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For further information regarding Indication, **Boxed WARNING** and other Important Safety Information for NUPLAZID, please click here: Prescribing Information.

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# NUPLAZID® (pimavanserin)

## Clinical trial and post-marketing mortality events in psychosis in Parkinson's disease

### 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

Click on each icon to learn more

### 6-week placebo-controlled trials

Mortality reported in the 6-week trials comparing pimavanserin and placebo groups during treatment or within 30 days of the last dose:[2]

| Pimavanserin 34 mg | Placebo |
|---|---|
| (n=202)<br>3 deaths | (n=232)<br>1 death |

### OLE study

Mortality reported during long-term open-label treatment with pimavanserin 34 mg daily or within 30 days of the last dose:[3]

**Pimavanserin 34 mg**
N=459; 59 (12.9%) deaths

### Post-marketing experience

The mortality rate observed in post-marketing assessments of patients receiving pimavanserin has remained consistent over time[4]

The estimated overall cumulative reported post-marketing mortality rate is 15.40/100 patient-years

Reported causes of death reflect common comorbidities and underlying conditions in an elderly, frail population with PD treated for psychosis

### Literature on mortality rate in PDP

Mortality data in PDP are available from 4 retrospective cohort analyses

### Retrospective studies

Mortality data for pimavanserin are available from several retrospective studies

Interpretation of these findings is limited due to the observational nature of the studies 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

Abbreviations and References

# NUPLAZID® (pimavanserin)

Clinical trial and post-marketing mortality events in psychosis in Parkinson's disease

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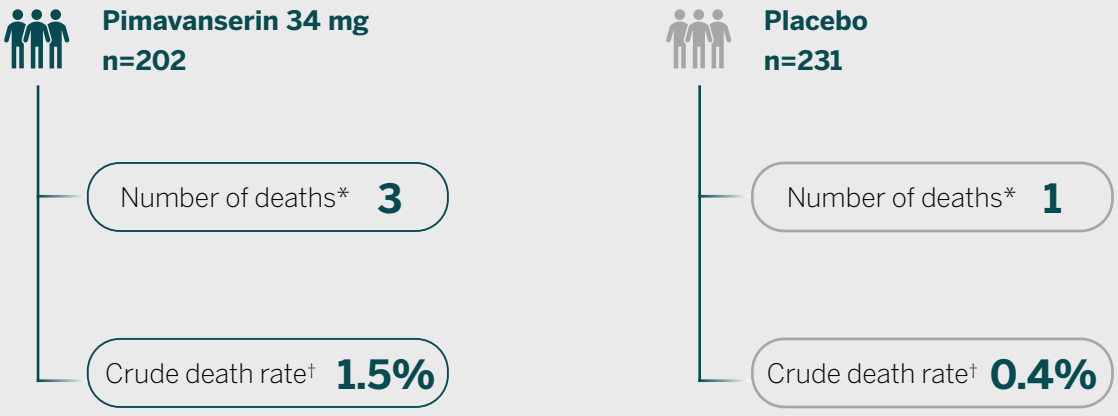
## Placebo-controlled trials

### PDP 6-week placebo-controlled trials at approval:[2]




*Participants who died during treatment or within 30 days after the last dose of the study drug

†Crude mortality rate in 6-week ACP-103-012 (Study 012; Phase 2b/3) and ACP-103-020 (Study 020; Phase 3)

## Clinical development experience

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

Abbreviations and References

## OLE study[3]

**Eligibility**
Participants who completed the 6-week placebo-controlled trials

**Pimavanserin dose**
34 mg QD

**Total participants**
N=459

**Mean age**
71.2 years

| Median duration of treatment | Longest duration of treatment | Entire study period |
|---|---|---|
| **454 days** | **~ 9 years** | **~ 11 years** |
| Number of deaths | Deaths at ≥1 year of treatment | Mortality rate |
| **59, occurred during treatment or within 30 days of the last dose of the study drug** | **43** | **6.45 per 100 patient-years of exposure** |

### Most common AEs with fatal outcomes in the OLE[3]

| AE | | Fatal outcomes, % |
|---|---|---|
| System | Cardiac disorders | 3.7 |
| | Respiratory disorders | 2.6 |
| Preferred term | Pneumonia | 1.1 |
| | PD | 1.1 |
| | Acute respiratory failure | 0.9 |
| | Acute myocardial infarction | 0.7 |
| | Dementia | 0.7 |
| | Cardiac arrest | 0.7 |

## Clinical development experience

The safety and efficacy of pimavanserin in participants with PDP were evaluated in 4 short-term placebocontrolled trials and 2 long-term open-label studies comprising over 1,200 participants receiving pimavanserin (including 616 participants with PDP and over 250 participants treated for >1 year)[2]


Abbreviations and References

◀ 3 ▶

## Post-marketing experience

Acadia continues to monitor all reported fatal cases[4]

### Cumulative post-marketing mortality rate per 100 patient-years[4]

| Time Period | Deaths | Minimum Patients* Exposed (Patient-Years) | Mortality Rate/100 Patient-Years | Exact 95% CI of Mortality Rate/100 Patient-Years |
|---|---|---|---|---|
| Launch to April 28, 2021 (cumulative) | 4,687† | 41,218 (30,426) | 15.40 | 14.97–15.85 |

*Based on unique patients tracked through Acadia's reimbursement HUB and specialty pharmacy distribution channel plus a limited number of LTC pharmacy partners. †Case processing was completed on May 3, 2021. The cumulative death count is through the data retrieval date of May 10, 2021

- A review of cases with fatal outcomes did not indicate a particular etiology that would suggest a causal relationship to pimavanserin[4]
- Overall, the reported causes of death reflect the common comorbidities and underlying conditions in an elderly, frail population with PD treated for psychosis, such as:[4]

PD | Disease progression | Dementia | Pneumonias | Respiratory events | Cardiac events

### Specialty pharmacy distribution and AE reporting[4]

- NUPLAZID is distributed via a specialty pharmacy model that enables
  - More frequent contact with each patient or caregiver
  - More frequent contact with the reimbursement HUB
  - Limited number of LTC pharmacy partners
- These frequent contacts generate solicited AE reports but enable Acadia to collect information on the safety of pimavanserin
- During the last reporting period, 96% (5,443/5,652) were considered solicited, resulting from the described outgoing contacts
- Any AEs mentioned during these regular calls are reported to the US FDA as part of Acadia's pharmacovigilance process[5]

