ACADIA

acadia
medical affairs

Acadia Pharmaceuticals Inc. is providing this letter in response to your unsolicited request for medical information. It is for scientific-exchange and individual educational purposes only, and should not be copied or distributed. Information included in this letter may not be consistent with the US FDA-approved Prescribing Information for NUPLAZID® (pimavanserin) or may be related to unapproved uses of NUPLAZID. This letter is not intended to advocate any unapproved or approved use, indication, dosage, or other treatment-related decision. Acadia strives to provide current, accurate, and fair-balanced information in compliance with current industry information dissemination guidelines.

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

12830 El Camino Real • Suite 400. • San Diego, California 92130 • USA • Tel. 858.558.2871 • Fax 858.558.2872 • www.acadia-pharm.com

NUPLAZID® (pimavanserin): Efficacy and Safety of Doses Above 34 mg

This letter is provided in response to your specific request for information regarding data on the efficacy and safety of pimavanserin doses greater than 34 mg.

The recommended dose of pimavanserin is 34 mg taken orally once daily, without titration.[1] The efficacy and safety of pimavanserin doses greater than 34 mg have not been established and approved by the FDA. Physicians should exercise clinical judgment when using this product at doses above 34 mg.

Summary

- There have been no clinical studies conducted to assess the impact of a dose increase on the efficacy of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease (PD) psychosis. Safety and tolerability data for pimavanserin doses greater than 34 mg are limited.
- In a **Phase 1 study in 4 healthy volunteers**, single doses of pimavanserin 85 mg did not provide additional saturation of 5-HT_{2A} receptors in the human brain compared with the 17 mg dose, as determined by positron emission tomography (PET).[2]
- In a **thorough QT (TQT) study**, 72 healthy volunteers received pimavanserin 68 mg once daily (QD) for 20 days.[3] While there were no meaningful effects with pimavanserin 68 mg on heart rate, or PR or QRS intervals in these healthy participants, the 68 mg dose showed a 10 to 15 msec effect on cardiac repolarization.[3,4]
- In a **Phase 2, placebo-controlled study** in 60 participants with PD psychosis where doses of pimavanserin were allowed to be increased weekly from 17 to 34 to 51 mg QD,[5] most participants in the active arm escalated to the 34 mg dose level, without need for further escalation to 51 mg.[4]
- In an **open-label label extension study** in 38 participants with PD psychosis and 1 participant with PD dyskinesia, doses of pimavanserin could be increased from 17 to 34 to 51 mg QD. For the 23 participants who received pimavanserin 51 mg, overall exposure was 40 patient-years (PY). In general, safety findings in this study were similar across doses.[4,6]

Clinical Studies in Healthy Volunteers

Studies of pimavanserin doses higher than 34 mg in healthy volunteers include a PET analysis of the 5-HT_{2A} receptor occupancy profile of single doses up to 85 mg in 4 participants,[2] and a TQT study of the electrocardiographic (ECG) effects of QD doses of up to 68 mg over a 20-day period in 252 participants.[3]

ACP-103-003 (PET Analysis)

Study 003 was an open-label, three-period, single-dose, dose-response, PET crossover study to evaluate the 5-HT_{2A} receptor occupancy profile of pimavanserin over a range of doses.[7]

[^{11}C]-N-methylspiperone was used as the radioligand. Four healthy participants each received three single doses of pimavanserin (either 0.85, 4.3, and 17 mg [n=2], or 1.7, 8.5, and 85 mg [n=2]), with ≥1-week washout between doses. Pimavanserin was generally detectable within 1-hour postdose, and C_{max} was 6 to 8 hours. Detectable levels in plasma persisted at 24 hours postdose. In all participants, PET examinations were performed either at or very near the time of maximum concentration.[2,7]

Near maximal 5-HT_{2A} receptor binding to cortical 5-HT_{2A} receptors was observed after the 8.5 mg dose (65–76% receptor occupancy), maximal binding was observed after the 17 mg dose (74–76% receptor occupancy), and higher doses did not result in a significantly increased displacement of radioligand. The observed interindividual variation was low.[2,7]

Seven mild or moderate treatment-emergent adverse events (TEAEs) were reported in 3 participants, including 4 occurrences of fatigue after administration of 0.85, 1.7, 8.5, and 85 mg pimavanserin, and 1 occurrence each of rash after 4.3 mg, eye movement disorder after 8.5 mg, and blurred vision after 85 mg. Fatigue in 1 participant after 1.7, 8.5, and 85 mg, and blurred vision in a second participant after 85 mg were considered possibly or probably treatment related. No participant died, experienced a serious TEAE, or discontinued due to a TEAE. No abnormal laboratory test, vital sign, ECG, physical or neurologic examination, or neuropsychological test results were reported as TEAEs.[7]

