Population Pharmacokinetic Analysis of Seladelpar in Patients With Primary Biliary Cholangitis

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Conclusions

- The population pharmacokinetic (PK) model developed herein adequately described seladelpar concentrations over time in healthy participants, patients with hepatic impairment, and patients with primary biliary cholangitis (PBC)
- The model-predicted increase in seladelpar exposure for Child-Pugh (CP) class A cirrhosis (with or without portal hypertension [PHT]) was modest
- Food intake had no clinically relevant effect on seladelpar exposure
- Other covariates, including age, sex, and concomitant proton pump inhibitor (PPI) use, were not significant or clinically relevant
- These findings further support the use of seladelpar 10 mg daily dosing in patients with PBC and CP class A cirrhosis, as well as its dosing without regard to food intake or PPI use

Plain Language Summary

- Patients with primary biliary cholangitis (PBC) have problems with the way their liver functions
- Seladelpar is a drug that can be used to treat patients with PBC
- This study used a computer program to understand what might happen to the amount of seladelpar that is in the body if seladelpar is given to different types of people
  - It tested whether the amount of seladelpar in the body would change based on a person's body weight or liver function
  - It also tested whether the amount of seladelpar in the body would change based on whether a person took seladelpar with or without food or was taking other types of medicines
- The study found that the amount of seladelpar in the body did not greatly change in different types of people, nor did it change based on a person's body weight or their liver function
  - It also did not change based on whether they had eaten food or taken other types of medicines

Introduction

- PBC is a chronic, progressive, autoimmune, cholestatic liver disease[1]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients who are unable to tolerate UDCA[2-4]

Objectives

- To develop a population PK model of seladelpar in healthy participants, patients with hepatic impairment of various aetiologies, and patients with PBC
- To evaluate the effects of intrinsic and extrinsic factors on seladelpar PK parameters

Methods

- This study used data that were pooled from eight Phase 1 and four Phase 2/3 studies of seladelpar to better understand the PK of seladelpar in healthy participants, patients with hepatic impairment of various aetiologies, and patients with PBC
- NONMEM v7.4 was used to conduct the population PK analysis[5]
- Population and individual model parameters were estimated using the first-order conditional estimation with eta-epsilon interaction (FOCE-I)
- A full covariate-modelling approach was implemented to evaluate covariate effects
- Covariates were retained in the final model if they resulted in a seladelpar exposure change of <80% or >125% compared with the reference
- The performance of the final model was evaluated with diagnostic plots and predictive checks
- Outcomes assessed consisted of parameter estimates of fixed and random effects (eg, bioavailability, clearance), seladelpar prediction-corrected visual predictive checks, typical steady-state PK profiles in patients with or without hepatic impairment, covariate effects on PK metrics, such as area under the concentration-time curve (AUC) and steady-state maximum observed concentration (C_{max}), and seladelpar exposure estimates based on PPI use

Results

- Seladelpar PK were characterised by a 2-compartment population PK model with sequential zero-order release and first-order absorption
- The analysis dataset included a total of 4781 PK observations of seladelpar from 488 participants (healthy participants, non-PBC patients with hepatic impairment of various aetiologies, and patients with PBC; **Table 1**)

Table 1. Summary of Pooled Covariate Data From 12 Studies of Seladelpar Included in the PK Model

	Pooled Patient Data From 12 Studies of Seladelpar[a] (N = 488)
Seladelpar dose, n (%)	
1 mg	6 (1.2%)
2 mg	12 (2.5%)
5 mg	53 (10.9%)
10 mg	414 (84.8%)
15 mg	3 (0.6%)
Health status, n (%)	
Healthy	165 (33.8%)
PBC	277 (56.8%)
Non-PBC patient[b]	46 (9.4%)
Fasting status, n (%)	
Fasted	225 (46.1%)
Fed	8 (1.6%)
Fasted/unknown[c]	255 (52.3%)
Sex, n (%)	
Female	341 (69.9%)
Male	147 (30.1%)
Age, years	
Mean (SD)	52.6 (13.2)
Median (range)	54.0 (19.0, 79.0)
Race, n (%)	
White	421 (86.3%)
Black	42 (8.6%)
Asian	14 (2.9%)
Other	11 (2.3%)
Weight, kg	
Mean (SD)	74.5 (15.4)
Median (range)	72.7 (45.8, 127.5)
Concomitant UDCA use, n (%)	
Yes	263 (53.9%)
No/unspecified	225 (46.1%)
Concomitant PPI use, n (%)	
Yes	85 (17.4%)
No/unspecified	403 (82.6%)
Cirrhosis, CP class with/without PHT, n (%)	
CP-A, no PHT[d]	51 (10.5%)
CP-A + PHT[d]	19 (3.9%)
CP-B	15 (3.1%)
CP-C	10 (2.0%)
None	189 (38.7%)
Unspecified	204 (41.8%)

