsonism were excluded, as well as those that received quetiapine only during an inpatient setting.

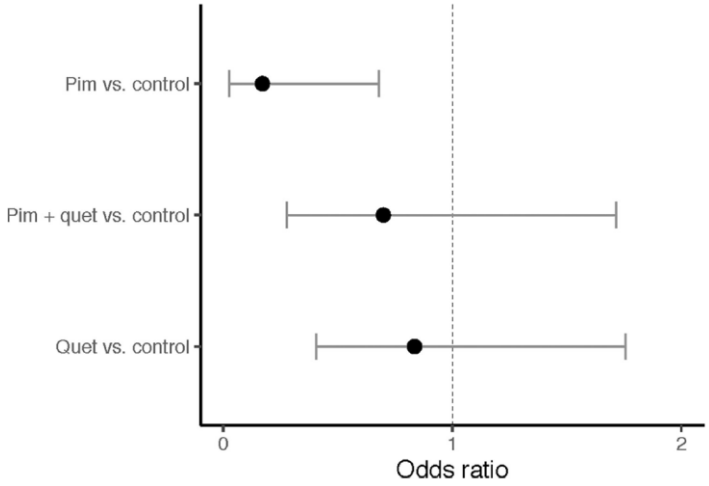
The risk of all-cause mortality was lower in patients treated with pimavanserin vs untreated patients. Compared to the untreated group, there were no differences in adjusted mortality for patients receiving quetiapine or those on combination therapy (**Table 9; Figure 5**).[13]

Table 9. Longardner et al: Mortality Outcomes vs Untreated Patients[13]

	PDP Medication		
	Pimavanserin	**Quetiapine**	**Pimavanserin + Quetiapine**
Sample size, n	34	147	68
Odds ratio (95% CI)[a]	0.171 (0.025–0.676)	0.833 (0.405–1.756)	0.697 (0.277–1.716)
p-value	0.026	0.624	0.433

[a]*Adjusted for age, sex, levodopa equivalent daily dose, and dementia.*
Abbreviations: CI=confidence interval; PDP=Parkinson's disease psychosis.

Figure 5. Longardner et al: Mortality Odds Ratios for Treated PDP Patients vs Untreated PDP Controls[13]



Abbreviations: PDP=Parkinson's disease psychosis; Pim=pimavanserin; Quet=quetiapine.

Alipour-Haris et al.

A retrospective new-user cohort study was conducted in a 15% random sample of Medicare beneficiaries aged ≥65 years with PD initiating pimavanserin (n=855) or quetiapine (n=2,505) from May 1, 2016 to December 30, 2018 to assess all-cause mortality and all-cause hospitalization.[14] Patients in the quetiapine cohort were required to have a diagnosis for psychosis, delusions or hallucinations. Patients were excluded if they had prescriptions for other antipsychotics before the index date or if they were in a hospital or skilled nursing home at the time of the index date. Follow-up for each patient started at the index date and ended on the date of death or censoring at the earliest occurrence of 1 of the following events: end of study period, disenrollment from Medicare, discontinuation of the index study drug, switch to another antipsychotic, or loss to follow-up. Standardized mortality ratio weighting (SMRW), based on propensity score, was used to balance pimavanserin initiators and quetiapine initiators on treatment group characteristics.

After SMRW weighting, there were no meaningful differences in patient characteristics between pimavanserin and quetiapine users.[14] The SMRW-weighted HR for all-cause mortality did not show any difference in risk of mortality among patients treated with pimavanserin vs quetiapine at any time point (**Table 10**). In sensitivity analyses, where patients were stratified based on quartiles of disease-risk scores, baseline frailty indices and propensity scores, the results were similar to the main analysis.

Table 10. Alipour-Haris et al: All-cause Mortality for Pimavanserin Use Compared to Quetiapine*[14]

Time Period	HR	95% CI
90 days	0.73	0.48–1.13
180 days	0.80	0.58–1.10
365 days	0.94	0.74–1.19

**SMRW-weighted analysis was conducted using standardized mortality ratio weighted (for all patient's covariates) Cox proportional hazards regression model.*
Abbreviations: CI=confidence interval; HR=hazard ratio; SMRW=standardized mortality ratio weighting.