On September 20, 2018, the FDA released a statement that described their recently completed review of all post-marketing reports of deaths and serious AEs reported with the use of NUPLAZID; it highlighted the following: no new or unexpected safety findings; NUPLAZID and other APs 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 patients with PDP, 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]


Abbreviations and References

◀ 4 ▶

## Available Literature Regarding Mortality Rate in PDP

- Retrospective cohort analyses have examined the mortality rate of patients with PD vs PDP, the mortality rate associated with APs in PD, and the mortality rate associated with concomitant AP use vs monotherapy in patients with PDP[7-10]
- Direct comparisons cannot be made between the studies

### Retrospective studies evaluating the mortality rate in PDP

| Study | Design | Active Comparator | Number of Patients | Primary Objective |
|---|---|---|---|---|
| Wetmore et al.[8] | Retrospective Medicare data extraction of patients with PDP (2007–2015) | No | PDP: 1,699<br>Non-PDP: 6,796 | Evaluate the association of death in patients with PDP vs direct-matched patients with PD without psychosis |
| Weintraub et al.[7] | Medicare claims database study of patients with PD and those with PDP | No | PD: 68,821<br>PDP: 38,072 | Age-standardized mortality in PDP vs PD with no psychosis |
| Weintraub et al.[9] | Retrospective, matched cohort study of patients with PD | 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 a multicenter OLE study of PIM in patients with PDP | No | PIM + APs: 66<br>PIM alone: 357 | Risk of mortality in patients using PIM + APs vs PIM alone |

Click on each study to learn more

Abbreviations and References

# NUPLAZID® (pimavanserin)

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## Wetmore et al.[8]

### Overview

- Retrospective study performed using Medicare data
- 20% random sample taken from 2007 to 2015
- Evaluated the association of death in patients with PDP

### Methodology

- Patients with PDP were direct matched to patients with PD without psychosis to compare the association of PDP with death
- The matched patients were followed until death, admission to custodial care, or end of the study period

### Results

- The cumulative incidence of death was significantly different between the matched groups ($p<0.0001$)
- **16.4%** of patients with PDP experienced death vs **13.8%** of patients with PD only in the first year of diagnosis
- PDP was associated with a greater risk of death (HR, 1.34; CI, 1.23–1.45; $p<0.0001$)*
- **Factors associated with death:**

Older age was associated with a higher HR for death

Female sex was associated with a lower HR for death (0.76, 0.70–0.82, $p<0.0001$)

### Conclusion

- Patients with PD with incident psychosis were associated with a nearly one-third increased risk of death

*Determined using a Cox model regression analysis.

Abbreviations and References

## Weintraub et al: Medicare claims database[7]

### Study design

- Patients diagnosed with PD (n=68,821) and those with PDP (n=38,072) were evaluated using data from Medicare claims

### Results

- Age-standardized mortality was significantly higher in patients with PDP vs those with PD and no psychosis (28.2 vs 7.3 deaths per 100 patient-years, respectively; p<0.0001)

## Weintraub et al: Veterans' Health Administration database[9]

### Overview

- Retrospective matched-cohort study
- Examined the risk of mortality associated with AP use in a cohort of patients with PD

### Methodology

- The rate of 180-day mortality was compared between matching cohorts of 7,877 patients in each of the following 2 groups:

Patients initiating AP therapy

Patients who did not initiate AP therapy

### Results

- There was an increased risk of mortality in patients taking APs vs those not taking APs (HR, 2.35; 95% CI, 2.08–2.66; p<0.001)

**Unadjusted mortality rates by AP exposure[9]**

| AP | No. of Patients Dead/ 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 | 462/5,270 (8.8) | 2,488.8 | 18.6 (16.9–20.3) |
| Risperidone | 164/1,155 (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 and References

◀ 8 ▶

# NUPLAZID® (pimavanserin)

Clinical trial and post-marketing mortality events in psychosis in Parkinson's disease

ACADIA®

## Ballard et al.[10]

### Study design

- Post hoc analysis of data from a multicenter OLE study of pimavanserin (n=423)

### Result

- Patients with PDP on concomitant APs (n=66) were found to be at an increased risk for mortality vs those on pimavanserin alone (n=357)

**IR ratio: 4.20 (95% CI, 2.13–7.96)**

Abbreviations and References

## Retrospective Studies of Pimavanserin Mortality in Patients With PDP

The evaluation of mortality with pimavanserin in the studies listed below is limited by the studies' observational nature and because most (but not all) did not study mortality as a primary objective. The methodology of each study should be reviewed and considered when interpreting the respective results.[11-23]

### Retrospective studies evaluating the mortality rate with pimavanserin in PDP

| Study | Design | Active Comparator | Number of Patients | Primary Objective |
|---|---|---|---|---|
| Layton et al.[11,*] | Retrospective, new-user cohort study of patients with PDP in Medicare; Apr 2016 to Dec 2019 | Yes | Matched PIM initiators: 2,891<br>Matched atypical AP initiators: 2,891 | All-cause mortality with PIM vs atypical APs |
| Rao et al.[12,*] | Retrospective, new-user cohort study of patients with PDP aged ≥65 years in Medicare; Apr 2016 to Dec 2021 | Yes | Matched PIM initiators: 4,381<br>Matched atypical AP initiators: 4,381 | All-cause mortality with PIM vs atypical APs |
| Longardner et al.[13] | Retrospective EMR data extraction of patients with PDP (UCSD Health System); Apr 2016 to Apr 2019 | Yes | Untreated controls: 66<br>PIM: 34<br>Quetiapine: 147<br>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 patients with PDP aged ≥65 years in Medicare; May 2016 to Dec 2018 | Yes | PIM: 844<br>Quetiapine: 2,505 | All-cause hospitalization and mortality with PIM vs quetiapine |
| Nguyen et al.[15] | Retrospective, new-user cohort study of patients with PD aged ≥40 years in Optum; May 2016 to Mar 2021 | Yes | PIM: 775<br>Preferred DRB atypical AP: 4,563<br>Non-preferred DRB atypical AP: 1,297 | All-cause mortality with PIM vs preferred or non-preferred DRB atypical APs |
| Mosholder et al.[16] | Retrospective, new-user cohort study of patients with PD in Medicare; Apr 2016 to Mar 2019 | Yes | PIM: 3,227<br>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 to Dec 2018 | No | PIM users (weighted): 2,089<br>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 FAERS; 2016 to Q3/2019 | Yes | Not applicable | PRR 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<br>Quetiapine: 47 | Time to discontinuation of PIM or quetiapine |
| Gupta et al.[20] | Retrospective chart review of patients with PDP (KUMC); Jun 2016 to Sep 2018 | No | PIM: 107 | Safety and efficacy of PIM in patients with PDP |
| Sellers et al.[21] | Retrospective chart review of patients with PDP (VUMC); May 2016 to Jul 2018 | No | 71/91 PD<br>11/91 DLB | Clinical experience with PIM |
| Moreno et al.[22] | Retrospective study of patients with PD (UCSD Health System); Apr 2016 to Apr 2018 | Yes | PIM: 113<br>Quetiapine: 505<br>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 Jul 2017 | No | PDP: 16<br>DLB: 1 | Descriptive analysis of efficacy, tolerability, and clinical outcomes |

Click on each study to learn more

*Rao et al. conducted a follow-up study to the analysis conducted by Layton et al. †The use of FAERS 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.