[a]Data were collected from eight Phase 1 studies (study identifiers: RWJ-800025-NAP-1001; CB8025-11732; CB8025-11733; CB8025-11734; CB8025-11836; CB8025-11840; CB8025-11941; CB8025-11942) and four Phase 2/3 studies (study identifiers: CB8025-21838; CB8025-21629 [NCT02955602]; CB8025-31731-RE [NCT03301506]; CB8025-32048 [NCT04620733]) of seladelpar in healthy participants, patients with hepatic impairment of various aetiologies, and patients with PBC. [b]Patients with renal or hepatic impairment but not PBC. Note, renal impairment was not tested in the population PK model. [c]Used for Phase 2/3 studies, in which fasting status was requested but could not be confirmed. [d]PHT in participants from study CB8025-11732 was identified using the following medical terms among those with CP-A: "ascites", "duodenal varices", "esophageal varices", "gastric antral vascular ectasia", "gastric varices", "hepatosplenomegaly", "intermittent esophageal varices bleeding", "intestinal varices", "portal hypertension", "splenomegaly", "splenorenal shunt", "thrombocytopenia", and "varicose veins of abdominal wall". PHT in participants from study CB8025-21629 was identified using the following medical terms: "ascites", "duodenal varices", "esophageal varices", "esophageal varices treated with banding", "gastric antral vascular ectasia", "gastric varices", "grade i esophageal varices", "non bleeding esophageal varices", "intestinal varices", "portal hypertension", "splenomegaly", "splenorenal shunt", "thrombocytopenia", and "varicose veins of abdominal wall". PHT in participants from study CB8025-21838 was defined for cohorts 1 and 2: cohort 1 had CP-A without PHT; cohort 2 had CP-A with PHT. CP assessment and cohort assignment were performed by the investigator during enrolment and were recorded on the case report form. PHT in participants from studies CB8025-31731-RE and CB8025-32048 was identified by the investigator and recorded on the case report form.
CP, Child-Pugh; PBC, primary biliary cholangitis; PHT, portal hypertension; PK, pharmacokinetics; PPI, proton pump inhibitor; UDCA, ursodeoxycholic acid.

Results

Table 2. Parameter Estimates of Fixed and Random Effects in the Final Model

	Fixed Effect		Random Effect			
	Value	RSE	SD	(CV%)[a]	RSE	Shrinkage
Apparent clearance, L/h	12.6	3.31%	0.390	(40.5%)	4.33%	6.81%
Apparent central volume, L	84.4	3.66%	0.287	(29.3%)	5.77%	29.0%
Apparent intercompartmental clearance, L/h	0.93	7.46%	0.584	(63.7%)	10.8%	52.2%
Different random effect in above in PBC studies	–	–	0.363	(37.5%)	36.7%	83.4%
Apparent peripheral volume, L	25.9	9.6%	0.584	(63.7%)	10.8%	52.2%
Zero-order release duration to depot, fasted/unknown, h	0.228	16.3%	1.75	(454%)	8.93%	46.0%
Zero-order release duration to depot, fed, h	6.87	14.6%	0.440	(46.3%)	42.2%	84.2%
First-order absorption rate, 1/h[b]	1.28	7.39%	0.629	(69.7%)	20.6%	60.6%
Inter-occasion variability of above	–	–	1.10	(154%)	6.63%	64.4%
Weight exponent on clearance	0.750	(fixed)	–	–	–	–
Weight exponent on central volume	1.00	(fixed)	–	–	–	–
Bioavailability multiplier for all non-PBC patients	0.853	4.10%	–	–	–	–
Bioavailability multiplier for CP-A HI, no PHT	1.13	6.4%	–	–	–	–
Bioavailability multiplier for CP-A HI + PHT, 2 studies[c]	1.54	9.28%	–	–	–	–
Bioavailability multiplier for CP-A HI + PHT, CB8025-21629[c]	0.839	14.3%	–	–	–	–
Bioavailability multiplier for CP-B HI, no PBC	3.34	9.30%	–	–	–	–
Bioavailability multiplier for CP-B HI with PBC	1.48	8.40%	–	–	–	–
Bioavailability multiplier for CP-C HI	2.45	6.71%	–	–	–	–
Central volume multiplier for HI, no PBC	1.00	(fixed)	–	–	–	–
Central volume multiplier for HI with PBC	0.789	5.4%	–	–	–	–
Clearance-central volume correlation	–	–	0.552	(59.7%)	10.2%	–
Proportional residual error in non-PBC studies	–	–	0.250	(25.4%)	0.647%	14.0%
Proportional residual error in PBC studies	–	–	0.479	(50.8%)	0.731%	16.5%