Nguyen et al.
A retrospective new-user cohort study was conducted using a large US commercial health insurance database (Optum Clinformatics® Data Mart) to assess all-cause mortality among PD persons aged ≥40 years initiating pimavanserin (n=775), preferred dopamine receptor blocking (DRB) atypical antipsychotics (n=4,563) or non-preferred DRB atypical antipsychotics (n=1,297) from May 1, 2016 to March 31, 2021.[15] Patients were excluded if they had concurrent diagnosis codes for atypical and drug-induced parkinsonism, amyotrophic lateral sclerosis, dementia with Lewy bodies, and bipolar disorder. Preferred DRB atypical antipsychotics were quetiapine and clozapine. Non-preferred DRB atypical antipsychotics were aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, risperidone, and ziprasidone. Patients were followed from their first prescription claim of atypical antipsychotics and ended on the date of death or censoring at the earliest occurrence of one of the following events: loss of insurance coverage or end of study period. Propensity score methods were used. The primary intention-to-treat (ITT) analyses used 1:1 greedy matching with a 0.2 caliper to match pimavanserin users to preferred DRB atypical antipsychotic users or non-preferred DRB atypical antipsychotic users.

There was no difference in mortality risk for pimavanserin vs preferred DRB atypical antipsychotics (adjusted HR [aHR] 0.99, 95% CI: 0.81–1.20), or pimavanserin vs non-preferred DRB atypical antipsychotics (aHR 0.98, 95% CI: 0.79–1.22) in ITT analyses (**Table 11**).[15] For the comparison with preferred DRB atypical antipsychotics, sensitivity analyses with an additional censoring criterion of discontinuation or switching of antipsychotic therapy, allowing for a 20% gap in prescription fill to account for imperfect adherence, resulted in up to 98% of the sample being censored and no change in the relative mortality risk (**Table 11**). For the comparison to non-preferred DRB atypical antipsychotics with additional censoring on discontinuation or switching of initial atypical antipsychotics, the aHR was 0.35 (95% CI 0.14–0.92), with up to 92% of the sample censored. However, these data should be interpreted with caution, especially due to statistical imprecision.

Table 11. Nguyen et al: Summary of All-cause Mortality Risk in the Matched Cohorts[15]

1:1 Matched Analysis	Primary ITT analyses		Sensitivity analysis: Additional censoring on discontinuation or switching of initial atypical AP	
	aHR (95% CI)	n per group	aHR (95% CI)	N per group
Pimavanserin vs preferred DRB atypical APs*	0.99 (0.81–1.20)	775	0.44 (0.19–1.03)	NR (≤98% were censored)
Pimavanserin vs non-preferred DRB atypical APs*	0.98 (0.79–1.22)	626	0.35 (0.14–0.92)	NR (≤92% were censored)

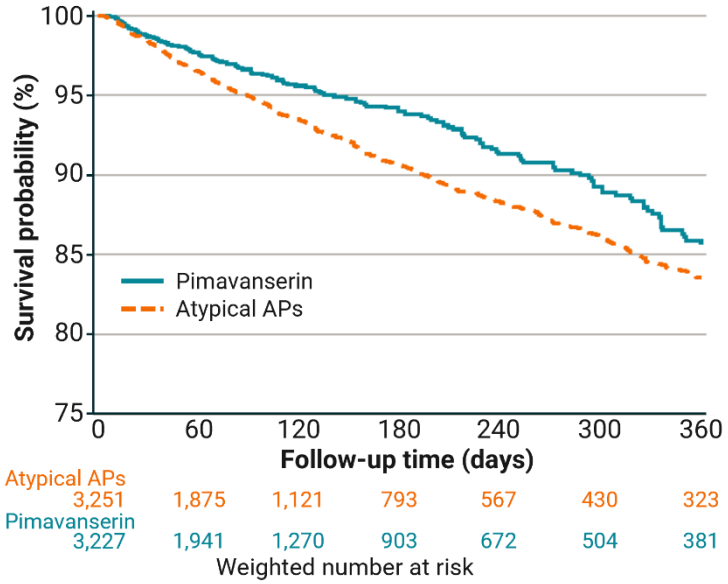
**Preferred DRB atypical APs were quetiapine and clozapine; non-preferred DRB atypical APs were aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, risperidone, and ziprasidone. Abbreviations: aHR=adjusted hazard ratio; AP=antipsychotic; CI=confidence interval; DRB=dopamine receptor blocking; ITT=intention to treat.*

