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

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

**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.
- The disease can progress to cirrhosis, particularly if patients do not respond adequately to ursodeoxycholic acid (UDCA), the first-line treatment for PBC.
- Seladelpar, a selective peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, has demonstrated potent anticholestatic and anti-inflammatory activity in phase 2 studies of patients with PBC, with or without cirrhosis.
- 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.
- We have reported 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, were enrolled (Table 1).
- Subjects with normal hepatic function were required to have normal serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels.
- Subjects with mild, moderate, and severe HI, as defined according to Table 1, were included 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 of the study.
- PK parameters analyzed: Cmax (ng/mL), AUC0–τ (ng·h/mL), Vz/F, CL/F, λz, and t1/2.
- Safety/tolerability parameters assessed: Physical examination findings, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory findings (hematologic, clinical chemistry, and urinalysis), monitoring of adverse events (AEs).
- Analysis datasets:
  - Analysis dataset
  - 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.

**Results**
- Demographics and Baseline Characteristics: Table 2
  - Subjects in the HI cohorts had a medical history consistent with chronic liver disease. These conditions included alcoholic cirrhosis, hepatitis C, NAS, and PBC.

**Pharmacokinetics**
- Figure 2: Seladelpar Mean Plasma Concentrations over Time
  - Thirty-nine of the 32 subjects completed the study; 1 subject in the CP-B HI group withdrew due to a family emergency*.
  - Exposure (Cmax, AUC0–τ, AUCinf) (Table 3, Figure 3):
    - CP-B HI vs normal hepatic function: no significant difference in Cmax, AUC0–τ, or AUCinf.
    - CP-B or CP-C HI vs normal hepatic function: -5-fold increase in Cmax and -2-fold increase in AUC0–τ and AUCinf.
  - Terminal elimination phase half-life (t1/2) (Table 3): mean t1/2 in subjects with CP-A, CP-B, or CP-C HI ranged from 6.2 to 7.2 hours; this was comparable with mean t1/2 in normal subjects.
  - Mean apparent clearance (CL/F) (Table 3): CP-B or CP-C HI vs normal hepatic function: CL/F decreased by ~50%.

**Safety**
- No deaths or treatment-emergent adverse events (TEAEs) that led to withdrawal or hospitalization 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).
- Three treatment-emergent adverse events (TEAEs) in 3 subjects with CP-A HI: gastroesophageal reflux disease, diarrhea, and arthralgia.
- No serious AEs or deaths were reported.
- All TEAEs were mild in severity, except for 1 case of 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 investigators.
- 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 (Cmax and AUC) was not significantly altered in subjects with CP-A HI compared with healthy subjects.
  - Notably, seladelpar exposure was similar between subjects with CP-B HI and CP-C HI.
  - Mean t1/2 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.

**Acknowledgement of Contributors**
We gratefully acknowledge study participants and site study staff for their contribution to the study.

**References**