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NUPLAZID® (pimavanserin): Use in Renal Impairment

This letter is provided in response to your specific request for information regarding the use of pimavanserin in patients with renal impairment.

Relevant Label Information[1]

- No dosage adjustment for NUPLAZID is needed in patients with mild to severe renal impairment or end stage renal disease (ESRD); however, increased exposure (C_{max} and AUC) to NUPLAZID occurred in patients with severe renal impairment (creatinine clearance [CrCL] <30 mL/min, Cockcroft-Gault) in a renal impairment study.
- NUPLAZID should be used with caution in patients with severe renal impairment and ESRD.
- In a renal impairment study, dialysis did not appear to significantly affect the concentrations of NUPLAZID.

Summary

- The pharmacokinetics (PK) and safety of a single oral dose of pimavanserin 34 mg in participants with severe renal impairment and ESRD have been compared with healthy participants in a **Phase 1 study** (N=24).[2]
- Increased exposure (C_{max} and AUC) to pimavanserin occurred in participants with severe renal impairment (CrCL <30 mL/min, Cockcroft-Gault). Dialysis did not appear to significantly affect the concentrations of pimavanserin.[1,2]

Background

There is no clinical data with pimavanserin in participants with Parkinson's disease psychosis who have renal impairment. Participants who had current evidence of a serious and/or unstable renal disorder that would affect their ability to participate in the study were excluded from the pivotal Phase 3 study, ACP-103-020.[3]

In PK evaluations, approximately 0.55% of the 34 mg oral dose of ^{14}C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days. Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.[1] The PK and safety of pimavanserin in participants with severe renal impairment and ESRD has been compared with healthy participants in a Phase 1 study, ACP-103-026.[2]

Study ACP-103-026

This was a Phase 1, open-label, multi-center, single-dose study. The primary objective was to evaluate the PK of pimavanserin and *N*-desmethyl-pimavanserin (AC-279) after a single oral dose of 34 mg pimavanserin in participants with severe renal impairment and ESRD compared with matched healthy controls. The secondary objective was to evaluate the safety and

tolerability profile of a single oral dose of 34 mg pimavanserin in participants with severe renal impairment, participants with ESRD on dialysis, and healthy participants.[2]

Study Design

Twenty four participants were enrolled into 3 group populations (**Table 1**).[2]

Table 1. Study Group Characteristics[2]

Group	N	Participant characteristics	Stage*	eGFR (mL/min/1.73 m^2)
1	6	Severe renal impairment	4	<30
2	6	ESRD	5	Requiring dialysis
3	12	Healthy adults†	1	≥90

**Stages of renal impairment are based on K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation 2002.*
†Matched for Groups 1 and 2 with respect to age, race, gender, and body mass index.
Abbreviations: eGFR=estimated glomerular filtration rate based on a Modification of Diet in Renal Disease (MDRD) equation; ESRD=end-stage renal disease.

On Study Day 1, participants received a single oral dose of pimavanserin 34 mg (2×17 mg tablet) following an overnight fast of approximately 10 hours. Samples for pimavanserin and AC-279 PK analysis were collected prior to pimavanserin dosing and at scheduled timepoints through Day 12. For Group 2 participants, who were scheduled for dialysis at 48 hours postdose, the 48-hour PK sample was collected immediately before the start of dialysis, and additional PK samples were collected at 30 minutes and 2 hours after the start of dialysis and immediately after dialysis was completed.

PK Results

Following a single oral 34 mg dose of pimavanserin, the PK characteristics of pimavanserin in participants with renal impairment (severe and ESRD) were, in general, qualitatively similar to those of matching controls and earlier studies, in which plasma pimavanserin concentrations appeared to be absorbed into the circulation slowly, distributed extensively, and cleared moderately/slowly until the end of study after 11 days.

Mean (standard deviation [SD]) PK parameters for pimavanserin following administration of a single 34 mg dose of pimavanserin are presented by renal function group in **Table 2**.

Table 2. Mean (SD) PK Parameters for Pimavanserin in Participants with Severe Renal Impairment, ESRD or Normal Renal Function – PK Analysis Set[2]

Parameter	Severe control (n=6)	Severe renal impairment (n=6)	ESRD control (n=6)	ESRD (n=6)	Total control (n=12)
C_{max} (ng/mL)	8.59 (1.75)	13.28 (6.44)	9.75 (2.81)	10.96 (2.99)	9.17 (2.31)
AUC_{0-t} (ng•h/mL)	815.93 (371.07)	1151.11 (755.92)	786.35 (261.86)	1011.03 (422.97)	801.14 (306.58)
$AUC_{0-\infty}$ (ng•h/mL)	1009.33 (576.88)	1806.25 (1361.95)*	845.11 (283.22)	1160.35 (310.63)	927.22 (441.68)
T_{max} (h)	10.50 (6.00, 36.00)	9.00 (2.00, 36.00)	12.50 (6.00, 24.00)	10.50 (6.00, 12.00)	10.50 (6.00, 36.00)
$t_{1/2}$ (h)	91.17 (26.358)	125.81 (55.00)*	65.79 (15.48)	76.6 (34.39)	78.48 (24.61)
λz (/h)	0.0081 (0.0019)	0.0064 (0.0027)*	0.0110 (0.0024)	0.0137 (0.0036)	0.0095 (0.0026)