Mosholder et al.
A retrospective new-user cohort study was conducted in Medicare beneficiaries (100% sample) with PD initiating pimavanserin (n=3,227) or atypical antipsychotics (n=18,442) from April 2016 to March 2019 to assess all-cause mortality.[16] Patients were excluded if they had a

diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder. Follow-up began the day after cohort entry and ended on the date of death or censoring at the earliest occurrence of one of the following events: disenrollment from Medicare, stopping treatment (i.e., gap of>14 days between study drug prescriptions), dispensing of a non-study antipsychotic, switching between pimavanserin and an atypical antipsychotic, or end of the study period. Quetiapine was the chief antipsychotic accounting for 78% of the atypical antipsychotic cohort, followed by risperidone (9%), olanzapine (6%), aripiprazole (5%), and other atypical antipsychotics (1%). Inverse probability of treatment weighting (IPTW) was used to address potential confounding. After weighting, the cohorts were closely balanced on all covariates. The mean age for both pimavanserin and atypical antipsychotic users was 78 years.

During follow-up, 207 pimavanserin users and 1,752 atypical antipsychotic users died. In the weighted Kaplan-Meier plot, pimavanserin users exhibited a lower risk of all-cause mortality through 360 days of follow-up (**Figure 6**).[16]

Figure 6. Mosholder et al: Kaplan-Meier Plot of Weighted Cumulative Survival Probability Among Patients with PD Treated with Pimavanserin or Atypical Antipsychotic[16]



Abbreviations: AP=antipsychotic; PD=Parkinson's disease.

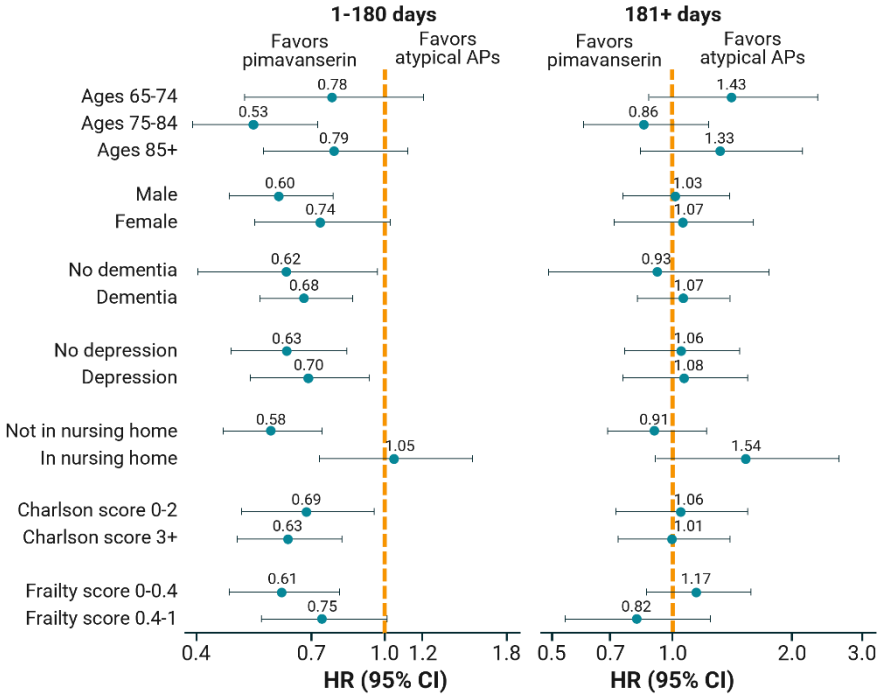
Overall, pimavanserin use was associated with significantly lower mortality vs atypical antipsychotics (HR 0.77, 95% CI 0.66–0.90).[16] However, statistical evaluation showed that the HR was not constant over the duration of follow-up, indicating that the proportional hazard assumption was violated. Segmented analyses (days 1–180 and days 181+) satisfied the proportional hazard assumption and showed that mortality risk with pimavanserin was lower than with atypical antipsychotics during the first 180 days of use (HR 0.65, 95% CI 0.53–0.79), while mortality risk was similar thereafter (HR 1.05, 95% CI 0.82–1.33).