Abbreviations and References

## Layton et al.[11]

**Study design** | Results

### Overview

- Retrospective, new-user cohort study conducted in Medicare beneficiaries (100% sample)
- Patients with PD-related psychosis who initiated pimavanserin (n=2,892) or comparator APs (n=19,083) from April 1, 2016, to December 31, 2019
- All-cause mortality was assessed for both treatment groups

### Methodology

- The comparator APs were clozapine, quetiapine, risperidone, olanzapine, aripiprazole, and brexpiprazole
- Patients were excluded if they had a diagnosis of:
  - Bipolar disorder
  - Schizoaffective disorder
  - Schizophrenia
  - Major depressive disorder with symptoms of psychosis
- Follow-up for each patient started at the index date and ended on the date of death or occurrence of 1 of the following events:
  - End of the study period
  - Disenrollment from Medicare
  - Discontinuation of the index study drug
  - 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

## Layton et al.

Study design | **Results**

### Demographics and patient characteristics

- After propensity score matching, the 2 groups were well balanced on all covariates, including demographic characteristics, psychiatric diagnoses, comorbidities, comedication use, and healthcare utilization

### Mortality findings

- All-cause mortality in the primary PDP cohort was 22% lower in patients treated with pimavanserin vs other atypical APs
- No difference in HR was seen in the matched long-term care/skilled nursing facility (LTC/SNF) subcohort

### Mortality in patients with PDP who initiated treatment with atypical APs

| 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) | – |

Of the matched comparator initiators, 85.7% were quetiapine users

In a sensitivity analysis not requiring a recorded psychosis diagnosis, the HR was 0.76 (95% CI, 0.68–0.85)

In a sensitivity analysis with extended follow-up after treatment discontinuation, the HR was 0.78 (95% CI, 0.70–0.86)

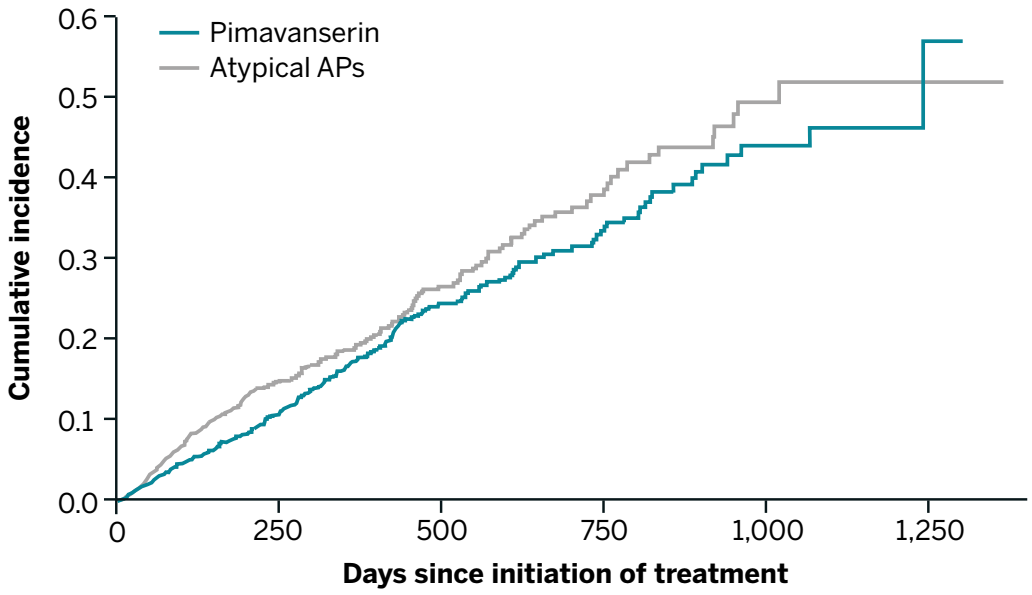

Click here to review the cumulative incidence of all-cause mortality

Click here to review matched HRs for all-cause mortality

Abbreviations and References

## Layton et al.[11]

**Cumulative incidence of all-cause mortality in the matched primary PDP cohort**



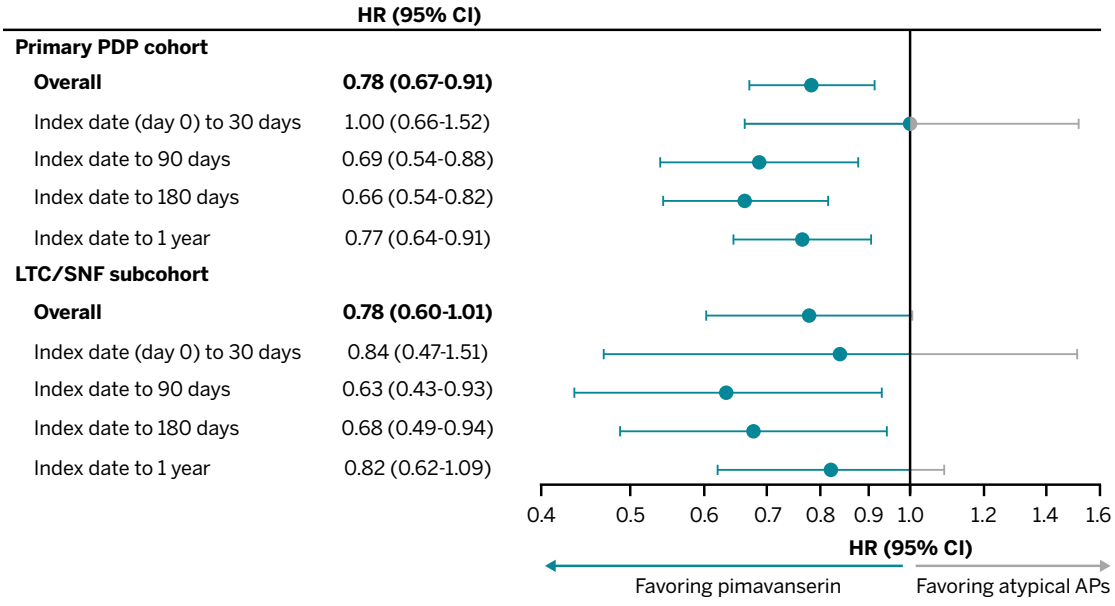

**No. patients at risk:**

| | | | | | | |
|---|---|---|---|---|---|---|
| Pimavanserin | 2,891 | 824 | 327 | 126 | 35 | <11 |
| Atypical APs | 2,891 | 609 | 220 | 80 | 25 | <11 |