These results were for a 72.6-kg patient with PBC. RSE was calculated as standard error/estimate.
[a]CV% was derived from SD: sqrt(exp(SD2)-1) × 100%. [b]Sequential zero-order release into the gut and first-order absorption from the gut were assumed. [c]Separate multipliers were used for studies CB8025-21838 together with CB8025-31731-RE (NCT03301506) and for CB8025-21629 (NCT02955602).
CP, Child-Pugh; CV%, coefficient of variation percentage; EXP, exponent; HI, hepatic impairment; PBC, primary biliary cholangitis; PHT, portal hypertension; RSE, relative standard error; SD, standard deviation; SQRT, square root.

- The final model included the covariate effects of body weight, food intake, patient status, and hepatic impairment (**Table 2**)
  - The effects of body weight were included using allometric scaling with fixed coefficients (0.75 for clearance, 1 for central volume)
- For a 72.6-kg patient with PBC, the apparent clearance (CL/F) and apparent central volume (V/F) (relative standard error) were estimated at 12.6 L/h (3.31%) and 84.4 L (3.66%), respectively
- The total apparent volume of distribution was 110.3 L
- Relative bioavailability (90% CI) was 15% (11%–19%) lower in healthy participants when compared with patients with PBC
- Hepatic impairment increased the bioavailability of seladelpar and decreased the CL/F and V/F
- Other covariates, including age, sex, baseline laboratory values (eg, alkaline phosphatase, albumin), cytochrome P450 2C9 phenotype, concomitant PPI use, and concomitant UDCA use, did not result in a change in seladelpar exposure of more than 10% compared with the reference and were not retained in the final model

Figure 1. Final Model Visual Predictive Checks of the Seladelpar Prediction-Corrected Concentration With Observations by Time After Dose

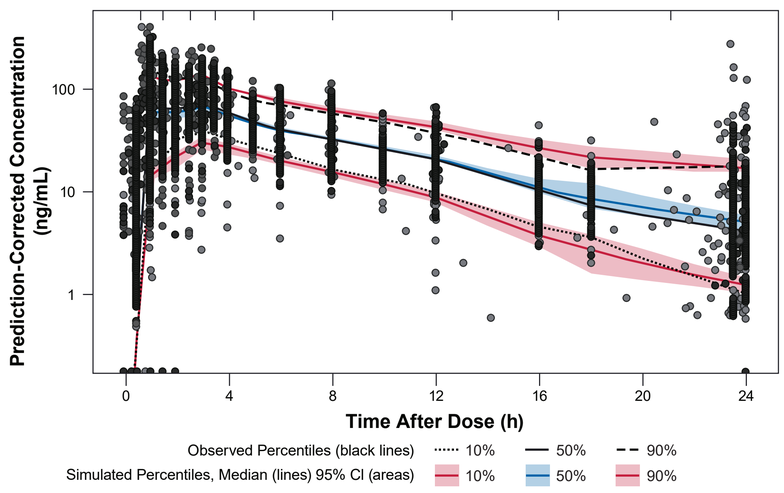
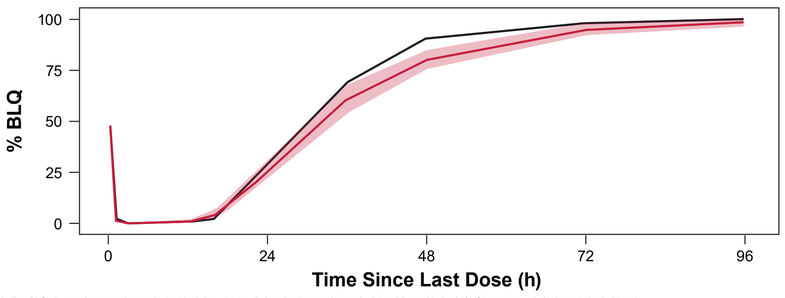