The median exposed follow-up time was 78 days (interquartile range [IQR] 44–202) for pimavanserin and 74 days (IQR 44–170) for atypical antipsychotics.[16] At 75 days of follow-up, 2.4% of pimavanserin initiators and 3.6% of atypical antipsychotic initiators had died, and the

number needed to harm for 1 excess death with atypical antipsychotic treatment vs pimavanserin treatment was 64 (95% CI 38–220). At 180 days of follow-up, 3.7% of pimavanserin initiators and 5.4% of atypical antipsychotic initiators had died and the number needed to harm was 30 (95% CI 19–73).

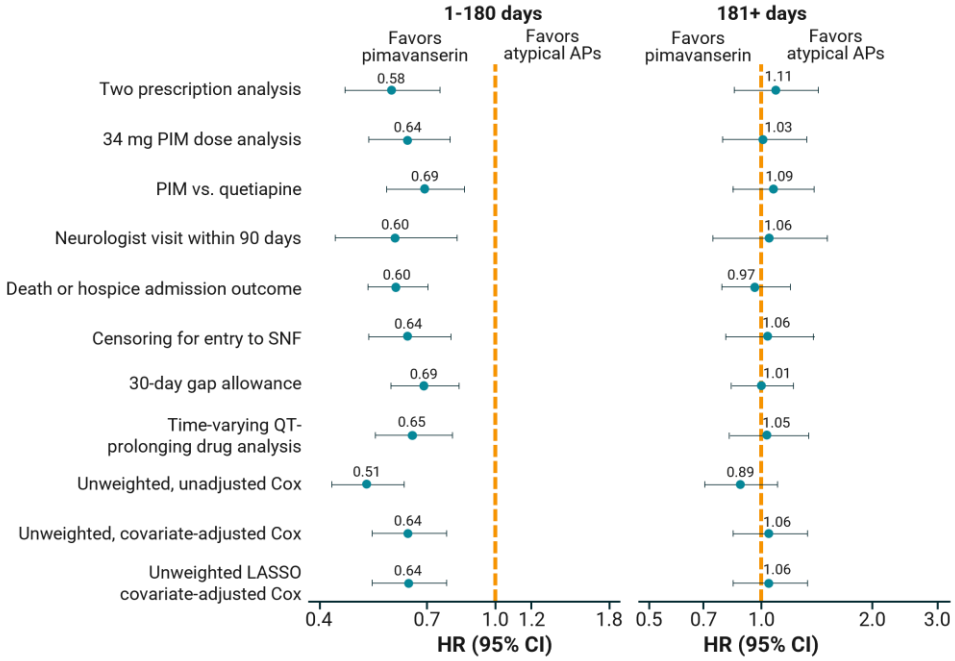
Results of subgroup (**Figure 7**) and sensitivity analyses (**Figure 8**) were largely consistent with the main analyses, except for a subgroup of patients residing in nursing homes (~15% of patients in the analysis).[16]

Figure 7. Mosholder et al: HRs and 95% CIs for Death Among Patients with PD Treated with Pimavanserin or Atypical Antipsychotics: Subgroup Analyses[16]



Abbreviations: AP=antipsychotic; CI=confidence interval; HR=hazard ratio; PD=Parkinson's disease.

Figure 8. Mosholder et al: HRs and 95% CIs for Death Among Patients with PD Treated with Pimavanserin or Atypical Antipsychotics: Sensitivity Analyses[16]



Abbreviations: AP=antipsychotic; CI=confidence interval; HR=hazard ratio; PD=Parkinson's disease; PIM=pimavanserin; SNF=skilled nursing facility.

