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NUPLAZID® (pimavanserin): Falls and Fractures

This letter is provided in response to your specific request for information on events of falls and fractures with pimavanserin in patients with Parkinson's disease (PD) psychosis.

Summary

- In a **pooled analysis** of 3 randomized, placebo-controlled, 6-week, Phase 2b/3 and Phase 3 studies in PD psychosis, the overall incidence of fall-related treatment-emergent adverse events (TEAEs) was 7.4% with pimavanserin 34 mg and 10.0% for placebo.[1]
- In **a placebo-controlled Phase 2 study, ACP-103-006**, evaluating pimavanserin doses up to 51 mg, 2 fall events were reported in 2 (6.9%) participants compared with 6 fall events in 3 (9.7%) participants in the placebo group.[2]
- In the **open-label extension study** ACP-103-015 evaluating pimavanserin 34 mg QD in participants who completed the treatment period of the double-blind studies (N=459), fall was reported as a TEAE in 32.0% of participants, and hip fracture was among the most common serious TEAEs, reported in 2.2% of participants.[3]
- In a **post hoc analysis** of an interim dataset from ACP-103-015, the incidence rate ratio (IRR) for fall-related events was 1.30 (95% CI 0.74–2.15) for participants who were concomitantly treated with another antipsychotic (n=66) compared with those receiving pimavanserin as monotherapy (n=357).[4]
- In a **retrospective claims analysis** of US Medicare patients with PD psychosis, incidence rate estimates for composite falls/fractures in matched treatment groups were 18.7 events per 100 person-years (PY; 95% CI 8.1–36.9) for patients who initiated pimavanserin (n=108) and 26.4 events per 100 PY (95% CI 16.3–40.3) for patients who initiated comparator antipsychotic treatment (n=215).[5]
- In a **retrospective claims analysis** of US Medicare long-term care (LTC) and nursing home (NH) residents with PD psychosis, the relative risk of falls and fractures was 0.63 (95% CI 0.46–0.86, $p<0.05$) for matched residents on pimavanserin (n=1,005) vs. other-AAP (n=1,005) and 0.59 (95% CI 0.43–0.81, $p<0.05$) for residents on pimavanserin vs. quetiapine only (n=1,005).[6]
- In a **retrospective claims analysis** of US Medicare LTC residents with attempted gradual dose reduction (GDR), 2.8% (20/691) of residents who continued pimavanserin experienced falls compared with 9.4% (41/436) of residents who did not continue pimavanserin ($p<0.05$).[7]

Background

The rates of falls and fractures occurring in patients taking pimavanserin have been assessed in randomized, placebo-controlled clinical trials,[1,2] a long-term, open-label extension study,[3,4] 2 retrospective claims analyses,[5,7] and in postmarketing experience.[8] The data from these analyses are summarized below.

Pooled Data From Placebo-controlled Phase 2b/3 and Phase 3 Studies

Safety data were pooled from 3 randomized, placebo-controlled, 6-week, Phase 2b/3 and Phase 3 studies in PD psychosis:[1]

- ACP-103-012: A randomized, double-blind, outpatient Phase 2b/3 study that evaluated the safety and efficacy of pimavanserin 8.5 mg and 34 mg once daily (QD) compared to placebo in 298 participants for up to 6 weeks.[9]
- ACP-103-014: A randomized, double-blind, outpatient Phase 2b/3 study that evaluated the safety and efficacy of pimavanserin 8.5 mg and 17 mg QD compared to placebo in 123 participants for up to 6 weeks.[10]
- The pivotal Phase 3 trial, ACP-103-020, was a randomized, double-blind, outpatient, Phase 3 study that evaluated the safety and efficacy of pimavanserin 34 mg QD compared to placebo in 199 participants with PDP for up to 6 weeks.[11]

The assessment of fall-related events in this population included the following terms: fall, ankle fracture, clavicle fracture, hip fracture, craniocerebral injury, head injury, joint dislocation, and spinal fracture. The overall incidence of TEAEs for fall-related events was lower in the pimavanserin 34 mg group (7.4%) than for the placebo group (10.0%) (**Table 1**). TEAEs of fall were the most frequently reported event in this category (6.0% and 9.1%, respectively). All other events were experienced by ≤1 subject per blinded treatment group with the exception of joint dislocation (2 participants [0.9%] in the placebo group).[1]

Table 1. TEAEs of Fall-related Events by Preferred Term (Pooled Safety Data)[1]