- Cumulative incidence curves for the matched cohort demonstrated a generally reduced risk of mortality in the pimavanserin group throughout the follow-up; however, after 2 years, small sample sizes limited interpretation

## Layton et al.[11]

### Matched HRs for All-cause Mortality, Overall and in Specified Follow-up Periods




- In the matched primary PDP cohort, when evaluated over time, no difference was seen in the first 30 days after treatment initiation
  - The largest difference in the mortality risk between the treatment groups was observed in the first 180 days of follow-up

- In the matched LTC/SNF subcohort, no difference was seen in the first 30 days after treatment initiation or in the analysis from the index date to 1 year


Abbreviations and References

◀ 14 ▶

## Rao et al.[12]

### Overview

- Follow-up study to the study by Layton et al.,[11] comprising an analysis of all-cause mortality in patients with PD-related psychosis aged ≥65 years initiating pimavanserin (n=4,384) or comparator atypical APs (n=28,042) from April 1, 2016, to December 31, 2021

### Methodology

- Similar to that of the previous analysis by Layton et al. with 2 additional years of data through the COVID-19 pandemic
- Comparator APs were aripiprazole, brexpiprazole, clozapine, lumateperone, olanzapine, quetiapine, or risperidone
- Propensity score matching was used to balance pimavanserin initiators (n=4,381) and comparator AP initiators (n=4,381) on treatment group characteristics
- Among comparator AP initiators, 67.2% initiated quetiapine

### Results

- All-cause mortality in the primary PDP cohort was 24% lower in patients treated with pimavanserin vs other atypical APs (HR, 0.76; 95% CI, 0.68–0.85)
- No difference in HR was seen in the matched LTC/SNF subcohort

**Mortality in patients with PDP who initiated treatment with atypical APs**

| 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) | – |

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 APs

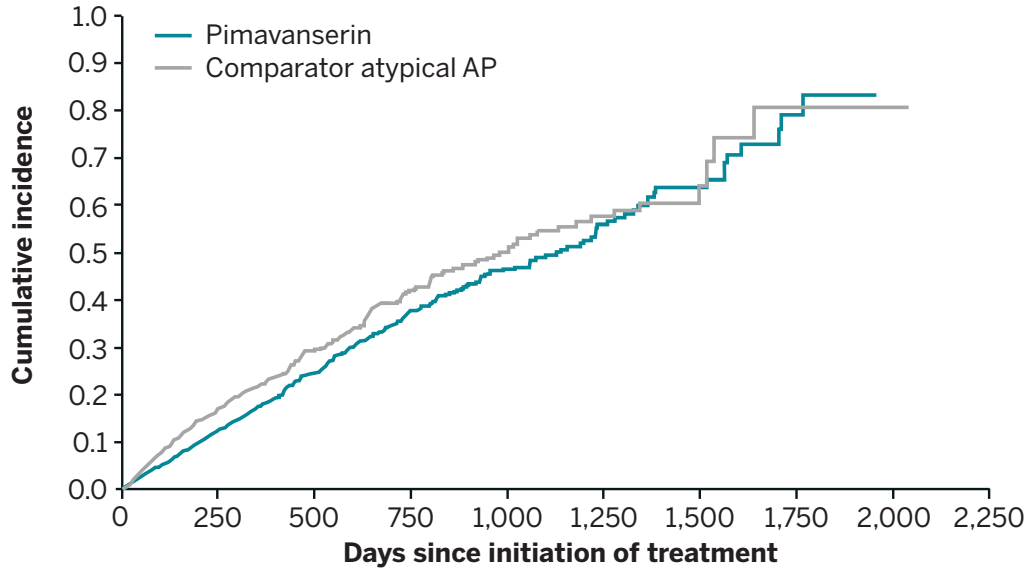

Click here to review the cumulative incidence of all-cause mortality in the matched primary PDP cohort

Click here to review the RR and risk difference for all-cause mortality in the matched primary PDP cohort

Abbreviations and References

## Rao et al.[12]

**Cumulative incidence of all-cause mortality in the matched primary PDP cohort**




**No. patients at risk:**

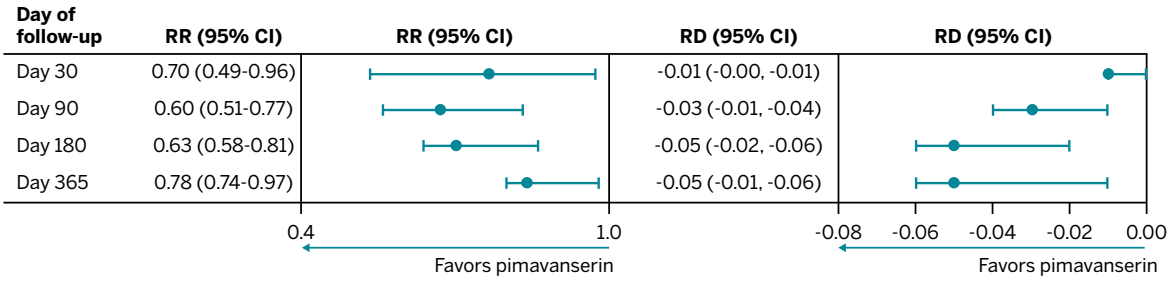
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pimavanserin | 4,381 | 1,399 | 645 | 275 | 128 | 63 | 24 | <11 | |
| Comparator | 4,381 | 1,028 | 437 | 176 | 88 | 36 | 11 | <11 | <11 |

- Cumulative incidence curves for the matched cohort demonstrated a generally reduced risk of mortality in the pimavanserin group throughout the follow-up; however, after approximately 3 years, small sample sizes limited interpretation