Hwang et al.

A retrospective study evaluated the risk of hospitalization and death up to 1 year in LTC residents aged ≥65 years with PD, comparing pimavanserin users (n=2,186) with nonusers (n=18,212), using the Minimum Data Set 3.0 linked Medicare claims data (100% sample).[17] Patients with comorbid psychiatric disorders were included in the study, including schizophrenia (13.3% of users and 11.2% of nonusers) and bipolar disorder (10.1% of users and 9.5% of nonusers). Concomitant antipsychotics were being used by 43.2% of pimavanserin users and 22.1% of nonusers. All-cause mortality was assessed at 30, 90, 180 and 365 days following pimavanserin initiation. Pimavanserin users were censored at the time of pimavanserin discontinuation (i.e., no prescription resupply within 30 days), and nonusers were censored upon pimavanserin initiation. Both users and nonusers were censored at the end of study period and end of prespecified follow-up period.

Propensity score-based IPTW was used to balance pimavanserin users (n=2,089) and nonusers (n=18,248) on 24 baseline characteristics.[17] After weighting, 16.0% of users and 11.5% of nonusers had schizophrenia, and 12.0% of users and 9.6% of nonusers had bipolar disorder; concomitant antipsychotics were being used by 28.1% of pimavanserin users and 24.6% of nonusers. Pimavanserin use vs nonuse in LTC residents was associated with an IPTW aHR of 0.76 at 30 days after initiation, 1.20 at 90 days, 1.28 at 180 days, and 1.56 at 1 year (**Table 12**).

Table 12. Hwang et al: Pimavanserin Use and Risk of All-cause Mortality[17]

	Incidence rate (100 person-years)		Unadjusted hazard ratio (95% CI)	IPTW adjusted hazard ratio (95% CI)
	Users	Nonusers		
30-day	36.8	41.1	0.86 (0.67–1.12)	0.76 (0.56–1.03)
90-day	46.0	40.0	1.13 (0.97–1.31)	1.20 (1.02–1.41)
180-day	48.3	38.7	1.23 (1.09–1.38)	1.28 (1.13–1.45)
1 year	57.5	38.5	1.53 (1.39–1.67)	1.56 (1.42–1.72)

Abbreviations: CI=confidence interval; IPTW=inverse probability of treatment weighting.

Results from secondary analyses (standard Cox proportional hazards regression and propensity score-matched analyses) for mortality in long-term care residents are presented in **Table 13.**

Table 13. Hwang et al: Secondary Analyses for Pimavanserin Use and Risk of All-cause Mortality[17]

Follow up period	Mortality		Adjusted hazard ratio (95% CI)	
	Users (n=2,186)	Nonusers (n=18,212)	Standard Cox proportional hazards regression analysis	Propensity score-matched analysis[a]
30-day	61 (2.8)	594 (3.3)	0.91 (0.54–1.51)	0.75 (0.59–0.96)
90-day	187 (8.6)	1,613 (8.9)	1.22 (1.00–1.49)	1.12 (0.96–1.30)
180-day	323 (14.8)	2,828 (15.5)	1.35 (1.18–1.54)	1.28 (1.13–1.45)
1 year	577 (26.4)	4,627 (25.4)	1.69 (1.53–1.88)	1.56 (1.40–1.74)

Values are mean±SD or number (percentage).
[a]Propensity score matched analysis was conducted in a 1:1 matched set of 2,186 pimavanserin users and 2,186 nonusers.
Abbreviations: CI=confidence interval; SD=standard deviation.

Brown et al.

A retrospective analysis of AE case reports submitted to the US FAERS from 2016 through Q3/2019 was conducted for a comparative pharmacovigilance assessment of pimavanserin vs treatment alternatives in patients.[18] The reports were assessed for exposure to pimavanserin, clozapine, quetiapine, haloperidol, and other antipsychotics. The outcome of interest was all-cause death.