ACP-103-018 (Thorough QT [TQT] Study)

The ECG effects of pimavanserin were investigated in a TQT study. Study 018 was a randomized, placebo-controlled, double-blind study in healthy participants to determine the effects of pimavanserin 17 and 68 mg QD on QTc after 20 days of dosing. A total of 252 participants were randomly assigned to receive either pimavanserin 17 mg (n=60), pimavanserin 68 mg (n=72), placebo plus moxifloxacin 400 mg (moxifloxacin on Day 20 only; n=59), or placebo alone (n=61). Equal numbers of males (n=126) and females (n=126) were randomized.[3]

Pimavanserin at 17 and 68 mg demonstrated no effect on heart rate, PR or QRS interval duration, or cardiac morphology, and no participant had an individualized QTc interval (QTcI) or corrected QT interval using Fridericia's formula (QTcF) interval >480 msec, or a QTcI or QTcF increase >60 msec. The effect of pimavanserin on cardiac repolarization using the QTcI change and the pharmacokinetic (PK)/pharmacodynamic (PD) relationship showed no signal at 17 mg, but a 10 to 15 msec effect was observed at 68 mg. The placebo-adjusted change from Baseline QTcI is shown in **Table 1**.[3,4] One participant receiving pimavanserin 68 mg/day had an increase from baseline in the QTcI of between 30 and 60 msec.[4]

Table 1. Maximal Mean Placebo-Adjusted Change from Baseline QTcI (Δ-Δ QTcI)[4]

	Pimavanserin 17 mg/day	Pimavanserin 68 mg/day
Maximal Mean Δ-Δ QTcI mean (upper 90% CI)	4.7 msec (6.8 msec)	13.9 msec (15.9 msec)

Abbreviations: Δ-Δ=delta-delta; CI=confidence interval; QTcI=individualized corrected QT interval.

The 68 mg dose yielded a median observed plasma concentration of 155 ng/mL and a median C_{max} of 197 ng/mL, which is approximately 2.5-fold higher than the median C_{max} associated with

pimavanserin 34 mg/day. There was a relative paucity of concentration values at higher exposures; only 10% of all concentration values for 68 mg were >230 ng/mL. The C_{max} for the 17 mg dose was approximately 43 ng/mL.[4]

With the exception of syncope in two (2.8%) participants in the pimavanserin 68 mg and one (1.7%) in the placebo/moxifloxacin group, no additional TEAEs were reported in any treatment group (pimavanserin 17 mg, pimavanserin 68 mg, placebo/moxifloxacin or placebo) suggestive of proarrhythmic potential or any clinically significant cardiovascular-related TEAEs.[3]

Clinical Studies in PD Psychosis

There have been no clinical studies conducted to assess the impact of a dose increase on the efficacy of pimavanserin for the treatment of hallucinations and delusions associated with PD psychosis. In participants with PD psychosis, pimavanserin doses up to 51 mg QD have been studied in a 4-week Phase 2 study (ACP-103-006) in 60 participants, and an open-label extension study (ACP-103-010) in 39 participants. Studies 006 and 010 were both conducted to determine the safety of pimavanserin in this population.[6,8]

ACP-103-006

Study 006 was a Phase 2, randomized, double-blind, placebo-controlled, multi-center trial to determine the safety of pimavanserin doses up to 51 mg in participants with PD psychosis. During the four-week trial, 60 participants 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).[4,8] Most participants 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.[4,9]

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).[8]

Overall, there was no significant difference in the incidence of adverse events in the placebo- and pimavanserin-treated participants. In total, 133 TEAEs were reported in 21 (72.4%) participants receiving pimavanserin and 24 (77.4%) participants receiving placebo. Fifty-one of the TEAEs were considered related to treatment. The most common TEAEs in the pimavanserin group were somnolence, peripheral edema, and increase in blood urea nitrogen (10.3% each). In the placebo arm, the most commonly occurring adverse events were hallucinations (n=5, 16.1%), dizziness (n=4, 12.9%), and fall, headache, confusional state and hypotension each occurring in 9.7% (n=3). There were no trends or clinically meaningful changes in clinical laboratories, vital signs, 12-lead ECG measurements, or neurological measurements.[8]