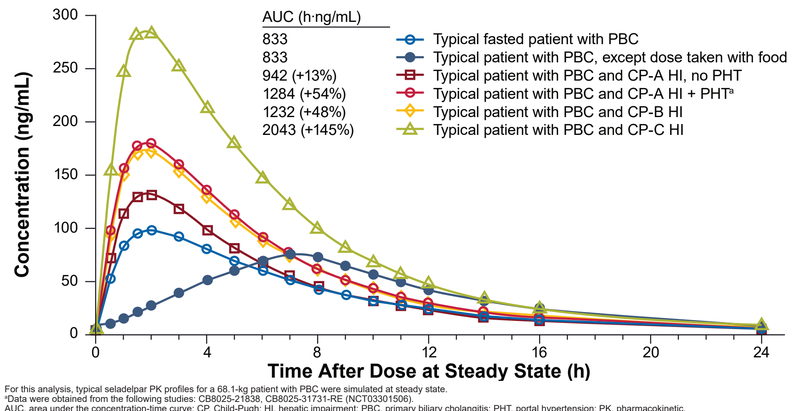
Figure 2. Final Model Visual Predictive Checks of the Proportion of BLQ Observations



Median BLQ observations are shown via the black line; the predictive checks are shown via the red line, with the 95% CI represented via the red shaded band.
BLQ, below the lower limit of quantitation.

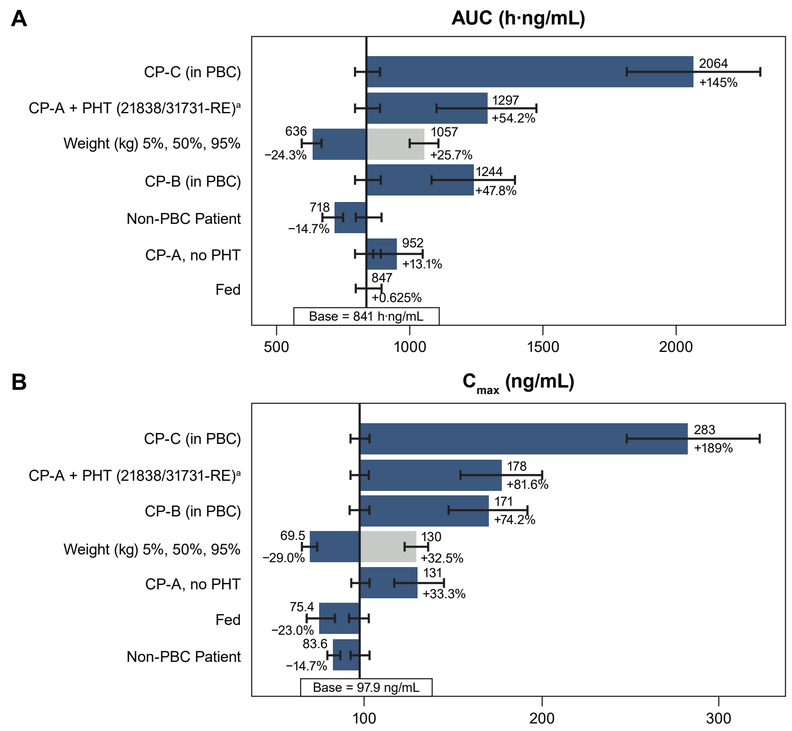
- Predictive checks for the final model are shown in **Figure 1** and **Figure 2**

Figure 3. Model-Predicted Typical Steady-State PK Profiles in Patients Receiving Seladelpar With and Without Hepatic Impairment



For this analysis, typical seladelpar PK profiles for a 68.1-kg patient with PBC were simulated at steady state.
[a]Data were obtained from the following studies: CB8025-21838, CB8025-31731-RE (NCT03301506).
AUC, area under the concentration-time curve; CP, Child-Pugh; HI, hepatic impairment; PBC, primary biliary cholangitis; PHT, portal hypertension; PK, pharmacokinetic.

