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NUPLAZID® (pimavanserin): Concomitant Use with Atypical Antipsychotics in Parkinson's Disease Psychosis

This letter is in response to your specific request for information on the concomitant use of pimavanserin with another antipsychotic in patients with Parkinson's disease (PD) psychosis. The safety of concomitant use of pimavanserin 34 mg and atypical antipsychotics in participants with PD psychosis was evaluated in a post hoc analysis from an open-label extension (OLE) study. These results should be interpreted cautiously, and the methodology-associated limitations of the OLE study should be considered.

Relevant Labeling Information[1]
NUPLAZID prolongs the QT interval. The use of pimavanserin should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including: Class 1A antiarrhythmics (e.g., quinidine, procainamide), Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin).

Summary

- No controlled studies have been conducted to assess the concomitant use of pimavanserin with atypical antipsychotics in participants with PD psychosis.
  - The 4 **placebo-controlled clinical studies** that evaluated the safety and efficacy of pimavanserin in PD psychosis did not permit the use of concomitant antipsychotics.[2,3]
- ACP-103-015 (Study 015), the OLE study, permitted the addition of antipsychotics after the first month.[3]
  - **Post hoc analysis** was conducted using a data set from Study 015 which included 423 of the 459 participants. From this group, 66 participants were concomitantly treated with another antipsychotic in addition to pimavanserin, and 357 participants received pimavanserin as monotherapy.[4]
- In Study 015, there was a significant increase in the mortality rate for participants taking concurrent antipsychotics vs those not taking antipsychotics (incidence rate ratio [IRR] 4.20, 95% confidence interval [CI] 2.13–7.96).[4]
- Participants who received a concurrent antipsychotic in Study 015 were more likely to experience the following: a serious treatment-emergent adverse event (TEAE) (IRR 2.95, 95% CI 2.02–4.24), any antipsychotic-related event (IRR 1.66, 95% CI 1.18–2.29), cognition-related events (IRR 2.70, 95% CI 1.19–5.58), infections (IRR 1.97, 95% CI 1.17–3.16), and edema (IRR 2.61, 95% CI 1.09–5.59).[4]

Clinical Studies in Parkinson's Disease Psychosis

No controlled studies have been conducted to assess the concomitant use of pimavanserin with atypical antipsychotics in participants with PD psychosis. The safety and efficacy of pimavanserin in participants experiencing PD psychosis was evaluated in 4 short-term, randomized, placebo-controlled trials: Studies 006, 012, 014 and 020, with a combined enrollment of 680 participants with PD psychosis.[3] No concomitant antipsychotics were allowed during these studies and prior antipsychotics needed to be discontinued at least 5 half-lives (in Studies 012, 014 and 020) or at least 2 weeks (in Study 006) before initiation of pimavanserin therapy.[2,3]

Study 015, an OLE study, enrolled 459 participants from previous double-blind, placebo-controlled studies or a previous OLE study to assess the long-term safety and tolerability of pimavanserin 34 mg once daily in participants with PD psychosis.[5] Other antipsychotics were prohibited during the first month of the OLE study; thereafter they could be added if approved by the Medical Monitor.[3] A post hoc analysis was performed using a subset of participants that were concomitantly treated with another antipsychotic in addition to pimavanserin compared to participants not taking concurrent antipsychotics.[4]

Study 015: Open-Label Extension Study

Background

This was a multicenter, Phase 3, OLE study that included participants who had previously completed 6-week, randomized, placebo-controlled studies with pimavanserin (i.e., Studies 012, 014, or 020).[5] The objective was to assess the long-term safety and tolerability of once daily pimavanserin 34 mg in 459 participants with PD psychosis (mean age: 71 years). Median duration of treatment was 454 days, and mean duration was 728 days (interquartile range: 134 days, 1107 days). The longest duration of treatment was approximately 9 years. Overall discontinuation rates of participants at 6 and 48 months were 30.9% (142/459) and 81.7% (375/459), respectively.[5] Primary reasons for study termination recorded in ≥10% of participants are summarized in **Table 1**. Overall, the most frequently reported reason for discontinuation was voluntary withdrawal of consent (36.4%, 167/459).

Table 1. Termination Reason Recorded in ≥10% of Participants[5]

Primary Reason	Overall (N=459) n (%)
Voluntary withdrawal of consent	167 (36.4)
Adverse event	88 (19.2)
Sponsor decision	55 (12.0)
Disease progression	46 (10.0)

**Termination reasons were determined by the Investigator. Other reasons for termination included death (n=34[†]), Investigator decision, non-compliance, and lost to follow-up.*

[†]Includes 1 participant who discontinued study drug to an adverse event of dysphagia and experienced an adverse event (not treatment-emergent) with a fatal outcome (Parkinson's disease, onset of the serious event was 54 days post-last dose). The total number of all-cause deaths in the study was 59 participants.