ACP-103-010

Study 010 was an open-label extension of Study 006 and Study ACP-103-004, a Phase 2 study in participants with PD dyskinesia. Overall, 39 participants (38 with PD psychosis, one with PD

dyskinesia) were enrolled. The primary objective was to determine the safety of pimavanserin during long-term oral administration to participants with PD. This study used a dose-escalation strategy such that all participants initially received 17 mg daily, and at the discretion of the Investigator and if the participant would benefit from a higher dose of pimavanserin, the daily dose was increased up to 34 mg and then 51 mg after at least 2 and 4 weeks, respectively. Similarly, dose reductions to 34 mg and/or 17 mg were allowed for AEs or intolerability and discontinuation of pimavanserin was allowed at any time.[4,6]

Participants were allowed to continue in the study for as long as they wished or until it was determined by the Investigator that continuation in the study would be detrimental to the participant's well-being. Mean duration of exposure for participants in this study was 639.8 days, and the median duration was 475.0 days (range: 19 to 2941 days).[6] The longest duration of treatment was >8 years.[4]

Most participants received a dose that was higher than the 17 mg starting dose. Using the exposure-adjusted per 100 PY calculation, exposure across the study population was 11 PY (n=39) at the 17 mg dose, 20 PY (n=33) at the 34 mg dose, 40 PY (n=23) at the 51 mg dose, and 71 PY (n=39) overall (all doses combined).[6]

The open-label design of the study and lack of control group for comparison should be considered when interpreting these data.

Safety Results

In general, safety findings in this study were similar across all doses and consistent with those observed during the previous double-blind studies. Most participants who experienced a serious TEAE or study drug discontinuation event did so after >1-year of exposure.[6] Data are presented for the exposure-adjusted incidence of TEAEs, which accounts for dose-specific exposure time and/or treatment duration.

The exposure-adjusted overall incidence of TEAEs per 100 PY was greater at the 17 mg dose (164 participants) than the 34 mg (100 participants) or 51 mg (48 participants) doses. When combining all doses, the exposure-adjusted incidence was 48 participants per 100 PY. The most common exposure-adjusted TEAEs across all doses were constipation and hallucination (both in 9 participants from a total of 71 PY, equivalent to about 13 participants per 100 PY) and anemia and urinary tract infection (both in 8 participants from a total of 71 PY, equivalent to about 11 participants per 100 PY). At the 51 mg dose, the most common exposure-adjusted TEAEs were hallucination (in 7 participants from a total of 40 PY, equivalent to 18 participants per 100 PY), anemia and agitation (both in 5 participants from a total of 40 PY, equivalent to about 13 participants per 100 PY). For many TEAEs, exposure-adjusted incidence was highest at the 17 mg dose, which may be due to the dosing sequence and due to the total number of days of exposure, which were greater for the 51 and 34 mg doses.[6]

The exposure-adjusted incidence of serious TEAEs per 100 PY was about 25 participants for all doses, and was greatest at the 34 mg dose (35 participants) compared to the 51 mg (25 participants) and 17 mg (about nine participants) doses (**Table 2**). The most commonly experienced exposure-adjusted serious TEAEs per 100 PY in participants both overall (all doses

combined) and at the 51 mg dose were hip fracture and myocardial infarction, subdural hematoma and PD.[6]

Table 2. Serious TEAEs Experienced by >2 Participants Per 100 PY of Exposure in Any SOC by Dose at Event Onset: Safety Analysis Set (Study ACP-103-010)[6]

