Pharmacokinetics, Safety, and Tolerability of Seladelpar in Subjects with Hepatic Impairment

Mao Z., Martin R., Steinberg A., Rohane P., Nguyen J., Standen M., Boudes P.
CymaBay Therapeutics, Newark, CA

DDW Digestive Disease Week®

Background

- Primary biliary cholangitis (PBC) is a rare, idiopathic autoimmune disease of the liver characterized by an inflammatory destruction of intrahepatic bile ducts that leads to chronic cholestasis[1]
- The disease can progress to cirrhosis, particularly if patients do not respond adequately to ursodeoxycholic acid (UDCA), the first-line treatment for PBC[2]
- Seladelpar, a selective peroxisome proliferator-activated receptor-delta (PPARδ) agonist, has demonstrated potent anticholestatic and anti-inflammatory activity in phase 2 studies of patients with PBC, with or without cirrhosis[3,4]
- Patients with PBC progress to cirrhosis, so it is important to evaluate candidate treatments in patients with impaired hepatic function, as drug exposure may be altered in this population[5]
- Here we report on the pharmacokinetics (PK) of seladelpar in patients with hepatic impairment (HI) compared with healthy volunteers

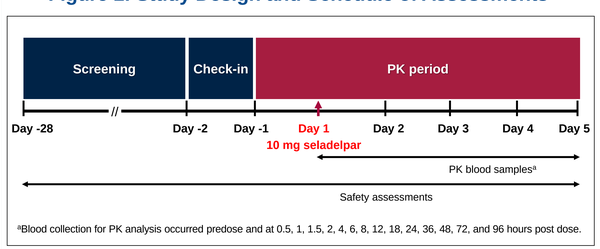
Objective

- To evaluate the PK and safety of a single oral 10 mg dose of seladelpar in subjects with varying degrees of HI vs matched control subjects with normal hepatic function

Methods

- Subjects with normal hepatic function and subjects with mild (class A), moderate (class B), or severe (class C) HI, as defined per Child-Pugh (CP) score,[6] were enrolled (**Figure 1**)
  - Subjects with normal hepatic function were required to have normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin values
  - CP scores of A, B, and C were defined according to **Table 1**
  - Planned enrollment was 32 subjects (male and female), with 8 subjects in each of 4 groups: healthy subjects with normal hepatic function, CP-A HI, CP-B HI, and CP-C HI
- Subjects with normal hepatic function were matched to those with CP-B HI based on gender, body mass index, and age
- All enrolled subjects received a single oral dose of 10 mg seladelpar at Day 1
- PK parameters analyzed: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, Vz/F, λz
- Safety/tolerability parameters assessed
  - Physical examination findings, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory findings (hematology, clinical chemistry, and urinalysis), monitoring of adverse events (AEs)
- Analysis datasets
  - PK Analysis Set: included all subjects who underwent plasma PK sampling and had evaluable PK assay results
  - Safety Analysis Set: included all subjects who received 10 mg seladelpar

Figure 1: Study Design and Schedule of Assessments



[a]Blood collection for PK analysis occurred predose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours post dose.

Table 1: Child-Pugh Classification Criteria

Finding	Points Scored for each Observed Finding		
	1	2	3
Encephalopathy	None	Grade 1-2 (Mild-Moderate)	Grade 3-4 (Severe)
Ascites	None	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

Child-Pugh Total Score Classification			
Subjects Enrolled	**Total Score**	**Group**	**Severity**
8	5-6	A	Mild
8	7-9	B	Moderate
8	10-15	C	Severe

INR, international normalized ratio; PT, prothrombin time.