As of Q3/2019, there were 2,287 reports of death associated with pimavanserin.[18] In the full FAERS base population, pimavanserin use yielded a Proportional Reporting Ratio (PRR) lower 95% CI confidence limit of 2.08 vs no use. Restricting to the PD population using levodopa only or multiple PD medications diminished the safety signal for pimavanserin (**Table 14**). Pimavanserin metrics in PD-restricted groups were similar in direction and magnitude to clozapine and quetiapine.

Table 14. Brown et al: Comparative PRRs for Treatment Alternatives[18]

	Baseline Population	PRR (95% CI)
Pimavanserin	Full FAERS population	2.15 (2.08–2.24)
	PD	1.14 (1.09–1.20)
	+Levodopa users	1.23 (1.15–1.32)
	+Multiple PD medications	1.86 (1.63–2.12)
Quetiapine	Full FAERS population	1.76 (1.72–1.81)
	PD	1.29 (1.20–1.39)

	Baseline Population	PRR (95% CI)
	+Levodopa users	1.36 (1.25–1.48)
	+Multiple PD medications	1.95 (1.65–2.29)
Clozapine	Full FAERS population	1.82 (1.77–1.88)
	PD	1.50 (1.33–1.69)
	+Levodopa users	1.53 (1.35–1.73)
	+Multiple PD medications	1.82 (1.37–2.42)

Abbreviations: CI=confidence interval; FAERS=US Food and Drug Administration Adverse Event Reporting System; PD=Parkinson disease; PRR=proportional reporting ratio.

Horn et al.

A retrospective cohort study compared patients (mean age: 73±8 years) seen at the University of Pennsylvania PD and Movement Disorders Center with PD or dementia with Lewy Bodies (DLB) initiated on quetiapine or pimavanserin for psychosis between April 2016 and May 2018.[19] Patients with an ICD code for schizophrenia or bipolar disorder were excluded. The primary outcome was time to discontinuation of pimavanserin or quetiapine using Kaplan-Meier survival analysis. Secondary outcomes included mortality, reason for antipsychotic discontinuation, change in motor Unified PD Rating Scale score, and subjective improvement in psychosis as reported by the patient or caregivers and documented in the EMR.

Forty-seven patients in the quetiapine cohort and 45 in the pimavanserin cohort were followed for a mean of 317±223 days.[19] Patients in the pimavanserin cohort were more likely to have a diagnosis of DLB (33% vs 11%, p=0.01) and to have been previously prescribed an antipsychotic (62% vs 6%, p<0.001); the groups were otherwise similar. Time to discontinuation analysis, which accounts for efficacy, safety and tolerability, revealed a lower early pimavanserin discontinuation rate and a higher late pimavanserin discontinuation rate (HR<1 before day 43, HR>1 after Day 43; p=0.04). Most patients remained on the antipsychotic in both cohorts; however, patients in the quetiapine cohort were more likely to discontinue the medication due to side effects, while patients in the pimavanserin cohort were more likely to discontinue due to lack of adequate improvement in psychosis. Symptoms of orthostatic hypotension were more common in the quetiapine group compared to pimavanserin (26% vs 4%, p=0.007). There was no difference in mortality in the pimavanserin group compared to the quetiapine group (9% vs 15%; HR 0.37, 95% CI 0.06–2.45, p=0.88).

Gupta et al.

A retrospective chart review was performed from June 2016 through September 2018 to investigate the safety and efficacy of pimavanserin in patients with PDP (n=107, mean age: 74.2 years, mean Montreal Cognitive Assessment [MoCA] score: 18.8) treated at the University of Kansas Medical Center.[20] Thirty patients died after initiation of pimavanserin; however, only 16 were taking pimavanserin at the time of death. The mortality rate was 20 per 100 patient-years. The deceased patients were taking pimavanserin for an average of 215 days before death. The deceased patients were older (mean age 78 years vs 73 years), had a longer disease duration (mean 13 years vs 11 years), were more cognitively impaired (MoCA score 16.6 vs 19.7), and were more often taking other antipsychotics with pimavanserin (20% vs 15.6%).

Sellers et al.
A retrospective chart review of patients prescribed pimavanserin at Vanderbilt University Medical Center between May 2016 and July 2018 was performed.[21] Patients who began pimavanserin (n=91) treatment were included in the main efficacy analysis, while patients where pimavanserin was prescribed but not started (n=16) were used as a control sample to assess safety.