Parameter	Severe control (n=6)	Severe renal impairment (n=6)	ESRD control (n=6)	ESRD (n=6)	Total control (n=12)
Vz/F (L)	5923.72 (1810.57)	5012.46 (2095.24)*	4812.14 (1597.45)	4165.52 (1548.59)	5367.93 (1728.29)
Cl/F (L/h)	49.66 (23.27)	33.57 (19.60)*	51.29 (14.58)	44.27 (24.95)	50.48 (18.53)

Note: T_{max}=median (min, max).
**n=5.*
Abbreviations: $AUC_{0-\infty}$=area under the concentration time course profile from time 0 (dosing) to infinity; AUC_{0-t}=area under the concentration time course profile from time 0 (dosing) to the time of last quantifiable concentration at time t; Cl/F=apparent systemic clearance; C_{max}=maximum observed plasma concentration; ESRD=end stage renal disease; λz=apparent terminal phase elimination rate constant; PK=pharmacokinetic; SD=standard deviation; $t_{1/2}$=apparent terminal elimination half-life; T_{max}=time to maximum plasma concentration; V_z/F=apparent volume of distribution.

A small increase in C_{max} was noted in participants with severe renal impairment or ESRD as compared with those with normal renal function. In addition, overall systemic exposure (as assessed by AUC) was higher in participants with severe renal impairment or ESRD as compared with that in participants with normal renal function. Elimination half-life was longer for participants with severe renal impairment than for participants with ESRD or those with normal renal function. There was no noticeable shift in T_{max} between participants with severe renal impairment or ESRD and their matched control.

Geometric mean values with ratios and associated confidence intervals (CIs) for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} of pimavanserin following administration of a single 34 mg dose in participants with severe renal impairment and their matched controls and participants with ESRD and their matched controls are provided in **Table 3** and **Table 4**, respectively.

Table 3. Pimavanserin PK Parameters in Participants with Severe Renal Impairment and Participants with Normal Renal Function – PK Analysis Set[2]

Parameter	Severe (n=6)	Control for severe (n=6)	Geometric mean ratio	90% CI
C_{max} (ng/mL)	12.0	8.4	1.42	1.07, 1.89
AUC_{0-t} (ng•h/mL)	968.7	754.6	1.28	0.85, 1.93
$AUC_{0-\infty}$ (ng•h/mL)*	1422.2	894.9	1.59	1.10, 2.29

Ratios and 90% CIs of geometric means for log-transformed C_{max} and AUC were calculated from an ANOVA model with effect for paired participant and renal impairment status.
**n=5.*
Abbreviations: ANOVA=analysis of variance; $AUC_{0-\infty}$=area under the concentration time course profile from time 0 (dosing) to infinity; AUC_{0-t}=area under the concentration time course profile from time 0 (dosing) to the time of last quantifiable concentration at time t; CI=confidence interval; C_{max}=maximum observed plasma concentration; PK=pharmacokinetic.

Table 4. Pimavanserin PK Parameters in Participants with ESRD and Participants with Normal Renal Function – PK Analysis Set[2]

Parameter	ESRD (n=6)	Control for ESRD (n=6)	Geometric mean ratio (ESRD/matching control)	90% CI
C_{max} (ng/mL)	10.3	9.4	1.12	0.88, 1.44
AUC_{0-t} (ng•h/mL)	928.5	754.5	1.23	0.75, 2.01
$AUC_{0-\infty}$ (ng•h/mL)	1027.3	810.0	1.27	0.71, 2.25

Ratios and 90% CIs of geometric means for log-transformed C_{max} and AUC were calculated from an ANOVA model with effect for paired participants and renal impairment status.
Abbreviations: ANOVA=analysis of variance; $AUC_{0-\infty}$=area under the concentration time course profile from time 0 (dosing) to infinity; AUC_{0-t}=area under the concentration time course profile from time 0 (dosing) to the time of last quantifiable concentration at time t; CI=confidence interval; C_{max}=maximum observed plasma concentration; ESRD=end stage renal disease; PK=pharmacokinetic.

Following pimavanserin administration, increases in C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were more pronounced in participants with severe renal impairment (approximately 40%, 30%, and 60%, respectively) than in participants with ESRD (approximately 10%, 20%, and 30%, respectively), as compared with their matched controls with normal renal function.

There was no noticeable difference in systemic exposure of AC-279, the active metabolite, in participants with severe renal impairment or ESRD relative to participants with normal renal function. A negligible amount of pimavanserin and AC-279 is cleared in the dialysate.

Safety Results

Higher plasma concentrations were not correlated with higher incidence of treatment-emergent adverse events (TEAEs). There were no deaths or other serious adverse events reported in the study. There were no discontinuations due to adverse events. All TEAEs were mild in intensity. No clinically meaningful treatment-emergent laboratory abnormalities were noted. Participants with severe renal impairment and those with ESRD were noted to have markedly abnormal elevated blood urea nitrogen and creatinine as well as decreased hemoglobin and hematocrit, which were present at baseline and typical in this population.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. ACP-103-026 Clinical Study Report. 2017.
3. Acadia Pharmaceuticals Inc. Data on File. ACP-103-020 Protocol. 2010.