	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Fall-related Events	7 (5.0)	3 (7.3)	15 (7.4)	25 (6.5)	23 (10.0)
Fall	7 (5.0)	3 (7.3)	13 (6.4)	23 (6.0)	21 (9.1)
Ankle fracture	0	0	1 (0.5)	1 (0.3)	0
Clavicle fracture	0	0	1 (0.5)	1 (0.3)	0
Hip fracture	1 (0.7)	0	0	1 (0.3)	1 (0.4)
Craniocerebral injury	0	0	0	0	0
Head injury	0	0	0	0	0
Joint dislocation	0	0	0	0	2 (0.9)
Spinal fracture	0	0	0	0	1 (0.4)

A TEAE was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.
Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.
Denominators for the percentages were the number of subjects in each treatment group.
Abbreviations: PIM=pimavanserin; TEAE=treatment-emergent adverse event.

ACP-103-006

Study 006 was a Phase 2, randomized, double-blind, placebo-controlled, multi-center trial conducted in the U.S. to determine the safety of pimavanserin doses up to 51 mg in participants with PD psychosis. During the four-week trial, participants (N=60) were randomized 1:1 to receive placebo or pimavanserin daily starting at 17 mg on study Day 1. The daily dose could be subsequently increased to 34 or 51 mg daily on study Days 8 and 15, respectively, based on clinical responsiveness. The primary endpoint was Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III (Activities of Daily Living and Motor Function, respectively).[1,2] Most subjects in the active arm escalated to the 34 mg dose level, without need for further escalation to 51 mg: the mean final daily dose was 38.1 mg.[1,12] At Day 28, no statistically significant differences were observed in treatment effect for the combined score of UPDRS, Parts II (Activities of Daily Living) and III (Motor Function) (p=0.74, 95% CI: –4.18, 5.80).[2]

In total, 133 TEAEs were reported in 21 (72.4%) patients receiving pimavanserin and 24 (77.4%) participants receiving placebo.[2] In the pimavanserin group, 2 fall events were reported in 2 (6.9%) participants compared with 6 fall events in 3 (9.7%) participants in the placebo group.

Open-Label Extension Study ACP-103-015

ACP-103-015 was a multicenter, open-label Phase 3 extension study that included participants who had previously completed the treatment period of the double-blind studies. The objective was to assess the long-term safety and tolerability of pimavanserin 34 mg daily in 459 participants with PD psychosis (mean age, 71 years; mean duration of treatment, 728 days).[3]

Overall, TEAEs were reported by 392 (85.4%) participants. The majority of TEAEs were of mild or moderate intensity. Fall was among the most common TEAEs, reported in 32.0% of participants.[3] Fall-related TEAEs were reported in 34.6% participants overall, including hip fracture in 2.6% of participants and head injury in 2.4% (**Table 2**).[13] Fall-related TEAEs reported as drug-related were fall in 17 (3.7%) participants, and contusion and femur fracture in 1 (0.2%) participant each.

Table 2. TEAEs of Fall-related Events in >2 Participants in ACP-103-015, by Onset Age Group (Safety Analysis Set)[13]

Preferred Term	≤50 Yrs N=3[a] n (%)	51-60 Yrs N=48[a] n (%)	61-70 Yrs N=169[a] n (%)	71-80 Yrs N=244[a] n (%)	≥81 Yrs N=83[a] n (%)	Overall (N=459) n (%)
Fall-related events	**0 (0.0)**	**6 (12.5)**	**50 (29.6)**	**78 (32.0)**	**36 (43.4)**	**159 (34.6)**
Fall	0 (0.0)	6 (12.5)	50 (29.6)	70 (28.7)	32 (38.6)	147 (32.0)
Hip fracture	0 (0.0)	0 (0.0)	2 (1.2)	7 (2.9)	3 (3.6)	12 (2.6)
Head injury	0 (0.0)	0 (0.0)	3 (1.8)	5 (2.0)	3 (3.6)	11 (2.4)
Spinal compression fracture	0 (0.0)	0 (0.0)	2 (1.2)	4 (1.6)	2 (2.4)	8 (1.7)
Hand fracture	0 (0.0)	0 (0.0)	2 (1.2)	2 (0.8)	2 (2.4)	6 (1.3)
Concussion	0 (0.0)	0 (0.0)	3 (1.8)	3 (1.2)	0 (0.0)	6 (1.3)
Femoral neck fracture	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	1 (1.2)	4 (0.9)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	1 (1.2)	4 (0.9)
Joint dislocation	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.6)	0 (0.0)	4 (0.9)