Abbreviations and References

## Rao et al.[12]

**RR and risk difference for all-cause mortality in the matched primary PDP cohort**




Time period–specific RR and 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 on days 90 and 180

On the **absolute scale (RD)**, the largest benefit of pimavanserin was seen from day 180 through day 365

In the matched LTC/SNF subcohort, no difference was seen in any time period–specific analysis


Abbreviations and References

◀ 17 ▶

## Longardner et al.[13]

### Overview

- Retrospective EMR data extraction by the UCSD, including data for clinically diagnosed patients with PD
- Patients with PDP were investigated for clinical, iatrogenic, and demographic factors associated with increased mortality between April 29, 2016, and April 29, 2019

### Methodology

- Mortality and clinical characteristics during the study period were compared between:

Untreated patients

Patients receiving pimavanserin, quetiapine, or both

- For patients prescribed APs, an individual chart review was performed to ascertain that the medication was prescribed for the treatment of psychosis (i.e., rather than for sleep or mood)*

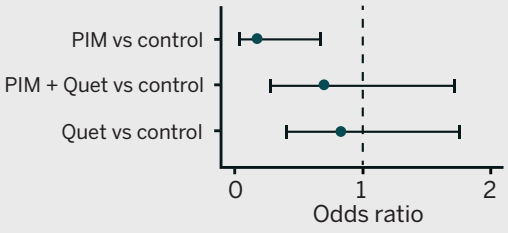
### Results

- The risk of all-cause mortality was lower in patients treated with pimavanserin vs untreated patients
- Compared with the untreated group, there were no differences in adjusted mortality for patients receiving quetiapine or patients on combination therapy

#### Mortality outcomes vs untreated patients

| | Patients | Events | PDP Medication |
|---|---|---|---|
| | PIM | Quet | PIM + Quet |
| Sample size, n | 34 | 147 | 68 |
| Odds ratio (95% CI)† | 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 |

#### Mortality odds ratios for treated patients with PDP vs untreated PDP controls




*Psychosis was diagnosed based on the ICD-10 code and AP prescription. †Adjusted for age, sex, levodopa equivalent daily dose, and dementia.


Abbreviations and References

## Alipour-Haris et al.[14]

### Overview

- Retrospective, new-user cohort study conducted in a 15% random sample of Medicare beneficiaries with PD initiating pimavanserin or quetiapine aged ≥65 years from May 1, 2016, to December 30, 2018, to assess all-cause mortality and all-cause hospitalization

### Methodology

Patients initiating pimavanserin (n=844)

Patients initiating quetiapine (n=2,505)

Required to have a diagnosis of
• Psychosis • Delusions • Hallucinations

- Patients were excluded if they had prescriptions for other APs 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 on the index date and ended on the date of death or censoring at the earliest occurrence of 1 of the following events:
  - End of the study period
  - Discontinuation of the index study drug
  - Loss to follow-up
  - Disenrollment from Medicare
  - Switch to another AP
- SMRW based on propensity score was used to balance pimavanserin initiators and quetiapine initiators on treatment group characteristics

### Results

- After SMRW, there were no meaningful differences in patient characteristics between pimavanserin and quetiapine users
- The SMRW HR for all-cause mortality did not indicate any difference in the risk of mortality in patients treated with pimavanserin vs quetiapine at any time point

**All-cause mortality for pimavanserin use compared with quetiapine use***

| 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 |

- In sensitivity analyses where patients were stratified based on quartiles of disease-risk scores, baseline frailty indices, and propensity scores, results were similar to those of the main analysis

*An SMRW analysis was conducted using standardized mortality ratio weighted (for all patient's covariates) Cox proportional hazards regression model.


Abbreviations and References

◀ 19 ▶

## Nguyen et al.[15]

**Study design** | Results

### Overview

- Retrospective, new-user cohort study using a large US commercial health insurance database (Optum Clinformatics® Data Mart)
- Assessed all-cause mortality among patients with PD aged ≥40 years initiating pimavanserin, preferred DRB atypical APs, or non-preferred DRB atypical APs from May 1, 2016, to March 31, 2021

### Methodology

Pimavanserin (n=775)

Preferred DRB atypical APs (n=4,563)

Non-preferred DRB atypical APs (n=1,297)

**Preferred DRB atypical APs**

- Quetiapine
- Clozapine

**Non-preferred DRB atypical APs**

- Aripiprazole
- Asenapine
- Brexpiprazole
- Cariprazine
- Iloperidone
- Lumateperone
- Lurasidone
- Olanzapine
- Paliperidone
- Risperidone
- Ziprasidone

**Patients were excluded if they had concurrent diagnosis codes for:**

- Atypical and drug-induced parkinsonism
- Amyotrophic lateral sclerosis
- DLB
- Bipolar disorder

- Follow-up started from the first prescription claim of atypical APs and ended on the date of death or censoring at the earliest occurrence of 1 of the following events: loss of insurance coverage or end of the study period
- Propensity score methods were used. The primary 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


Abbreviations and References

◀ 20 ▶

## Nguyen et al.[15]

Study design | **Results**

### Results

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

### Summary of the all cause mortality risk in the matched cohorts

| 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 and References

◀ 21 ▶

## Mosholder et al.[16]

**Study design** | Results

### Overview

- Retrospective, new-user cohort study conducted in Medicare beneficiaries (100% sample) with PD initiating pimavanserin or atypical APs from April 2016 to March 2019 to assess all-cause mortality

### Methodology

Patients initiating pimavanserin (n=3,227)

Patients receiving atypical APs (n=18,442)

**Atypical APs:**

- Quetiapine (78%)
- Risperidone (9%)
- Olanzapine (6%)
- Aripiprazole (5%)
- Others (1%)

- **Patients were excluded if they had a diagnosis of:**
  - Schizophrenia
  - Schizophreniform disorder
  - Schizoaffective disorder
- Follow-up began on the day after cohort entry and ended on the date of death or censoring at the earliest occurrence of 1 of the following events: disenrollment from Medicare, stopping treatment (i.e., gap of >14 days between study drug prescriptions), dispensing of a non-study AP, switching between pimavanserin and an atypical AP, or end of the study period
- IPTW was used to address potential confounding. After weighting, the cohorts were closely balanced on all covariates


