Fall and fracture findings in patients receiving NUPLAZID® (pimavanserin) for Parkinson's disease psychosis

The following information is provided for educational and scientific exchange purposes only.

Indication and Important Safety Information

NUPLAZID is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Important Safety Information

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- 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.

- **Contraindication:** NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported.
- **Warning and Precautions:** QT Interval Prolongation
  - NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval (e.g., Class 1A antiarrhythmics, Class 3 antiarrhythmics, certain antipsychotics or antibiotics).
  - NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.
- **Adverse Reactions:** The adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).
- **Drug Interactions:**
  - Coadministration with strong CYP3A4 inhibitors increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
  - Coadministration with strong or moderate CYP3A4 inducers reduces NUPLAZID exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.

Dosage and Administration

Recommended dose: 34 mg capsule taken orally once daily, without titration, with or without food.

NUPLAZID is available as 34 mg capsules and 10 mg tablets.

Please read the full NUPLAZID® Prescribing Information, including **Boxed WARNING** for more details.

Background: Falls and fractures in PD with and without psychosis

Patients with PD are at increased risk of falls and fractures;[1-3] risk factors include history of falls, postural instability, freezing of gait, leg muscle weakness, and cognitive impairment[2,4]

Retrospective claims analysis of US Medicare patients with PD (2008–2018)[5]*

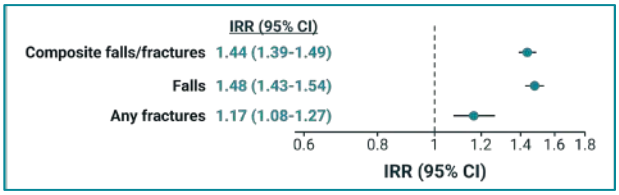
Study population: patients aged ≥40 years with diagnosis of PD between January 2008 to June 2018, with ≥6 months of continuous enrollment prior to PD diagnosis date

- Rates of falls and fractures were compared between matched cohorts:†

PD without psychosis n=24,164	PD with psychosis n=12,082

- Matched PD psychosis patients had higher incidence of falls and fractures than PD patients without psychosis (IRR=1.44; 95% CI, 1.39–1.49)
- The higher incidence was noted separately for:
  - Falls (IRR = 1.48; 95% CI, 1.43–1.54)
  - Any fractures (IRR = 1.17; 95% CI, 1.08–1.27)

Incidence rate ratios (IRRs) of falls and fractures for the matched PD-PD psychosis cohort



Limitations:

- Potential for missing or misclassified study variables
- Falls/fractures may only represent a subset of events
- Prescription claims may not reflect actual exposure to medications and use by the patient
- Inpatient medication history not available

***This study was funded by Acadia Pharmaceuticals Inc.** †The impact of antipsychotic treatment was not assessed.

Falls and fractures among nursing home residents with PD psychosis treated with atypical APs[6*]

Retrospective cohort study using Medicare database (2013–2019):†‡

To examine risk of all-cause falls or fractures among LTC/NH residents with PD psychosis treated with pimavanserin vs. other atypical APs or vs. quetiapine

Study population (N=7,187)

- PD psychosis residents initiating (i.e., index date) continuous monotherapy of pimavanserin or other atypical APs (aripiprazole, risperidone, quetiapine, olanzapine) for ≥6-months during January 2014 to December 2018 without any prior atypical AP use for ≥1 year prior to the index period
- *Exclusion criteria:* PD psychosis residents with a pre-index diagnosis of psychosis, secondary parkinsonism, delirium, other psychotic disorders, alcohol/drug-induced psychosis, schizophrenia, paranoia, or personality disorders

Study outcomes during 6-month follow-up

- **Falls,** defined using ICD-9 or ICD-10 diagnostic claims for ≥1 of the following:
  - Falls on the same level
  - Falls from a different level
  - Unspecified falls for any other reason
- **Fractures,** defined using ICD-9 or ICD-10 diagnostic claims for hip, pelvic or femur fractures
- **Composite of falls or fractures**

