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NUPLAZID® (pimavanserin): Use in Hepatic Impairment

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

Relevant Label Information[1]

- No dosage adjustment for NUPLAZID is recommended in patients with hepatic impairment based on the exposure differences observed in patients with and without hepatic impairment in a hepatic impairment study.

Summary

- The pharmacokinetics (PK) of single oral doses of pimavanserin 17 mg in participants with mild, moderate, and severe hepatic impairment was assessed in a **Phase 1 study** in 45 unique participants.[2]
- The **PK findings** for pimavanserin in participants with hepatic impairment were comparable to their respective matched controls and those of earlier studies. Impaired hepatic function did not appear to have an effect on the exposure to pimavanserin.[2]
- There is **no data** with pimavanserin 34 mg in patients with hepatic impairment.

Study ACP-103-025[2]

This was a Phase 1, open-label study to evaluate the PK of pimavanserin and *N*-desmethyl-pimavanserin (AC-279) after a single oral dose of 17 mg pimavanserin in participants with mild, moderate, and severe hepatic impairment compared with matched healthy controls with normal hepatic function.

Study Design

On Study Day 1, participants received a single oral dose of 17 mg pimavanserin in the four populations under fasting conditions. Blood samples for pimavanserin and AC-279 analysis were collected pre-dose and at scheduled timepoints through Day 21.

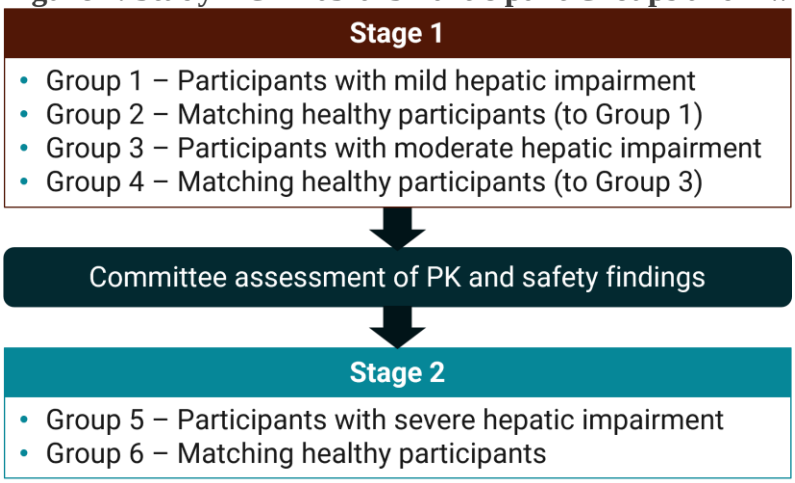
Hepatically-impaired participants were classified as mild, moderate or severe by Child-Pugh classification, and matched with healthy participants.

- Mild hepatic impairment: Child-Pugh score 5 to 6, inclusive
- Moderate hepatic impairment: Child-Pugh score 7 to 9, inclusive
- Severe hepatic impairment: Child-Pugh score 10 to 15, inclusive
- Healthy control participants were age, race, gender, and body mass index (BMI) matched (±10 years in age, but between 40-85 years old, and ±20% in BMI) for participants with hepatic impairment

This study was conducted in two stages (**Figure 1**). Upon completion of Stage 1, a committee of qualified individuals including the Principal Investigators and a Sponsor Medical Monitor or designee evaluated participant safety profiles (i.e., adverse events, clinical laboratory results,

electrocardiograms, vital signs); in addition, PK area under the concentration-versus-time curves (AUCs) were reviewed by the committee in conjunction with a clinical pharmacologist to determine if the level of exposure in participants with mild or moderate hepatic impairment was more than 3× that of the healthy participants. If exposure was within that limit, and there were no clinical safety concerns, then Groups 5 and 6, participants with severe hepatic impairment and their matches, were enrolled during Stage 2.

Figure 1. Study ACP-103-025 Participant Groups and Two-stage Design[2]



Abbreviation: PK=pharmacokinetic.

Results

A total of 45 unique participants (or 49 including duplicated participants) with hepatic impairment or matching healthy controls were enrolled and dosed with pimavanserin. Following a single oral dose of 17 mg pimavanserin, plasma pimavanserin concentrations appeared to be absorbed into the circulation slowly, distributed extensively, and cleared slowly until the end of study after 20 days with levels below the limit of quantitation in most participants beyond Day 15.

The mean (standard deviation [SD]) C_{max} values for pimavanserin for mild, moderate, and severe groups of hepatic impairment and respective matching controls are presented in **Table 1**.

