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12830 El Camino Real · Suite 400 · San Diego, California 92130 · USA · Tel. 858.558.2871 · Fax 858.558.2872 · acadia.com

NUPLAZID® (pimavanserin): Hallucination Adverse Events in Parkinson's Disease Psychosis

This letter is provided in response to your specific request for information regarding hallucination adverse events (AEs) during pimavanserin clinical trials in Parkinson's disease (PD) psychosis.

Summary

- Hallucination was one of the documented adverse reactions observed in the **6-week, placebo-controlled studies** of pimavanserin for hallucinations and delusions associated with PD psychosis.[1] Specifically, hallucination AEs occurred in 10 participants receiving pimavanserin 34 mg (N=202) and 7 participants receiving placebo (N=231).[2]
- In the pimavanserin clinical trials, the **timing of the 17 hallucination AEs** showed that 12 of the events occurred within 10 days after Day 1 of the study and the last 5 after 27 days. Therefore, the majority of hallucination AEs (~71%) occurred in the first two weeks of the study.[3]

Background

Atypical antipsychotics are typically active at multiple receptor types (including dopaminergic, serotonergic, histaminergic, adrenergic and/or muscarinic receptors). In addition, antipsychotics vary in their plasma level profiles through differences in half-life and time to peak concentration.[4-7] According to Correll et al., the potential for rebound and withdrawal phenomena when switching antipsychotics is greatest when the pre- and post-switch antipsychotics differ considerably regarding binding affinity (i.e., pharmacodynamic rebound) for specific receptors or regarding their respective half-lives (i.e., pharmacokinetic rebound).[4] Psychosis (i.e. hallucinations and/or delusions) is among the different potential rebound/withdrawal effects that can occur during switching.

Pooled Data from Placebo-Controlled Phase 2B/3 and Phase 3 Studies

Safety data were pooled from three randomized, double-blind, placebo-controlled Phase 2b/3 and Phase 3 studies in PD psychosis:[2]

- ACP-103-012: A 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.
- ACP-103-014: A 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 (original planned sample size was 279) for up to 6 weeks.
- Pivotal Phase 3 trial, ACP-103-020: A Phase 3 study that evaluated the safety and efficacy of pimavanserin 34 mg QD compared to placebo in 199 participants for up to 6 weeks.

Antipsychotic Use Prior to Study Entry

Antipsychotics other than pimavanserin were not permitted in any of the placebo-controlled clinical studies that evaluated the safety and efficacy of pimavanserin in patients with hallucinations and delusions associated with PD psychosis, and were discontinued at no less than 5 half-lives prior to baseline visit.[8-11] Among participants who received pimavanserin 34 mg or placebo in the 6-week, placebo controlled studies (012, 014 and 020; N=433), 65 (15%) had previously been prescribed antipsychotics. Quetiapine was the most common prior antipsychotic, prescribed in 58 (13.4%) participants, followed by clozapine, risperidone, ziprasidone, and haloperidol in less than 1% of participants (**Table 1**).[12]

Table 1. Antipsychotic Use Prior to Study Entry in 6-week, Placebo-controlled Trials (Safety Analysis Set)[12]

Antipsychotic	Pimavanserin 34 mg (N=202) n (%)	Placebo (N=231) n (%)	Total (N=433) n (%)
Quetiapine	30 (14.9)	28 (12.1)	58 (13.4)
Clozapine	3 (1.5)	0 (0.0)	3 (0.7)
Risperidone	1 (0.5)	2 (0.9)	3 (0.7)
Ziprasidone	0 (0.0)	1 (0.4)	1 (0.2)
Haloperidol	0 (0.0)	1 (0.4)	1 (0.2)

Hallucination Adverse Events

In the 6-week placebo-controlled studies, hallucination AEs were observed as described in a total of 10 (5%) participants treated with pimavanserin 34 mg and 7 (3%) participants who received placebo (**Table 2**).[2]

Table 2. Hallucination AEs in 6-week, Placebo-controlled Trials[2,3]

Study	Pimavanserin 34 mg (N=202)	Placebo (N=231)
012	3	4
014	0	2
020	7	1
Total	**10**	**7**

Abbreviation: AE=adverse event.

The timing of the 17 hallucination AE reports shows that 12 of the events occurred within 10 days after Day 1 of the study, and the remaining 5 events occurred after 27 days (**Table 3**).[3] Therefore, the majority of hallucination AE reports (71%) occurred in the first two weeks of the study. This may be attributed to both pharmacokinetic and pharmacodynamic rebound,[4] since the atypical antipsychotics that patients were previously taking differ in receptor affinity[5-7] as compared to pimavanserin.[1] Additionally, the half-life of pimavanserin (i.e. 57 hours[1]) is considerably longer than several other atypical antipsychotics,[5-7] and steady state is typically achieved in ~12 days of continuous once daily pimavanserin dosing.[2]

Table 3. Timing of Hallucination AEs in 6-week, Placebo-controlled Trials[3]

AE study day	Pimavanserin 34 mg	Placebo
≤5	3	3
>5 and ≤10	4	2
>10 and ≤25	0	0
>25 and ≤36	3	2

Abbreviation: AE=adverse event.

Exposure-Response Analysis for Hallucination Adverse Events

Exposure-response analyses were conducted for four AE categories which were identified in the 020 study as occurring at a higher incidence in the pimavanserin 34 mg arm compared to placebo: hallucination, confusion, edema, and gait disturbance.[12,13] However, in the subsequent integrated database that included all participants from the 6-week, placebo-controlled studies (012, 014 and 020), the incidence of hallucination did not show any increase in incidence for pimavanserin over placebo.[12] For each of the four categories of AEs, percentile ranks for mean plasma concentration (Cp) values varied broadly. There was no evidence that any of the adverse events were associated with a cluster of high (or low) mean Cp values.[13]

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