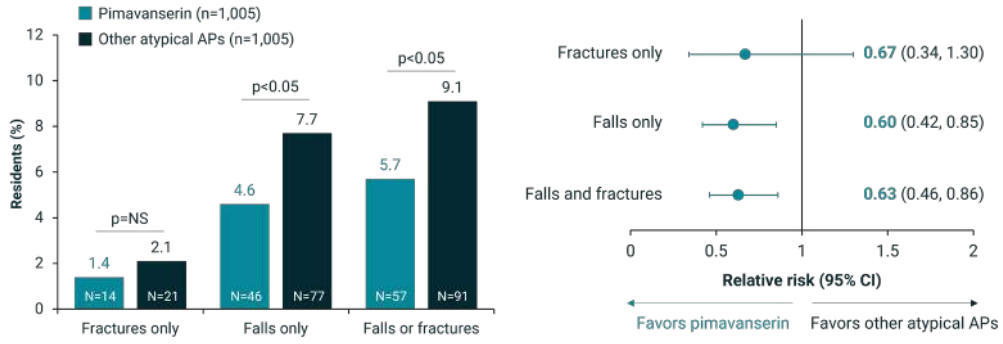
Propensity score matching

- Residents on pimavanserin were 1:1 matched on 31 variables with residents on other atypical APs or quetiapine

Matched PIM residents n=1,005

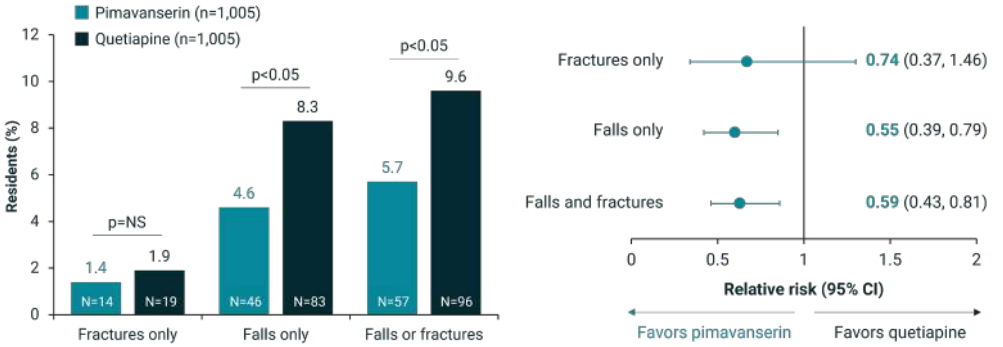
Matched other atypical AP residents n=1,005

Risk of falls and fractures in matched residents treated with pimavanserin vs. other atypical APs



- The relative risk ratio for falls only was 0.60 (95% CI 0.42, 0.85; p<0.05), indicating a lower risk of falls with pimavanserin
- The relative risk ratio for the composite of falls and fractures was 0.63 (95% CI 0.46, 0.86; p<0.05), indicating a lower risk of falls with pimavanserin

Risk of falls and fractures in matched residents treated with pimavanserin vs. quetiapine



- The relative risk ratio for falls only was 0.55 (95% CI 0.39, 0.79; p<0.05), indicating a lower risk of falls with pimavanserin
- The relative risk ratio for the composite of falls and fractures was 0.59 (95% CI 0.43, 0.81; p<0.05), indicating a lower risk of falls with pimavanserin

Study limitations and considerations

- Sampling errors due to miscoding or under coding of claims may have occurred
- Biased estimates may have resulted due to the absence of variables such as medical/clinical characteristics, socioeconomic resident characteristics or other factors in claims data
- Residual imbalance may exist even after propensity score matching (pimavanserin cohort had lower obesity, higher diabetes, and higher hypertension rates)
- Baseline or prior risk of falls and fractures were not included as a covariate in the adjusted analysis
- Granular details about the usage of antihypertensives at differing dose ranges were outside of scope of this research
- Underlying PD or PD psychosis severity was not controlled for since severity cannot be defined in claims data
- Since only major fractures were considered, this analysis might not capture the full picture of other fractures resulting from falls. Fractures of the wrist, fingers, or other bones that may result from falls could be underestimated

***This study was funded by Acadia Pharmaceuticals Inc.** †Parts A, B, and D claims from 100% Medicare sample. ‡Risk of falls/fractures were compared and reported for 6-months follow-up, controlling for age, gender, region, race, co-existing insomnia, or co-existing dementia

Falls and fractures in patients with PD psychosis treated with atypical APs[7*]

Retrospective cohort study using US commercial insurance and supplemental Medicare claims (2015–2019):

To examine risk of all-cause falls or fractures among patients with PD psychosis treated with pimavanserin vs. other atypical APs

Study population (N=38,942)

- PD psychosis patients initiating (i.e., index date) monotherapy with pimavanserin or other atypical APs (clozapine, quetiapine, risperidone, olanzapine, aripiprazole, brexpiprazole) between May 1, 2015, and December 31, 2019, without prior use of any atypical or conventional AP medication
- *Exclusion criteria:* diagnoses of bipolar disorder, schizophrenic disorders, or Huntington's disease, or pathologic fracture that may have resulted from conditions such as cancer, infection, osteomalacia, and Paget's disease before the index date