Preferred Term	≤50 Yrs N=3[a] n (%)	51-60 Yrs N=48[a] n (%)	61-70 Yrs N=169[a] n (%)	71-80 Yrs N=244[a] n (%)	≥81 Yrs N=83[a] n (%)	Overall (N=459) n (%)
Facial bones fracture	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.8)	0 (0.0)	3 (0.7)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	2 (2.4)	3 (0.7)
Humerus fracture	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	1 (1.2)	3 (0.7)
Wrist fracture	0 (0.0)	1 (2.1)	1 (0.6)	1 (0.4)	0 (0.0)	3 (0.7)

The analysis of fall-related TEAEs included the following terms: ankle fracture, clavicle fracture, compression fracture, concussion, craniocerebral injury, facial bones fracture, fall, femoral neck fracture, femur fracture, foot fracture, hematuria traumatic, hand fracture, head injury, hip fracture, humerus fracture, joint dislocation, lower limb fracture, lumbar vertebral fracture, radius fracture, rib fracture, spinal compression fracture, spinal fracture, subdural hematoma, subdural hemorrhage, thoracic vertebral fracture, upper limb fracture, and wrist fracture.

[a]The denominator for an age group is the number of subjects on treatment (including a 30-day follow-up) while in that particular age group.

Abbreviations: TEAE=treatment-emergent adverse event; yrs=years.

Fall-related TEAEs by maximum severity are shown in **Table 3**.

Table 3. TEAEs of Fall-related Events in >2 Participants in ACP-103-015, by Maximum Severity (Safety Analysis Set)[13]

Preferred Term	N=459, n (%)		
	Mild	Moderate	Severe
Fall	66 (14.4)	69 (15.0)	12 (2.6)
Hip fracture	1 (0.2)	3 (0.7)	8 (1.7)
Head injury	4 (0.9)	6 (1.3)	1 (0.2)
Spinal compression fracture	1 (0.2)	5 (1.1)	2 (0.4)
Hand fracture	1 (0.2)	5 (1.1)	0 (0.0)
Concussion	3 (0.7)	3 (0.7)	0 (0.0)
Femoral neck fracture	0 (0.0)	1 (0.2)	3 (0.7)
Femur fracture	1 (0.2)	1 (0.2)	2 (0.4)
Joint dislocation	2 (0.4)	2 (0.4)	0 (0.0)
Facial bones fracture	1 (0.2)	2 (0.4)	0 (0.0)
Clavicle fracture	2 (0.4)	1 (0.2)	0 (0.0)
Humerus fracture	0 (0.0)	1 (0.2)	2 (0.4)
Wrist fracture	1 (0.2)	1 (0.2)	1 (0.2)

Abbreviation: TEAE=treatment-emergent adverse event.

Serious TEAEs were reported by 188 (41.0%) participants overall. Hip fracture was among the most common serious TEAEs, reported in 2.2% of participants,[3] with fall, femoral neck fracture and femur fracture reported in 1.3%, 0.9% and 0.9%, respectively.[13] A serious TEAE leading to discontinuation occurred in 80 (17.4%) participants.[3] Of these, hip fracture was reported in 3 (0.7%) participants, fall, femoral neck fracture and femur fracture were reported in 1 participant each.[13]

The following methodology-associated limitations of this open-label extension study should be considered:[3]

- The open-label design, the lack of a comparison group, the likelihood of informative missing data, and the inability to assess participants long term after discontinuation.
- Safety findings should be interpreted with caution given the overall attrition rate over the 11-year study duration.

Post Hoc Analysis

A post hoc analysis was conducted on an interim data set from Study 015 (as of December 13, 2013) to assess adverse events associated with the use of atypical antipsychotic medications.[4] Other antipsychotics were prohibited during the first month of the ACP-103-015, thereafter they could be added if approved by the study Medical Monitor.[13] Four hundred and twenty three of the 459 participants enrolled in Study 015 were eligible for the post hoc analysis (36 participants without concurrent antipsychotic use but with previous or posttreatment antipsychotic use were excluded). Of these patients, 66 received pimavanserin plus an add-on antipsychotic at any time during the study period (with the median time to first use of concurrent antipsychotics at 247 days from baseline) and 357 received pimavanserin monotherapy during the study period.[4]