Abbreviations and References

◀ 22 ▶

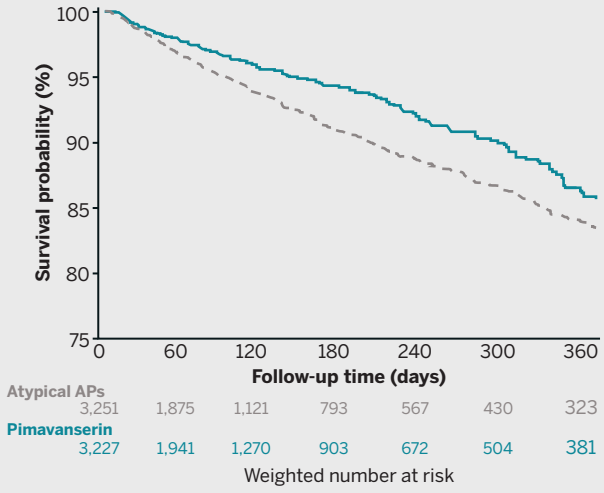
## Mosholder et al.[16]

Study design | **Results**

### Mortality findings

- During follow-up, 207 pimavanserin users and 1,752 atypical AP users died
- In the weighted Kaplan–Meier plot, pimavanserin users exhibited a lower risk of all-cause mortality through 360 days of follow-up
- Overall, pimavanserin use was associated with significantly lower mortality vs atypical AP use (HR, 0.77; 95% CI, 0.66–0.90)
- However, statistical evaluation showed that 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 the mortality risk was lower with pimavanserin than with atypical APs during the first 180 days of use (HR, 0.65; 95% CI, 0.53–0.79) and was similar thereafter (HR, 1.05; 95% CI, 0.82–1.33)

**Kaplan–Meier plot of weighted cumulative survival probability among patients with PD treated with pimavanserin or atypical APs**




### Median follow-up time and mortality at 75 and 180 days of follow-up

| | Median Exposed Follow-up Time | At 75 Days of Follow-up | | At 180 Days of Follow-up | |
|---|---|---|---|---|---|
| | | Mortality (%) | Number needed to harm (95% CI)* | Mortality (%) | Number needed to harm (95% CI)* |
| Pimavanserin | 78 days (IQR, 44–202) | 2.4 | 64 (38–220) | 3.7 | 30 (19–73) |
| Atypical APs | 74 days (IQR, 44–170) | 3.6 | | 5.4 | |

*Defined as the number needed to harm for 1 excess death with atypical AP treatment vs pimavanserin treatment.


Click here to review the results of the subgroup analyses

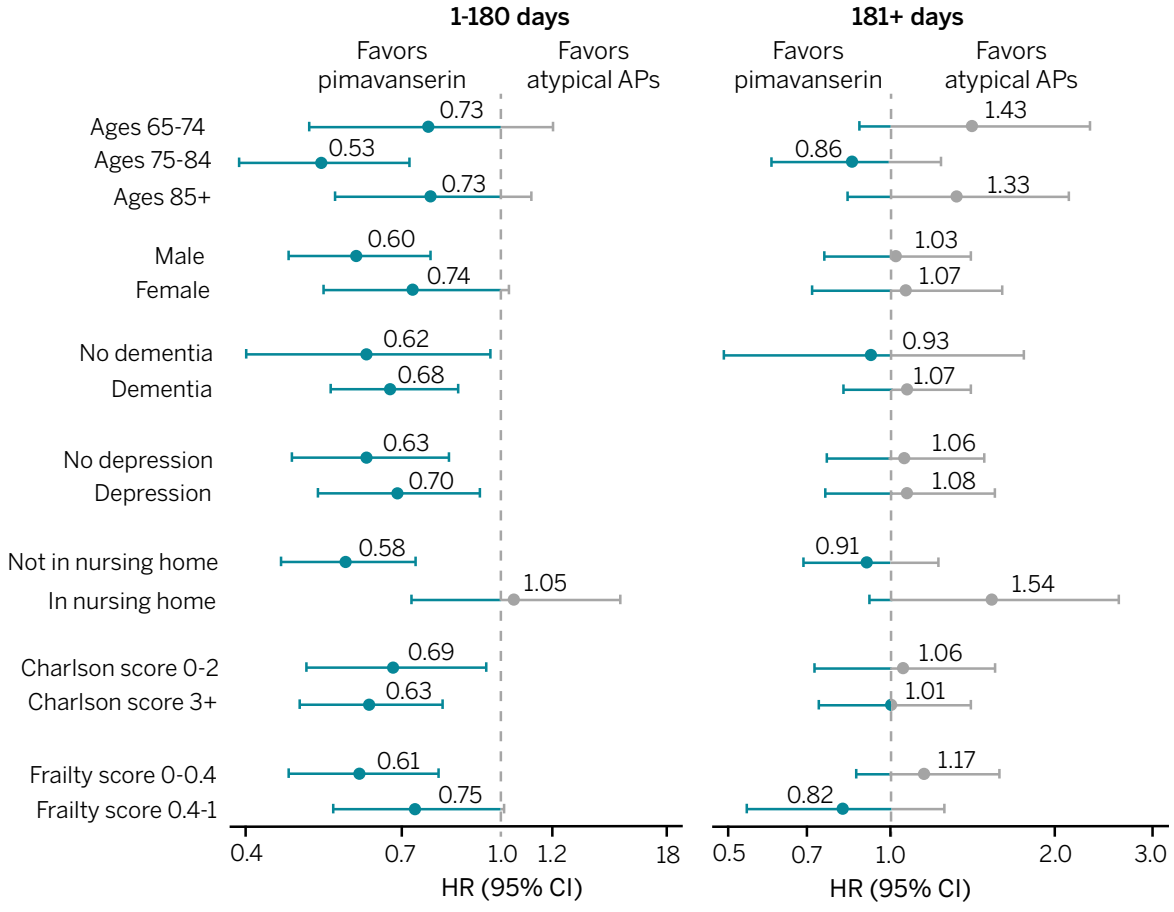
Click here to review the the results of the sensitivity analyses

Abbreviations and References

## Mosholder et al.[16]

- Results of subgroup analyses were largely consistent with those of the main analyses, except for the results of a subgroup of patients residing in nursing homes (~15% of patients in the analysis)