MedDRA system organ class/ Preferred term	Number of participants (exposure-adjusted count/100 PY)			
	PIM 17 mg (PY=11)	PIM 34 mg (PY=20)	PIM 51 mg (PY=40)	All Doses (PY=71)
Any serious TEAE	**1 (9.1)**	**7 (35.0)**	**10 (25.0)**	**18 (25.4)**
Cardiac disorders	**0**	**0**	**4 (10.0)**	**4 (5.6)**
Cardiac failure	0	0	1 (2.5)	1 (1.4)
Myocardial infarction	0	0	3 (7.5)	3 (4.2)
Gastrointestinal disorders	**0**	**1 (5.0)**	**1 (2.5)**	**2 (2.8)**
Diarrhea	0	0	1 (2.5)	1 (1.4)
Inguinal hernia	0	1 (5.0)	0	1 (1.4)
Infections and infestations	**0**	**1 (5.0)**	**1 (2.5)**	**2 (2.8)**
Bronchitis	0	1 (5.0)	0	1 (1.4)
Cellulitis	0	0	1 (2.5)	1 (1.4)
Injury, poisoning & procedural complications	**0**	**1 (5.0)**	**3 (7.5)**	**4 (5.6)**
Hip fracture	0	1 (5.0)	2 (5.0)	3 (4.2)
Joint dislocation	0	0	1 (2.5)	1 (1.4)
Subdural hematoma	0	0	2 (5.0)	2 (2.8)
Musculoskeletal & connective tissue disorders	**0**	**2 (10.0)**	**0**	**2 (2.8)**
Intervertebral disc protrusion	0	1 (5.0)	0	1 (1.4)
Rhabdomyolysis	0	1 (5.0)	0	1 (1.4)
Nervous system disorders	**1 (9.1)**	**0**	**2 (5.0)**	**3 (4.2)**
Cerebrovascular accident	1 (9.1)	0	0	1 (1.4)
Depressed level of consciousness	0	0	1 (2.5)	1 (1.4)
Parkinson's disease	0	0	2 (5.0)	2 (2.8)
Psychiatric disorders	**0**	**2 (10.0)**	**1 (2.5)**	**3 (4.2)**
Agitation	0	0	1 (2.5)	1 (1.4)
Delusion	0	1 (5.0)	0	1 (1.4)
Mental status changes	0	1 (5.0)	0	1 (1.4)
Respiratory, thoracic & mediastinal disorders	**0**	**0**	**2 (5.0)**	**2 (2.8)**
Aspiration	0	0	1 (2.5)	1 (1.4)
Pneumonia aspiration	0	0	1 (2.5)	1 (1.4)

Notes: Adverse events were coded using MedDRA 9.1; TEAEs were those with an onset date ≥ the first dose of study drug and no later than the last dose plus 30 days (or death, if earlier); patient-years (PY) were the number of years participants were at risk for reporting an event, and a year was defined as 365.25 days for this calculation.
Abbreviations: PIM=pimavanserin; PY=patient-years; SOC=system organ class; TEAE=treatment-emergent adverse event.

The exposure-adjusted incidence of TEAEs resulting in study drug discontinuation by dose at event onset experienced by >2 participants per 100 PY in any system organ class is presented in **Table 3**. The exposure-adjusted incidence for all doses was about 27 participants per 100 PY, and was greatest at the 34 mg (30 participants) and 51 mg (about 28 participants) doses compared to the 17 mg dose (about 18 participants).[6]

Table 3. TEAEs Resulting in Discontinuation of Study Drug Experienced by >2 Participants Per 100 PY of Exposure in Any SOC by Dose at Event Onset: Safety Analysis Set (Study ACP-103-010)[6]

MedDRA system organ class/ Preferred term	Number of participants (exposure-adjusted count/100 PY)			
	PIM 17 mg (PY=11)	PIM 34 mg (PY=20)	PIM 51 mg (PY=40)	All doses (PY=71)
Any discontinuation TEAE	**2 (18.2)**	**6 (30.0)**	**11 (27.5)**	**19 (26.8)**
Cardiac disorders	**0**	**0**	**4 (10.0)**	**4 (5.6)**
Cardiac failure	0	0	1 (2.5)	1 (1.4)
Myocardial infarction	0	0	3 (7.5)	3 (4.2)
Injury, poisoning & procedural complications	**0**	**1 (5.0)**	**1 (2.5)**	**2 (2.8)**
Hip fracture	0	1 (5.0)	0	1 (1.4)
Subdural haematoma	0	0	1 (2.5)	1 (1.4)
Metabolism & nutrition disorders	**1 (9.1)**	**0**	**1 (2.5)**	**2 (2.8)**
Dehydration	0	0	1 (2.5)	1 (1.4)
Failure to thrive	1 (9.1)	0	0	1 (1.4)
Musculoskeletal & connective tissue disorders	**0**	**1 (5.0)**	**1 (2.5)**	**2 (2.8)**
Musculoskeletal disorder	0	0	1 (2.5)	1 (1.4)
Rhabdomyolysis	0	1 (5.0)	0	1 (1.4)
Nervous system disorders	**1 (9.1)**	**0**	**3 (7.5)**	**4 (5.6)**
Confusional state	0	0	1 (2.5)	1 (1.4)
Memory impairment	0	0	1 (2.5)	1 (1.4)
Parkinson’s disease	0	0	1 (2.5)	1 (1.4)
Somnolence	1 (9.1)	0	0	1 (1.4)
Psychiatric disorders	**0**	**3 (15.0)**	**2 (5.0)**	**5 (7.0)**
Agitation	0	0	1 (2.5)	1 (1.4)
Delusion	0	1 (5.0)	0	1 (1.4)
Depression	0	1 (5.0)	0	1 (1.4)
Mental status changes	0	1 (5.0)	0	1 (1.4)
Psychotic disorder	0	0	1 (2.5)	1 (1.4)
Respiratory, thoracic & mediastinal disorders	**0**	**1 (5.0)**	**2 (5.0)**	**3 (4.2)**
Aspiration	0	0	1 (2.5)	1 (1.4)
Atelectasis	0	1 (5.0)	0	1 (1.4)
Pneumonia aspiration	0	0	1 (2.5)	1 (1.4)