Results

Demographics and Baseline Characteristics

Table 2: Subject Demographics and Baseline Characteristics

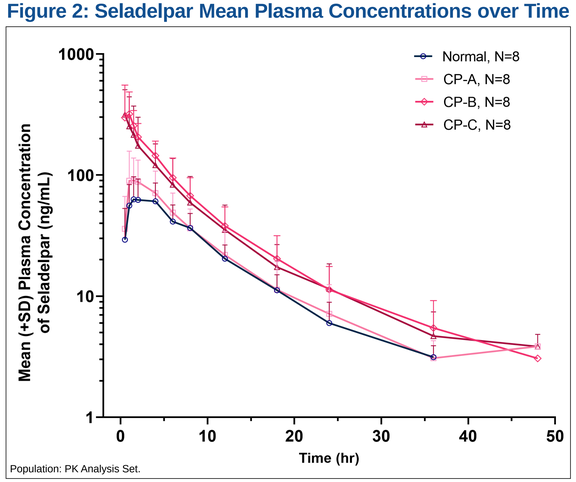
Characteristic	Normal N=8	CP-A N=8	CP-B N=8	CP-C N=8	Overall N=32
Male / Female, n	6 / 2	6 / 2	6 / 2	6 / 2	24 / 8
Age (years), mean (SD)	58.9 (5.1)	57.8 (6.8)	60.6 (7.5)	54.1 (4.0)	57.8 (6.2)
BMI (kg/m^2), mean (SD)	31.0 (2.4)	31.9 (5.1)	29.8 (3.5)	28.1 (4.7)	30.2 (4.1)
CP score, mean (SD)	n/a	5.0 (0)	7.8 (0.9)	10.3 (0.5)	n/a
Cirrhosis, n (%)	0	5 (63)	8 (100)	8 (100)	21 (66)
Prothrombin INR, mean (SD)	1.01 (0.06)	1.05 (0.05)	1.26 (0.17)	1.36 (0.20)	n/a
ALT (IU/L), mean (SD)	19.0 (9.9)	35.8 (14.7)	30.9 (27.3)	31.3 (19.6)	n/a
AST (IU/L), mean (SD)	18.1 (5.7)	33.3 (12.9)	52.6 (32.2)	58.5 (25.7)	n/a
Albumin (g/dL), mean (SD)	4.3 (0.2)	4.3 (0.3)	3.6 (0.5)	2.9 (0.4)	n/a
Bilirubin (mg/dL), mean (SD)	0.5 (0.2)	0.5 (0.2)	1.5 (0.5)	2.0 (0.9)	n/a
Platelets (×10^9/L), mean (SD)	217.8 (43.6)	218.9 (61.5)	105.0 (44.5)	104.4 (43.5)	n/a

BMI, body mass index; n/a, not applicable; NASH, nonalcoholic steatohepatitis.
Population: Safety Analysis Set.

- Subjects in the HI cohorts had a medical history consistent with chronic liver disease. These conditions included alcoholic cirrhosis, hepatitis C, NASH, and PBC

Pharmacokinetics

Figure 2: Seladelpar Mean Plasma Concentrations over Time



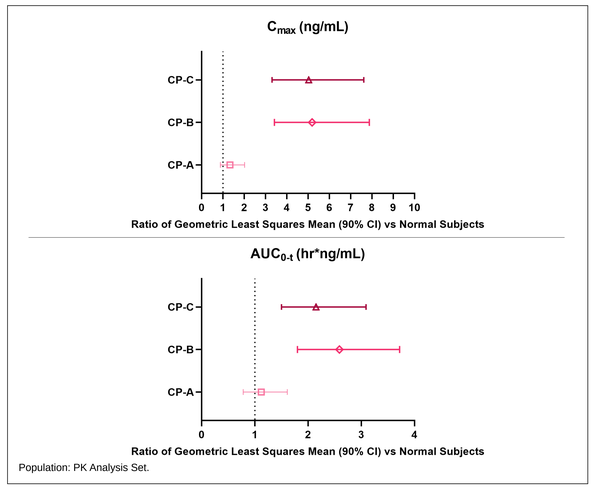
Population: PK Analysis Set.

Table 3: PK Parameters for Seladelpar in Subjects with Normal Hepatic Function and Varying Degrees of Hepatic Impairment

PK Parameter	Normal N=8	CP-A N=8	CP-B N=8	CP-C N=8
C_{max} (ng/mL)[a]	71.9 ± 28.0	101 ± 58.7	398 ± 199	379 ± 180
T_{max} (hr)[b]	2.0 (0.5, 4.0)	1.5 (0.5, 4.0)	1.0 (0.5, 1.5)	0.50 (0.5, 4.0)
$AUC_{0\text{-}t}$ (hr*ng/mL)[a]	668 ± 217	785 ± 423	1763 ± 606	1570 ± 886
$AUC_{0\text{-}inf}$ (hr*ng/mL)[a]	705 ± 227	815 ± 432	1807 ± 612	1616 ± 879
$t_{1/2}$ (hr)[a]	6.7 ± 1.6	6.2 ± 1.6	6.2 ± 1.4	7.2 ± 1.6
CL/F (L/hr)[a]	15.4 ± 4.5	14.3 ± 4.9	6.3 ± 3.0	7.8 ± 3.5
Vz/F (L)[a]	141 ± 29.0	120 ± 36.5	54.6 ± 21.2	78.7 ± 30.6

$AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 until the last quantifiable measurement; CL/F, apparent total body clearance; C_{max}, maximum observed plasma drug concentration; $t_{1/2}$, terminal elimination phase half-life; T_{max}, time to reach maximum plasma concentration; Vz/F, apparent volume of distribution.
[a]Arithmetic mean ± SD.
[b]Median (minimum, maximum).
Population: PK Analysis Set.