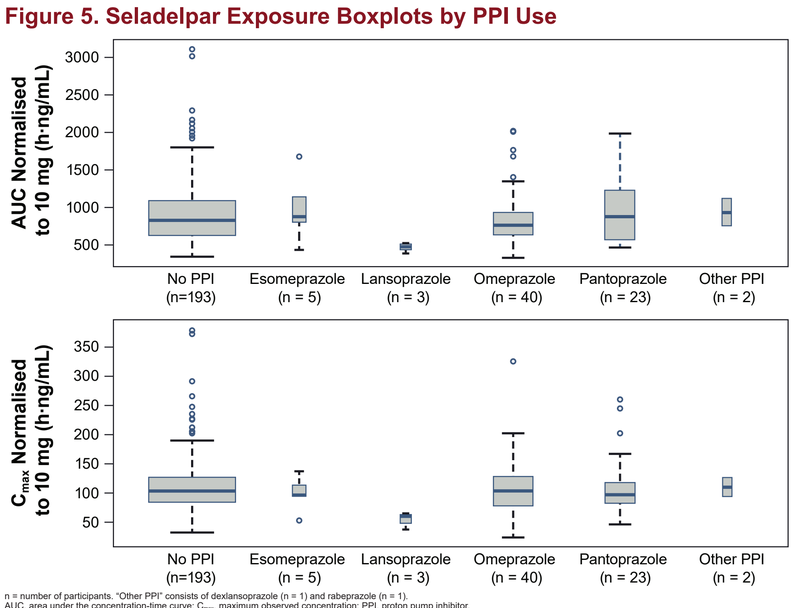
Figure 4. Final Model Forest Plots Depicting the Covariate Effects on Steady-State Seladelpar AUC (A) and C_{max} (B)



The 'Base' (bolded, vertical black line) shows the output with all inputs at typical or median values in the PBC studies; these results were for a 57-year-old, 68-kg, female patient with PBC without hepatic impairment, who was fasted, with eGFR = 95 mL/min/1.73 m^2, albumin = 4.1 g/dL, and ALP = 270 IU/L. Each covariate was varied one at a time to low (gray) and/or high (blue) cases to show relative impacts on AUC or C_{max}, which are shown as a percentage change (if any) on each bar. Shaded bars were sorted in descending order of effect magnitude. Black error bars indicate 90% CIs around the parameter estimates based on 500 simulations.
[a]Data were obtained from the following studies: 21838, study CB8025-21838; 31731-RE, study CB8025-31731-RE (NCT03301506). PHT and CP class were identified by investigators and recorded on the CRF.
ALP, alkaline phosphatase; AUC, area under the concentration-time curve; C_{max}, maximum observed concentration; CP, Child-Pugh; CRF, case report form; eGFR, estimated glomerular filtration rate; PBC, primary biliary cholangitis; PHT, portal hypertension.

- As shown in **Figure 3** and **Figure 4**, relative to a fasted patient with PBC, steady-state AUC (90% CI) was predicted to increase by:
  - 13% (2%–25%) for patients with PBC and CP class A without PHT
  - 54% (32%–75%) for patients with PBC and CP class A with PHT
  - 48% (29%–66%) for patients with PBC and CP class B
  - 145% (116%–176%) for patients with PBC and CP class C based on limited data
- Seladelpar administration with food was predicted to reduce the steady-state C_{max} (90% CI) by 23% (15%–31%; **Figure 4**)

Figure 5. Seladelpar Exposure Boxplots by PPI Use



n = number of participants. "Other PPI" consists of dexlansoprazole (n = 1) and rabeprazole (n = 1).
AUC, area under the concentration-time curve; C_{max}, maximum observed concentration; PPI, proton pump inhibitor.

- Differences between PPI groups were not significant (P >.05) by the Kruskal-Wallis rank sum test (**Figure 5**)

References: 1. European Association for the Study of the Liver. *J Hepatol*. 2017;67:145-72. **2.** Livdelzi (seladelpar). US prescribing information. Gilead Sciences, Inc.; 2024. **3.** Livdelzi (seladelpar). UK summary of product characteristics. Gilead Sciences, Inc.; 2025. **4.** Seladelpar. Summary of product characteristics. European Medicines Agency. Gilead Sciences Inc.; 2025. **5.** Beal SL, et al. (Eds.) NONMEM 7.4 users guide. ICON plc; 2018.

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