The follow-up time for the pimavanserin monotherapy group ranged between 1 and 1969 days with a median of 421 days and the follow-up time for the add-on antipsychotic group (counting from the earliest administration of any antipsychotic drug) ranged between 1 and 1544 days with a median of 172 days. At study baseline, these two groups were well matched with respect to age, gender, severity and duration of PD, cognition, and severity of baseline psychotic symptoms. The majority of participants prescribed an add-on antipsychotic were taking quetiapine (n=52; 79%), mostly at daily doses of 25 to 50 mg (range 12.5–350 mg), although 10 of these individuals did receive a different antipsychotic at some point during follow-up. Four (6%) participants received clozapine alone (range 6.25–50 mg) and a further 4 (6%) participants were prescribed risperidone (range 0.125–1 mg), with the remaining 6 (9%) participants receiving a range of different antipsychotics.[4]

The exposure-adjusted incidence rates of fall-related TEAEs are summarized in **Table 4**.[4]

Table 4. Exposure Adjusted Incidence and Incidence Rate Ratios for Fall-related TEAEs (Study ACP-103-015)[4]

Pimavanserin monotherapy (N=357; PY=557)			Pimavanserin + antipsychotic (N=66; PY=74)			IRR (95% CI)
n*	%	EAIR (per 100 PY)	n†	%	EAIR (per 100 PY)	
92	25.8	16.5	16	24.2	21.5	1.30 (0.74, 2.15)

The analysis of fall-related TEAEs included the following terms: ankle fracture, clavicle fracture, compression fracture, concussion, craniocerebral injury, facial bones fracture, fall, femoral neck fracture, femur fracture, foot fracture, hematuria traumatic, hand fracture, head injury, hip fracture, humerus fracture, joint dislocation, lower limb fracture, lumbar vertebral fracture, radius fracture, rib fracture, spinal compression fracture, spinal fracture, subdural hematoma, subdural hemorrhage, thoracic vertebral fracture, upper limb fracture, and wrist fracture.

**All TEAEs are included for participants who did not take concurrent APD.*

†Only TEAEs started after first dose of antipsychotic are included for participants who took concurrent APD.

‡Exposure-adjusted participant-count incidence rate ratio (concurrent APD EAIR/no APD EAIR); 95% CI estimated from a Poisson regression model.

Abbreviations: APD=antipsychotic; CI=confidence interval; EAIR=exposure-adjusted incidence rate; IRR=Incidence Rate Ratio; PY=person-years of exposure; TEAE=treatment-emergent adverse event.

Interpretations of the data from this post hoc analysis of participants in an open-label extension study should be made with caution.

Retrospective Claims Analysis of US Medicare Patients

Layton et al. compared the risk of falls and fractures among patients with PD psychosis treated with pimavanserin vs. other atypical antipsychotics as a primary objective in a retrospective claims analysis of US Medicare patients.[5] The study population consisted of patients with PD-related psychosis aged ≥40 years initiating either pimavanserin or a comparator antipsychotic (clozapine, quetiapine, risperidone, olanzapine, aripiprazole, brexpiprazole) in US commercial insurance and supplementary Medicare claims (May 1, 2015, to December 31, 2019). Psychosis was identified by using diagnosis codes for conditions related to delusions, hallucinations, psychosis, or paranoia in the inpatient or outpatient setting in any diagnosis position. Falls and fractures were identified by using both inpatient and outpatient diagnosis codes.

Patients who initiated comparator antipsychotics (n=216) were matched 2:1 to patients who initiated pimavanserin (n=108). The characteristics of the matched patients were well-balanced between the 2 groups. When comparing the matched treatment groups, the incidence rate estimate for the pimavanserin group for composite falls/fractures (18.7 events per 100 person-years; 95% CI 8.1–36.9) was lower than the rate in the comparator antipsychotic group (26.4 events per 100 person-years; 95% CI 16.3–40.3), though the small number of cases resulted in a relatively imprecise matched IRR of 0.71 (95% CI 0.27–1.67) (**Table 5**). Most of the composite events were falls—very few fracture events were identified—resulting in imprecise incidence rate and IRR estimates for the analyses of overall and site-specific fractures.

Table 5. IRs and IRRs of Falls and Fractures for the Matched Cohort[5]

Outcome	Treatment group	Number of patients	Number 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*	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*	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

**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.*
Abbreviations: CI=confidence interval; IR=incidence rate; IRR=incidence rate ratio; PY=person-years.