**Subgroup analyses: HRs for death among patients with PD treated with pimavanserin or atypical APs**



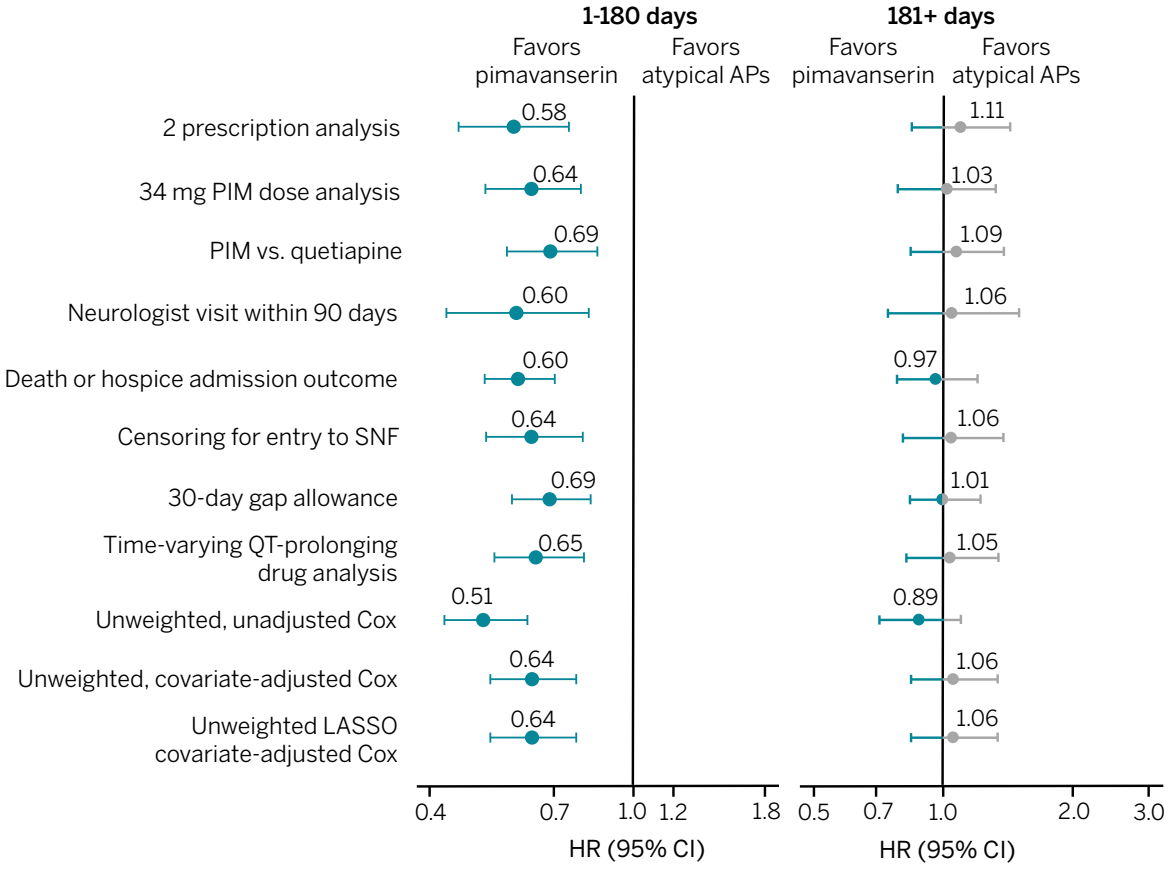


Abbreviations and References

## Mosholder et al.[16]

- Results of sensitivity analyses were largely consistent with those of the main analyses, except for the results of a subgroup of patients residing in nursing homes (~15% of patients in the analysis)

**Sensitivity analyses: HRs for death among patients with PD treated with pimavanserin or atypical APs**





Abbreviations and References

## Hwang et al.[17]

**Study design** | Results

### Overview

- Retrospective study in LTC residents aged ≥65 years with PD performed using Minimum Data Set 3.0–linked Medicare claims data (100% sample) to evaluate the risk of hospitalization and death up to 1 year in pimavanserin users and non-users

### Methodology

**Pimavanserin users (n=2,186)**
**43.2%** were using concomitant APs

**Non-users (n=18,212)**
**22.1%** were using concomitant APs

- Patients with comorbid psychiatric disorders included in the study were as follows:

**Schizophrenia**
13.3% users | 11.2% non-users

**Bipolar disorder**
10.1% users | 9.5% non-users

- All-cause mortality was assessed at 30, 90, 180, and 365 days following pimavanserin initiation
- Both users and non-users were censored at the end of the study period and the end of the prespecified follow-up period*
- Propensity score-based IPTW was used to balance pimavanserin users (n=2,089) and non-users (n=18,248) on 24 baseline characteristics
  - After weighting:

**Schizophrenia**
16.0% users | 11.5% non-users

**Bipolar disorder**
12.0% users | 9.6% non-users

**Concomitant APs**
28.1% pimavanserin users | 24.6% non-users

*Pimavanserin users were censored at the time of pimavanserin discontinuation (i.e., no prescription resupply within 30 days), and non-users were censored upon pimavanserin initiation.

## Hwang et al.[17]

Study design | **Results**

### Mortality findings

- Pimavanserin use vs non-use in LTC residents was associated with an IPTW aHR of 0.76 at 30 days after initiation, 1.20 at 90 days after initiation, 1.28 at 180 days after initiation, and 1.56 at 1 year after initiation

### Pimavanserin use and risk of all-cause mortality

| Follow-up Period | IR (100 Person-Years) | | Unadjusted HR (95% CI) | IPTW aHR (95% CI) |
|---|---|---|---|---|
| | Users (n=2,186) | Non-users (n=18,212) | | |
| 30 days | 36.8 | 41.1 | 0.86 (0.67–1.12) | 0.76 (0.56–1.03) |
| 90 days | 46.0 | 40.0 | 1.13 (0.97–1.31) | 1.20 (1.02–1.41) |
| 180 days | 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) |

### Secondary analyses for pimavanserin use and risk of all-cause mortality

| Follow-up Period | Mortality Events, n (%) | | aHR (95% CI) | |
|---|---|---|---|---|
| | Users (n=2,186) | Non-users (n=18,212) | Standard Cox Proportional Hazards Regression Analysis | Propensity Score–Matched Analysis* |
| 30 days | 61 (2.8) | 594 (3.3) | 0.91 (0.54–1.51) | 0.75 (0.59–0.96) |
| 90 days | 187 (8.6) | 1,613 (8.9) | 1.22 (1.00–1.49) | 1.12 (0.96–1.30) |
| 180 days | 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) |

*A propensity score–matched analysis was conducted in a 1:1 matched set of 2,186 pimavanserin users and 2,186 non-users.

## Brown et al.[18]

### Overview

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

### Results

- As of Q3/2019, there were 2,287 reports of death associated with pimavanserin
- In the full FAERS base population, pimavanserin use yielded a PRR lower 95% CI 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
- Pimavanserin metrics in PD-restricted groups were similar in direction and magnitude to those of clozapine and quetiapine

### Comparative PRRs for treatment alternatives

| | 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) |
| | +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) |

The use of the 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.