Figure 3: Change in C_{max} and $AUC_{0\text{-}t}$ in Subjects with HI Relative to Subjects with Normal Hepatic Function



Population: PK Analysis Set.

- Thirty-one of the 32 subjects completed the study; 1 subject in the CP-B HI group withdrew due to a family emergency*
- Exposure (C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$) (**Table 3, Figure 3**)
  - CP-A HI vs normal hepatic function: no significant difference in C_{max}, $AUC_{0\text{-}t}$, or $AUC_{0\text{-}inf}$
  - CP-B or CP-C HI vs normal hepatic function: ~5-fold increase in C_{max} and ~2-fold increase in $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$
- Terminal elimination phase half-life ($t_{1/2}$) (**Table 3**)
  - Mean $t_{1/2}$ in subjects with CP-A, CP-B, or CP-C HI ranged from 6.2 to 7.2 hours; this was comparable with mean $t_{1/2}$ for normal subjects (6.7 hours)
- Mean apparent clearance (CL/F) (**Table 3**)
  - CP-A HI vs normal hepatic function: no difference in CL/F
  - CP-B or CP-C HI vs normal hepatic function: CL/F decreased by ~50%

*Data from all 32 subjects were available for the PK analysis, as samples were collected up to 24 hours post dose from the subject who withdrew and were included in the analysis.

Safety

- No deaths or treatment-emergent adverse events (TEAEs) that led to study withdrawal were reported
- Overall, 8/32 subjects had ≥1 TEAE (12 TEAEs in total): 2 subjects with normal hepatic function, 3 subjects with CP-A HI, 1 subject with CP-B HI, and 2 subjects with CP-C HI
- TEAEs were reported in 1 subject except for fatigue (occurred in 2 subjects)
- TEAEs were considered unrelated to seladelpar except for 3 TEAEs in 3 subjects with CP-A HI: gastroesophageal reflux disease, diarrhea, and arthralgia. All resolved during study participation
- All TEAEs were mild in severity, except for 1 case of a severe SAE: esophageal varices hemorrhage. This occurred in a subject with CP-C HI and a history of recurrent bleeding from esophageal varices. This event was considered unlikely to be related to seladelpar by the Investigator
- No relevant changes in mean vital signs, 12-lead safety ECG parameters, physical examination findings, or mean laboratory values were observed

Discussion

- Mean seladelpar exposure (C_{max} and AUC) was not significantly altered in subjects with CP-A HI compared with healthy subjects
- C_{max} and AUC more than doubled in subjects with CP-B or CP-C HI compared to subjects with normal hepatic function
  - Notably, seladelpar exposure was similar between subjects with CP-B and CP-C HI
- Mean $t_{1/2}$ did not appear to be impacted by the degree of HI
- Mean seladelpar clearance (CL/F) decreased with increasing HI
- Seladelpar appeared to be safe and well tolerated in subjects with varying degrees of HI
- All TEAEs were mild except for a severe SAE of esophageal varices hemorrhage, which was consistent with the patient's previous history (recurrent bleeding from esophageal varices)

Conclusions

- Single-dose administration of seladelpar appeared to be safe and well tolerated in subjects with varying degrees of HI
- Compared with healthy controls, CP-A HI did not significantly change the PK of seladelpar, and dose adjustments in this population do not appear necessary
- Given the magnitude of the increases in seladelpar exposure in subjects with CP-B and CP-C HI, further characterization of dose exposure in PBC patients with or without cirrhosis may be warranted

References

1. Khanna A, Jones DE. Novel strategies and therapeutic options for the management of primary biliary cholangitis. *Therap Adv Gastroenterol.* 2017;10(10):791-803.
2. Goldstein J, Levy C. Novel and emerging therapies for cholestatic liver diseases. *Liver Int.* 2018;38(9):1520-1535.
3. Jones D, Boudes PF, et al. Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. *Lancet Gastroenterol Hepatol.* 2017;2(10):716-726.
4. Mayo MJ, et al. Seladelpar for the treatment of primary biliary cholangitis: Experience with 25 cirrhotic patients. Presented at EASL 2019. Abstract PS-122.
5. Edwards JE, et al. Modeling and experimental studies of obeticholic acid exposure and the impact of cirrhosis stage. *Clin Transl Sci.* 2016;9(6):328-336.
6. Pugh RN, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973;60(8):646-649.

Acknowledgement of Contributors

We gratefully acknowledge study participants and site study staff for their contribution to the study.
The authors acknowledge the medical writing assistance of ETHOS Health Communications in Yardley, USA.
Presented at The International Liver Congress™ 2019; 10-14th April 2019; Vienna, Austria.