The most frequently prescribed concomitant antipsychotics during Study 015 are summarized in **Table 2**.[3]

Table 2. Concomitant Antipsychotic Medications (Safety Analysis Set)[3]

Antipsychotic	Overall (N=459) n (%)
Quetiapine	71 (15.4)
Risperidone	10 (2.2)
Haloperidol	9 (2.0)
Clozapine	9 (2.0)
Olanzapine	3 (0.7)
Aripiprazole	2 (0.4)
Levomepromazine	1 (0.2)
Paliperidone	1 (0.2)
Ziprasidone	1 (0.2)

The following methodology-associated limitations of this OLE study should be considered:[5]

- 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.[4] Four hundred and twenty three (423) 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 post treatment antipsychotic use were excluded). Of these participants, 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 participants received pimavanserin monotherapy during the study period.

The follow-up time for the pimavanserin monotherapy group ranged between 1 and 1969 days with a median of 421 days.[4] 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 2 groups were well matched with respect to age, gender, severity and duration of PD, cognition, and severity of baseline psychotic symptoms. Most participants prescribed an add-on antipsychotic were taking quetiapine (79%, 52/66), mostly at daily doses of 25 to 50 mg (range: 12.5–350 mg); 10 of these individuals did receive a different antipsychotic at some point during follow-up. Of the 66 participants, 4 (6%) received clozapine alone (range: 6.25–50 mg), 4 (6%) were prescribed risperidone (range: 0.125–1 mg), and 6 (9%) received a range of different antipsychotics.

The exposure-adjusted incidence rates of events of deaths, any TEAE, any serious TEAE, and serious adverse events occurring at a proportion >2% in either group are summarized in **Table 3**.[4]

Table 3. Exposure Adjusted Incidence and Incidence Rate Ratios: Deaths, Serious TEAEs, and TEAEs of Special Interest from Study 015 Post hoc Analysis[4]

	Pimavanserin (n=357; PY=557)			Pimavanserin + Antipsychotic (n=66; PY=74)			
	n*	%	EAIR (per 100 PY)	n†	%	EAIR (per 100 PY)	IRR (95% CI)‡
Death	25	7.0	4.5	14	21.2	18.8	4.20 (2.13–7.96)
Any Serious TEAE	99	27.7	17.8	39	59.1	52.5	2.95 (2.02–4.24)
Any AP-related Event§	194	54.3	34.8	43	65.2	57.9	1.66 (1.18–2.29)
CVA/Stroke-related Events	5	1.4	0.9	2	3.0	2.7	3.00 (0.43–13.91)
Cognition-related Events	25	7.0	4.5	9	13.6	12.1	2.70 (1.19–5.58)
Fall-related Events	92	25.8	16.5	16	24.2	21.5	1.30 (0.74–2.15)
Infection-related Events	76	21.3	13.6	20	30.3	26.9	1.97 (1.17–3.16)
Edema-related Events	23	6.4	4.1	8	12.1	10.8	2.61 (1.09–5.59)
Orthostatic Hypotension-related Events	59	16.5	10.6	11	16.7	14.8	1.40 (0.70–2.55)
Sedation-related Events	14	3.9	2.5	4	6.1	5.4	2.14 (0.61–5.97)
Thromboembolic Events	12	3.4	2.2	4	6.1	5.4	2.50 (0.70–7.18)

**All TEAEs are included for participants who did not take concurrent AP.*
†Only TEAEs started after first dose of AP are included for participants who took concurrent AP.
‡Exposure-adjusted participant-count IRR (concurrent AP EAIR/no AP EAIR); 95% CI estimated from a Poisson regression model.
§AP-related events include all of the following: blood dyscrasia-related events, CVA/stroke-related events, cognition-related events, EPS-related events, fall-related events, infection-related events, metabolic-related events, NMS-related events, edema-related events, orthostatic hypotension-related events, sedation-related events, seizure-related events, thromboembolic events.
Abbreviations: AP=antipsychotic; CI=confidence interval; CVA=cerebrovascular accident; EAIR=exposure-adjusted incidence rate; EPS=extrapyramidal symptoms; IRR=incidence rate ratio; NMS=non-motor symptoms; PY=person-years of exposure; TEAE=treatment-emergent adverse event.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. [Link]
2. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet.* 2014;383(9916):533-540. [PubMed]
3. Acadia Pharmaceuticals Inc. Data on File. San Diego, CA.
4. 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]
5. 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]