Study outcomes

- **Falls,** identified from ICD-9 or ICD-10 diagnosis codes for accidental falls in any setting diagnostic position
- **Fractures,** defined using ICD-9 or ICD-10 diagnosis codes in any diagnostic position
- **Composite of falls or fractures**
- **Site-specific fractures of interest** (femur, hip, pelvis, upper limb, vertebrae)

Propensity score matching

- Patients on pimavanserin were 1:2 matched on predefined variables with patients on other atypical APs

Matched PIM patients n=108

Matched other atypical AP patients n=216

IRs and IRRs of falls and fractures for the matched cohort

Outcome	Treatment group	No. of patients	No. of events	IR (95% CI) per 100 PYs	IRR (95% CI)
Composite falls/fractures	Pimavanserin	108	8	18.74 (8.09–36.93)	0.71 (0.27–1.67)
	Comparator	215[a]	21	26.38 (16.33–40.32)	Reference
Falls	Pimavanserin	108	8	18.74 (8.09–36.93)	0.88 (0.33–2.15)
	Comparator	215[a]	17	21.34 (12.43–34.16)	Reference
Any fracture	Pimavanserin	108	1	2.34 (0.06–13.01)	0.31 (0.01–2.56)
	Comparator	216	6	7.50 (2.75–16.33)	Reference

[a]Sample sizes at the index date were reduced because of fall events occurring before the index date, resulting in patients being not at risk at the beginning of the follow-up.

IRs for falls/fractures were numerically lower for patients taking pimavanserin vs. other atypical APs; small event numbers led to imprecise IRRs

Study limitations and considerations

- Use of administrative claims data introduces the potential for missing or misclassified study variables, which may change over time because of the transition in coding systems from ICD-9-CM to ICD-10-CM during the study period
- The methodology for identifying fall and fracture events may have resulted in undercounting
- Because of the relatively small number of fractures identified in the study, estimates of individual fracture sites were imprecise and relatively uninformative
- Patients with evidence of pathologic fractures were excluded or censored, but claims data may lack the granularity to determine etiology of all fracture events or differentiate accidental falls/fractures from those with external causes
- Pharmacy claims for medications may not reflect actual use of the medication by the patient
- These data from employer-based commercial insurance or supplementary Medicare plans may not be generally representative of all patients with PD psychosis

References

1. Kalilani L, et al. *PLoS ONE*. 2016;1(9):e0161689.
2. Allen NE, et al. *Parkinsons Dis*. 2013;906274.
3. Huang YF, et al. *Osteoporos Int*. 2015;26:1723-1732.
4. Pickering RM, et al. *Mov Disord*. 2007;22(13):1892-1900.
5. Forns J, et al. *PLoS ONE*. 2021;16(1):e0246121.
6. Rajagopalan K, et al. *Drugs Real World Outcomes*. 2024;11(3):441-449.
7. Layton JB, et al. *Drugs Real World Outcomes*. 2022;9(1):9-22.

Abbreviations

AP = antipsychotic; CI = confidence interval; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision; IR = incidence rate; IRR = incidence rate ratio; PD = Parkinson's disease; PIM = pimavanserin; PY = person-year.

***This study was funded by Acadia Pharmaceuticals Inc.**

Important disclosures

This information is disseminated per United States Food and Drug Administration (FDA) draft guidance for industry titled “Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products – Recommended Practices.”

Information has not been reviewed by the FDA and may not be consistent with the FDA-approved Prescribing Information (PI). Comparisons of efficacy or safety between or among drugs should not be drawn or inferred without head-to-head clinical data. The benefit-risk profile of NUPLAZID as described in the current FDA-approved PI has not changed. It is important to note that falls have been identified during postapproval use of NUPLAZID and are listed as a postmarketing adverse reaction in the FDA-approved PI.

By providing this information, Acadia is not recommending or suggesting that any drug mentioned herein should be used for conditions, purposes, or uses other than the one(s) for which the FDA has approved it. Acadia recommends the use of NUPLAZID consistent with the FDA-approved PI.

As always, healthcare professionals should exercise their professional judgment to make clinically sound decisions for individual patients, including reviewing the FDA-approved PI prior to initiating NUPLAZID or any other drug mentioned herein and appropriately monitoring patients as they continue their treatment for hallucinations and delusions associated with Parkinson’s disease psychosis.