Demographic characteristics, age (71.4±8.1 years), gender, diagnosis, and reported psychiatric symptoms were similar to those patients who did begin pimavanserin treatment.[21] Efficacy was defined as a clinically significant improvement in psychosis symptoms after taking pimavanserin for at least 6 weeks–the length of time used to evaluate clinical efficacy in clinical trials. Seventy-one (71) patients were diagnosed with PD and 11 were diagnosed with DLB. The remaining 9 had diagnoses of PD with early cognitive symptoms (n=7), PD with logopenic aphasia (n=1), or PD with concern of normal pressure hydrocephalus (n=1). For analysis, these 9 were included in the PD group.

Fifteen percent (15%; 14/91) of patients on pimavanserin died vs 44% (7/16) of those who were prescribed but did not start pimavanserin (x^2=6.94, p<0.01).[21]

Moreno et al.
A retrospective review of patients seen at the UCSD Health System diagnosed with PD and prescribed pimavanserin (n=113), quetiapine (n=505), or both agents (n=58) during April 29, 2016 to April 29, 2018, showed that mortality was higher between quetiapine vs pimavanserin and combination vs pimavanserin (**Table 15**), but differences were not statistically significant (p=0.17 and p=0.28, respectively).[22] The mean age of the deceased cohorts was similar between the groups, and age was similar to those not deceased (p=0.12). The mortality in a cohort of patients with PD not receiving treatment with quetiapine or pimavanserin and a similar mean age of 80 (range: 78–82; n=784) was 5.9%. Odds ratios showed an increased risk of mortality in the quetiapine group and a trend toward increased risk in the combination therapy group (p=0.07) compared to PD patients not taking an antipsychotic.

Table 15. Moreno et al: Patient Demographics and Mortality Outcomes[22]

	PDP Medication		
	Pimavanserin	**Quetiapine**	**Pimavanserin + Quetiapine**
Sample size, n	113	505	58
Mean age, y (SD)	75.9 (9.1)	75.2 (12.4)	74.1 (10.4)
% Female	38.1	42	37.9
Total deaths (April 29, 2016–April 29, 2018)	8	58	7
Mortality, %	7.1	11.5	12.1
Age of deceased, y, mean (SD)	81.4 (7.4)	79.6 (8.7)	82 (8)
Odds ratio (95% CI)	1.23 (0.57–2.68)	1.74 (1.15–2.62)	2.16 (0.93–5.01)

Abbreviations: CI=confidence interval; PDP=Parkinson's disease psychosis; SD=standard deviation; y=years.