Table 1. Mean (SD) PK Parameters for Pimavanserin in Participants with Hepatic Impairment and Respective Controls Following a Single 17 mg Oral Dose of Pimavanserin (PK Analysis Set)[2]

PK parameters	Mild (n=8)[a]		Control for mild (n=8)		Moderate (n=8)		Control for moderate (n=8)		Severe (n=8)		Control for severe (n=8)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max} (ng/mL)	4.13	1.09	4.60	1.33	5.40	1.50	5.60	1.07	5.92	2.95	6.16	2.38
T_{max} (h)[b]	7.50	6.00-24.0	6.00	1.00-12.0	1.50	1.00-16.0	6.00	1.00-9.00	2.00	1.00-36.0	10.5	6.00-24.0
V_z/F (L)	5404	1031	5218	1714	5384	1296	4142	854	5579	1795	3799	1005
AUC_{0-t} (ng•h/mL)	376	85.1	418	188	552	204	517	176	591	236	571	242

PK parameters	Mild (n=8)[a]		Control for mild (n=8)		Moderate (n=8)		Control for moderate (n=8)		Severe (n=8)		Control for severe (n=8)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
$AUC_{0-\infty}$ (ng•h/mL)	392	85.6	438	196	585	220	536	183	627	242	599	253
Cl/F (L/h)	53.1	11.1	53.4	20.7	38.5	13.4	41.1	12.9	36.7	15.8	38.9	15.6
$t_{1/2}$ (h)	71.8	12.3	70.6	12.7	102	25.6	73.2	15.2	111	33.8	72.7	20.4

[a] *One participant was excluded from the descriptive statistics since the participant has no matched control.*
[b] *Note: T_{max}=median (min, max).*
Abbreviations: $AUC_{0-\infty}$=area under the concentration-versus-time curve from time 0 to infinity; AUC_{0-t}=area under the concentration-versus-time curve from time 0 to the time of last quantifiable concentration at time t; Cl/F=apparent systemic clearance; C_{max}=maximum observed plasma concentration; 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.

The respective geometric mean ratios (GMRs) and 90% confidence intervals (CIs) (hepatic impairment groups versus respective controls) for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of pimavanserin are presented in **Table 2**.

Table 2. Statistical Comparison of C_{max} and AUC of Pimavanserin Between Hepatic Impairment Groups and Respective Controls[2]

Group	Parameter	Hepatic impairment group geometric means (n=8)	Control group geometric means (n=8)	Geometric mean ratio	90% CI
Mild / Control	AUC_{0-t} (ng•h/mL)	367	384	0.9561	0.6879, 1.3290
	$AUC_{0-\infty}$(ng•h/mL)	384	403	0.9528	0.6921, 1.3118
	C_{max} (ng/mL)	4.00	4.44	0.8996	0.7123, 1.1363
Moderate / Control	AUC_{0-t} (ng•h/mL)	521	492	1.0592	0.7573, 1.4815
	$AUC_{0-\infty}$ (ng•h/mL)	551	510	1.0794	0.7606, 1.5318
	C_{max} (ng/mL)	5.24	5.50	0.9527	0.8076, 1.1240
Severe / Control	AUC_{0-t} (ng•h/mL)	552	529	1.0427	0.7065, 1.5389
	$AUC_{0-\infty}$ (ng•h/mL)	586	554	1.0587	0.7221, 1.5521
	C_{max} (ng/mL)	5.33	5.75	0.9266	0.6748, 1.2724

Note: Geometric mean, geometric mean ratios, and 90% CIs for log-transformed AUC and C_{max} were calculated from an analysis of variance (ANOVA) model with effects for participant group and paired participant.
Abbreviations: ANOVA=analysis of variance; AUC=area under the concentration-versus-time curve; $AUC_{0-\infty}$=under the concentration-versus-time curve from time 0 to the time of last quantifiable concentration at time t; AUC_{0-t}=area under the concentration-versus-time curve from time 0 to the time of last quantifiable concentration at time t; C_{max}=maximum observed plasma concentration; CI=confidence interval.

Discussion

There is no data with the 34 mg dose of pimavanserin in patients with hepatic impairment. Following a single oral dose of 17 mg pimavanserin, pimavanserin appeared to be absorbed into the circulation slowly, distributed extensively, and cleared slowly until the end of study collection after 20 days with levels below the limit of quantitation in most participants beyond Day 15, both in participants with hepatic impairment (mild, moderate, and severe) and matching controls. These PK findings with pimavanserin in participants with hepatic impairment were comparable to their respective matched controls and those of earlier studies.

Although pimavanserin is extensively metabolized, impaired hepatic function did not appear to have an effect on the exposure to pimavanserin. As shown from the GMRs and 90% CIs of C_{max}

and AUC between hepatic impairment participants and corresponding controls, there did not appear to be any effect of hepatic impairment on the exposure to pimavanserin.

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

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. ACP-103-025 Clinical Study Report. 2017.
3. Acadia Pharmaceuticals Inc. Data on File. ACP-103-020 Protocol. 2010.