Notes: Adverse events were coded using MedDRA 9.1; TEAEs were those with an onset date ≥ the first dose of study drug and no later than the last dose plus 30 days (or death, if earlier); patient-years (PY) were the number of years participants were at risk for reporting an even, and a year was defined as 365.25 days for this calculation.
Abbreviations: PIM=pimavanserin; PY=patient-years; SOC=system organ class; TEAE=treatment-emergent adverse event.

Eight (21%) participants died during the study or within 30 days post-last dose, 7 of whom experienced the onset of the event while receiving the 51 mg dose (**Table 4**). For these 7 participants, the event with an outcome of death had an onset within 406 to 1561 days of starting study drug treatment. All events with an outcome of death were judged as unrelated or unlikely related to study drug.[6]

Table 4. TEAEs Leading to Death: Safety Analysis Set (Study ACP-103-010)[6]

Pimavanserin dose	Age[a]/Sex	Preferred term	Onset day	Causality
17 mg	89/M[b]	Cerebrovascular accident	39	Unrelated
51 mg	69/M	Aspiration	705	Unlikely
51 mg	64/M[c]	Parkinson's disease	406	Unrelated
51 mg	75/M	Aspiration pneumonia	561	Unrelated
51 mg	69/M	Myocardial infarction	418	Unrelated
51 mg	83/M	Myocardial infarction	1561	Unrelated
51 mg	72/M	Cardiac failure	1309	Unrelated
51 mg	83/M	Myocardial infarction	1196	Unrelated

[a]Age at death (years).
[b]Participant discontinued the study on Day 35 due to a TEAE of failure to thrive (PT) and died on Day 40 (5 days post-last dose).
[c]Participant discontinued the study on Day 406 (last dose on Day 405) due to a TEAE of acute compensation of severe parkinsonism (PT: Parkinson's disease) and died 44 days post-last dose.
Abbreviations: M=male; PT=preferred term; TEAE=treatment emergent adverse event.

Review of chemistry and hematology laboratory results indicated no clinically relevant mean changes or unexpected findings during treatment. No noteworthy changes from baseline to the last assessment were observed for the mean change in any ECG parameter, including corrected QT interval using Bazett's formula (QTcB) or QTcF intervals.[6]

Efficacy Results

Although this study was not designed to evaluate efficacy, Clinical Global Impression – Severity (CGI-S) scores were recorded. The median CGI-S score at baseline was 4.0 (denoting moderate severity of psychotic symptoms). In general, participants continuing with treatment did not worsen over time.[6]

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Nordstrom AL, Mansson M, Jovanovic H, et al. PET analysis of the 5-HT2A receptor inverse agonist ACP-103 in human brain. *Int J Neuropsychopharmacol.* 2008;11(2):163-171. **[PubMed]**
3. Acadia Pharmaceuticals Inc. Data on File. ACP-103-018 Clinical Study Report. 2012.
4. Acadia Pharmaceuticals Inc. Data on File. Investigator's Brochure. July 17, 2020.
5. Acadia Pharmaceuticals Inc. Data on File. ACP-103-006 Clinical Study Report. 2014.
6. Acadia Pharmaceuticals Inc. Data on File. ACP-103-010 Clinical Study Report. 2014.
7. Acadia Pharmaceuticals Inc. Data on File. ACP-103-003 Clinical Safety Summary. 2014.
8. Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. *Neuropsychopharmacology.* 2010;35(4):881-892. **[PubMed]**
9. Acadia Pharmaceuticals Inc. NUPLAZID®: Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee on 29 March 2016. 2016.