Mahajan et al.
A retrospective chart review of patients receiving pimavanserin at the Henry Ford PD and Movement Disorders Clinic was conducted in 2017.[23] Demographic data and AE data were collected using telephone interviews. Of the patients included, 16 were diagnosed with PDP. One (1) patient died within 8 months of the interview.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Acadia Pharmaceutical Inc. NUPLAZID® Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee on 29 March 2016.
3. Ballard CG, Kreitzman DL, Isaacson S, et al. Long-term evaluation of open-label pimavanserin safety and tolerability in Parkinson's disease psychosis. *Parkinsonism Relat Disord.* 2020;77:100-106. **[PubMed]**
4. Acadia Pharmaceuticals Inc. Data on File. In. San Diego, CA.
5. US Department of Health and Human Services. FDA Adverse Event Reporting System (FAERS) public dashboard - frequently asked questions. **[Link]**. Accessed June 15, 2022.
6. US Food and Drug Administration (FDA). FDA analysis finds no new or unexpected safety risks associated with NUPLAZID (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis. **[Link]**. Published 2018. Accessed Aug 11, 2022.
7. Weintraub D, Willis A, Torres P, et al. Parkinson's disease psychosis associated comorbidities and mortality in the Medicare population. Paper presented at: International Parkinson and Movement Disorder Society (MDS); Oct 8, 2018, 2018; Philadelphia, PA, USA.
8. Wetmore JB, Li S, Yan H, et al. Increases in institutionalization, healthcare resource utilization, and mortality risk associated with Parkinson disease psychosis: Retrospective cohort study. *Parkinsonism Relat Disord.* 2019;68:95-101. **[PubMed]**
9. Weintraub D, Chiang C, Kim HM, et al. Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease. *JAMA Neurol.* 2016;73(5):535-541. **[PubMed]**
10. Ballard C, Isaacson S, Mills R, et al. Impact of current antipsychotic medications on comparative mortality and adverse events in people with Parkinson disease psychosis. *J Am Med Dir Assoc.* 2015;16(10):898 e891-897. **[PubMed]**
11. Layton JB, Forns J, McQuay LJ, et al. Mortality in Patients with Parkinson's Disease-Related Psychosis Treated with Pimavanserin Compared with Other Atypical Antipsychotics: A Cohort Study. *Drug Saf.* 2023;46(2):195-208. **[PubMed]**
12. Rao S, McQuay LJ, Forns J, et al. Evaluation of Mortality in Users of Pimavanserin Compared with Other Atypical Antipsychotics in Patients with Parkinson's Disease Psychosis: An Update. *Drug Saf.* 2025. **[PubMed]**
13. Longardner K, Wright BA, Alakkas A, et al. Assessing the risks of treatment in Parkinson disease psychosis: An in-depth analysis. *PLoS One.* 2023;18(1):e0278262. **[PubMed]**
14. Alipour-Haris G, Armstrong MJ, Okun M, Brown JD. Comparison of Pimavanserin Versus Quetiapine for Hospitalization and Mortality Risk Among Medicare Beneficiaries

with Parkinson's Disease Psychosis. *Mov Disord Clin Pract.* 2023;10(3):406-414. **[PubMed]**
15. Pham Nguyen TP, Thibault D, Hamedani AG, Weintraub D, Willis AW. Atypical antipsychotic use and mortality risk in Parkinson disease. *Parkinsonism Relat Disord.* 2022;103:17-22. **[PubMed]**
16. Mosholder AD, Ma Y, Akhtar S, et al. Mortality Among Parkinson's Disease Patients Treated With Pimavanserin or Atypical Antipsychotics: An Observational Study in Medicare Beneficiaries. *Am J Psychiatry.* 2022;179(8):553-561. **[PubMed]**
17. Hwang YJ, Alexander GC, An H, Moore TJ, Mehta HB. Risk of Hospitalization and Death Associated With Pimavanserin Use in Older Adults With Parkinson Disease. *Neurology.* 2021;97(13):e1266-e1275.
18. Brown JD, Cicali B, Henriksen C, Malaty I, Okun MS, Armstrong MJ. Comparative pharmacovigilance assessment of mortality with pimavanserin in Parkinson disease-related psychosis. *J Manag Care Spec Pharm.* 2021;27(6):785-790. **[PubMed]**
19. Horn S, Richardson H, Xie SX, Weintraub D, Dahodwala N. Pimavanserin versus quetiapine for the treatment of psychosis in Parkinson's disease and dementia with Lewy bodies. *Parkinsonism Relat Disord.* 2019;69:119-124. **[PubMed]**
20. Gupta H, Lyons K, Pahwa R. Clinical experience in over 100 using pimavanserin for Parkinson’s disease psychosis. Paper presented at: American Academy of Neurology (AAN) Annual Meeting; May 4-10, 2019, 2019; Philadelphia, PA, USA.
21. Sellers J, Darby RR, Farooque A, Claassen DO. Pimavanserin for Psychosis in Parkinson's Disease-Related Disorders: A Retrospective Chart Review. *Drugs Aging.* 2019;36(7):647-653. **[PubMed]**
22. Moreno GM, Gandhi R, Lessig SL, Wright B, Litvan I, Nahab FB. Mortality in patients with Parkinson disease psychosis receiving pimavanserin and quetiapine. *Neurology.* 2018;91(17):797-799. **[PubMed]**
23. Mahajan A, Bulica B, Ahmad A, et al. Pimavanserin use in a movement disorders clinic: a single-center experience. *Neurol Sci.* 2018;39(10):1767-1771. **[PubMed]**