Abbreviations and References

◀ 28 ▶

## Horn et al.[19]

### Overview

- Retrospective cohort study conducted at PDMDC
- Patients with PD or DLB who were initiated on quetiapine (n=47) or pimavanserin (n=45) for psychosis between April 2016 and May 2018 (mean age, 73±8 years)

### Methodology

- Patients with an ICD code for schizophrenia or bipolar disorder were excluded

**1 Primary outcome:**

- Time to discontinuation of pimavanserin or quetiapine, assessed using Kaplan–Meier survival analysis

**2 Secondary outcomes:**

- Mortality
- Reason for antipsychotic discontinuation
- Change in motor Unified PD Rating Scale score
- Subjective improvement in psychosis as reported by the patient or caregivers and documented in the EMR

### Results

- Mean follow-up duration was 317±223 days

**Baseline differences:**

- More DLB in the pimavanserin cohort vs quetiapine cohort (33% vs 11%; p=0.01)
- More prior AP exposure in the pimavanserin cohort vs quetiapine cohort (62% vs 6%; p<0.001)

**Outcomes:**

- 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 AP in both cohorts; however, patients in the quetiapine cohort were more likely to discontinue the medication due to side effects, whereas 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 with the pimavanserin group (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)


Abbreviations and References

◀ 29 ▶

## Gupta et al.[20]

### Overview

- Retrospective chart review to investigate the safety and efficacy of pimavanserin in patients with PDP treated at KUMC (n=107) from June 2016 to September 2018

### Baseline characteristics

Mean age
**74.2 years**

Mean MoCA score
**18.8**

### Results

- Thirty patients died after initiation of pimavanserin; however, only 16 were taking pimavanserin at the time of 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 APs with pimavanserin (20% vs 15.6%)

**Characteristics and outcomes among deceased patients on pimavanserin**

| Outcome Category | Pimavanserin (n=107) |
|---|---|
| Mortality rate | 20 per 100 patient-years |
| Average pimavanserin exposure before death | 215 days |

## Sellers et al.[21]

### Overview

- Retrospective chart review of patients prescribed pimavanserin at VUMC between May 2016 and July 2018
- Patients who began pimavanserin treatment (n=91) were included in the main efficacy analysis*, and patients who were prescribed but not started on pimavanserin (n=16) were used as controls to assess safety

### Patient characteristics

Initiated pimavanserin (n=91) | Not on pimavanserin (n=16) | Age: Mean±SD age 71.4±8.1 years

| Diagnosis | Patients who began pimavanserin (n=91) |
|---|---|
| PD | 71 |
| DLB | 11 |
| PD with early cognitive symptoms | 7 |
| PD with logopenic aphasia | 1 |
| PD with concern of normal pressure hydrocephalus | 1 |

Included in the PD group for analysis

- Demographic characteristics, including gender, age, diagnosis, and reported psychiatric symptoms, were similar to those of patients who began pimavanserin treatment

### Results

**Pimavanserin**
15% (14/91) died

**Not on pimavanserin**
44% (7/16) died

($x^2$=6.94; p<0.01)

*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).

## Moreno et al.[22]

### Overview

- Retrospective review of patients in the UCSD Health System diagnosed with PD and prescribed pimavanserin (n=113), quetiapine (n=505), or both (n=58) during April 29, 2016, to April 29, 2018

### Baseline demographics

| | PDP Medication | | |
|---|---|---|---|
| | **Pimavanserin (n=113)** | **Quetiapine (n=505)** | **Pimavanserin + Quetiapine (n=58)** |
| Age, years, mean (SD) | 75.9 (9.1) | 75.2 (12.4) | 74.1 (10.4) |
| % Female | 38.1 | 42 | 37.9 |

### Results

- Mortality was higher for quetiapine vs pimavanserin and for combination therapy vs pimavanserin, but the differences were not statistically significant (p=0.17 and p=0.28, respectively)

| **Outcome Category** | PDP Medication | | |
|---|---|---|---|
| | **Pimavanserin (n=113)** | **Quetiapine (n=505)** | **Pimavanserin + Quetiapine (n=58)** |
| Total deaths (April 29, 2016–April 29, 2018) | 8 | 58 | 7 |
| Mortality, % | 7.1 | 11.5 | 12.1 |
| Age of the deceased, years, 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) |

- The mean age of the deceased cohorts was similar between the groups, and the 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 having a similar mean age of 80 years (range, 78–82; n=784) was 5.9%
- Odds ratios showed an increased risk of mortality in the quetiapine group and a trend toward an increased risk in the combination therapy group (p=0.07) compared to patients with PD not taking APs


Abbreviations and References

◀ 32 ▶

## Mahajan et al.[23]

### Overview

- Retrospective chart review of patients receiving pimavanserin
- Study was conducted in 2017 and included data collected from the Henry Ford Parkinson's Disease and Movement Disorders Clinic

### Methodology

- Demographic data and AE data were collected using telephone interviews

### Results

- Of the patients included, 16 were diagnosed with PDP
- 1 patient died within 8 months of the interview


Abbreviations and References

X

## Abbreviations and References

**Abbreviations: AE,** adverse event; **aHR,** adjusted hazard ratio; **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; **FDA,** Food and Drug Administration; **HR,** hazard ratio; **ICD-10,** International Classification of Diseases, 10th Revision; **ICD,** International Classification of Diseases; **IPTW,** inverse probability of treatment weighting; **IQR,** interquartile range; **IR,** incidence rate; **ITT,** intent to treat; **KUMC,** University of Kansas Medical Center; **LASSO,** Least Absolute Shrinkage and Selection Operator; **LTC,** long-term care; **MoCA,** Montreal Cognitive Assessment; **NR,** not reported; **OLE,** open-label extension; **PD,** Parkinson's disease; **PDMDC,** University of Pennsylvania Parkinson's Disease and Movement Disorders Center; **PDP,** Parkinson's disease psychosis; **PIM,** pimavanserin; **PRR,** proportional reporting ratio; **QD,** once daily; **Quet,** quetiapine; **RD,** absolute risk difference; **RR,** relative risk; **SD,** standard deviation; **SMRW,** standardized mortality ratio weighting; **SNF,** skilled nursing facility; **UCSD,** University of California San Diego; **US,** United States; **VUMC,** Vanderbilt University Medical Center.

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