Retrospective Claims Analysis of US Medicare LTC/NH Residents

Rajagopalan et al. compared the risk of falls and fractures among LTC/NH residents with PD psychosis who initiated and maintained at least 6 months of monotherapy with pimavanserin, other atypical antipsychotics (quetiapine, risperidone, olanzapine, or aripiprazole), or quetiapine only in a retrospective claims analysis of US Medicare patients. An eligible sample of residents was identified using Medicare Parts A, B, and D claims from January 1, 2013, to December 31, 2019. The PD psychosis population was identified using ICD-9 and ICD-10 diagnostic claims for PD with a concurrent psychosis diagnosis.[6]

Study outcomes were falls, fractures, and a composite of falls or fractures, defined based on ICD-9 or ICD-10 diagnostic claims. Residents initiating pimavanserin vs. other atypical antipsychotics (or pimavanserin vs. quetiapine in a secondary analysis) were propensity score-matched 1:1 to create a balanced sample between cohorts (n=1,005 per group).[6]

After matching, resident characteristics and rates of comorbidities were balanced between the cohorts. Outcome events and relative risks for fractures only, falls only, and composite falls/fractures for the pimavanserin, other atypical antipsychotics, and quetiapine cohorts are summarized in **Table 6** and **Table 7**. The proportion of residents with falls-only and falls/fractures combined was significantly lower for residents on pimavanserin vs. other atypical antipsychotics or quetiapine only ($p<0.05$ for both comparisons).[6]

Table 6. Risk of Falls and Fractures in LTC/NH Residents Treated with Pimavanserin or Other Atypical Antipsychotics[6]

Outcome Events	Pimavanserin n (%)	Other atypical APs n (%)	RR (95% CI)	p-value
Fractures only	14 (1.4)	21 (2.1)	0.67 (0.34, 1.30)	NS
Falls only	46 (4.6)	77 (7.7)	0.60 (0.42, 0.85)	<0.05
Falls or Fractures	57 (5.7)	91 (9.1)	0.63 (0.46, 0.86)	<0.05

Abbreviations: AP=antipsychotic; CI=confidence interval; NS=not significant; RR=relative risk.

Table 7. Risk of Falls and Fractures in LTC/NH Residents Treated with Pimavanserin or Quetiapine[6]

Outcome Events	Pimavanserin n (%)	Quetiapine n (%)	RR (95% CI)	p-value
Fractures only	14 (1.4)	19 (1.9)	0.74 (0.37, 1.46)	NS
Falls or Fractures	46 (4.6)	83 (8.3)	0.55 (0.39, 0.79)	<0.05
Falls only	57 (5.7)	96 (9.6)	0.59 (0.43, 0.81)	<0.05

Abbreviations: CI=confidence interval; NS=not significant; RR=relative risk.

Retrospective Claims Analysis of US Medicare LTC Residents

Rajagopalan et al. compared the risk of falls and fractures among LTC residents who continued vs. discontinued pimavanserin treatment following attempted GDR as a secondary objective in a retrospective claims analysis of US Medicare beneficiaries. The primary objective of this study was to estimate the proportion of residents treated with pimavanserin in LTC settings with appropriate clinician-recorded contraindication to GDR documentation, and the proportion of residents with GDR attempts vs. those without GDR attempts. The secondary objective was to understand the association between pimavanserin treatment-continuity among other factors, and discharge-to-community as well as clinical outcomes (i.e., falls and fractures) among the discharged residents. Residents in LTC (>100-day stay) who initiated pimavanserin and had a completed N0450 questionnaire assessment with a response to use of antipsychotic medication GDR were identified from Medicare Part D claims and Minimum Data Set 3.0 (January 01, 2016, to December 31, 2018).[7]

Residents who continued pimavanserin after an attempted GDR (691/1,181) had significantly lower ($p<0.05$) fall incidents (2.8%, 20/691) compared with those who discontinued pimavanserin treatment (9.4%, 41/436) after a GDR attempt. In the same population, the proportion of residents with hip fractures were numerically greater in pimavanserin-discontinued residents (0.69%, 3/436) compared with those who continued the pimavanserin treatment (0.29%, 2/691). These numerical differences were not statistically significant. The proportion of residents with pelvic/femur fractures was higher ($p<0.05$) in pimavanserin-discontinued

residents (0.92%, 4/436) compared with those who continued pimavanserin treatment (0%, 0/691).[7]

Postmarketing Experience

The following adverse reactions have been identified during post approval use of NUPLAZID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include rash, urticaria, reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea), somnolence, falls, agitation, aggression and fecal incontinence.[8]

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