Pharmacokinetics, Safety, and Tolerability of Seladelpar in People With Renal Impairment

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Conclusions

- Exposure to seladelpar was not meaningfully changed with different degrees of renal impairment when compared with normal renal function
- Results were similar between analyses that defined renal function category by body surface area indexed estimated glomerular filtration rate (eGFR) or by absolute eGFR
- Seladelpar appeared safe and well tolerated following a single 10-mg dose, regardless of renal impairment status
- These data support that dose adjustment is not necessary for people with mild, moderate, or severe renal impairment receiving seladelpar

Plain Language Summary

- Seladelpar is a drug used to treat primary biliary cholangitis (PBC)
- It is broken down into smaller parts by the body and then removed from the body in urine, which is made by the kidneys
- This study tested how well seladelpar is removed from the body in people whose kidneys do not work as well as they should
- The study found that there was no meaningful difference in the removal of seladelpar between people who have normal kidneys and those who have kidneys that do not work as well as they should
- This means that people can receive the same seladelpar treatment for PBC whether their kidneys work well or not

References: **1.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **2.** Livdelzi. UK Summary of Product Characteristics. Gilead Sciences, Inc.; 2024. **3.** Seladelpar Gilead. EMA prescribing information. Gilead Sciences, Inc.; 2025.

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Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

- 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 with an inadequate response to UDCA or as monotherapy in patients who are unable to tolerate UDCA[1-3]
- Seladelpar is primarily eliminated in the urine as metabolites (M1, M2, and M3), which are not expected to have clinically relevant pharmacological activities[1]
- In a mass balance study in humans, a single 10-mg oral dose of radiolabelled seladelpar was recovered primarily as metabolites in urine (73.4%) and faeces (19.5%)[1]
- To evaluate the effect of different degrees of renal impairment on seladelpar pharmacokinetics (PK) and safety, a Phase 1, single-dose, open-label study (CB8025-11942) was conducted

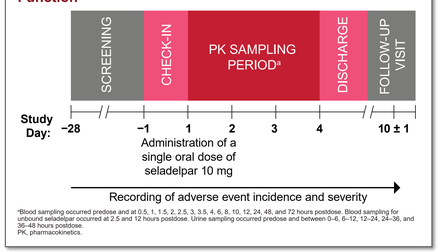
Objective

- To describe the PK, safety, and tolerability of a single 10-mg dose of seladelpar in participants with mild, moderate, or severe renal impairment compared with healthy participants who have normal renal function

Methods

- In a Phase 1, open-label, parallel-group study (CB8025-11942), the PK, safety, and tolerability of seladelpar were evaluated in participants with different degrees of renal impairment when compared with those who had normal renal function
- Categories of normal renal function and renal impairment were defined by eGFR using the modification of diet in renal disease (MDRD) equation, as follows:
  - Normal renal function: ≥90 mL/min/1.73 m^2
  - Mild renal impairment: ≥60 to <90 mL/min/1.73 m^2
  - Moderate renal impairment: ≥30 to <60 mL/min/1.73 m^2
  - Severe renal impairment: <30 mL/min/1.73 m^2
- Participants with normal renal function were demographically matched by age, sex, and body mass index to participants with mild, moderate, or severe renal impairment
- Participants receiving haemodialysis were excluded
- Participants were administered a single oral dose of seladelpar 10 mg on Day 1 (**Figure 1**)
- Blood and urine samples were collected for 3 days and 2 days, respectively, after seladelpar administration, and the concentrations of seladelpar and its metabolites were quantitated using validated liquid chromatography tandem mass spectrometry methods
  - Details of seladelpar metabolite PK are not reported here, as seladelpar metabolites are not pharmacologically active
- The main PK parameters analysed included area under the plasma concentration curve from time 0 to the last measurable concentration (AUC_{0-t}) and to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), the terminal half-life ($T_{1/2}$), the amount of seladelpar excreted in urine (Ae), and renal clearance (CL_R)
- The plasma protein binding of seladelpar was also evaluated
- ANOVA was used to compare the PK parameters in participants in each renal impairment group to the matched participants with normal renal function
- A regression analysis was used to evaluate the relationship between eGFR and seladelpar PK parameters
- In addition to body surface area indexed eGFR, a post hoc analysis of PK was conducted after regrouping participants based on the absolute eGFR
  - Absolute eGFR was calculated as: body surface area indexed eGFR (mL/min/1.73 m^2) × body surface area / 1.73 m^2
- Safety was assessed by the incidence and severity of adverse events (AEs), laboratory parameters, electrocardiogram parameters, and vital signs

Figure 1. Study Design for the Phase 1 Study of Seladelpar in Participants With Renal Impairment vs Normal Renal Function



[a]Blood sampling occurred predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 48, and 72 hours postdose. Blood sampling for unbound seladelpar occurred at 2.5 and 12 hours postdose. Urine sampling occurred predose and between 0–6, 6–12, 12–24, 24–36, and 36–48 hours postdose.
PK, pharmacokinetics.

Results

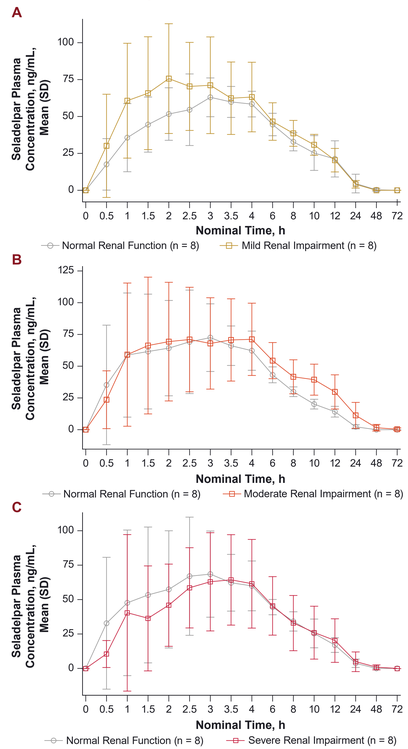
Table 1. Demographics and Baseline Characteristics by Renal Function Group

	Normal Renal Function (n = 12)	Mild Renal Impairment (n = 8)	Moderate Renal Impairment (n = 8)	Severe Renal Impairment (n = 8)
Age, years, mean (SD)	58.9 (7.3)	65.4 (5.0)	63.8 (8.6)	65.6 (9.5)
Female, n (%)	4 (33)	2 (25)	3 (38)	2 (25)
Race, n (%)				
Black or African American	2 (17)	0	1 (13)	0
White	10 (83)	8 (100)	7 (88)	8 (100)
Weight, kg, mean (SD)	82.4 (11.4)	85.2 (16.1)	84.6 (9.3)	93.7 (10.7)
BMI, kg/m^2, mean (SD)	30.3 (2.7)	28.9 (3.2)	31.1 (2.6)	32.5 (2.0)
eGFR, mL/min/1.73 m^2, mean (SD)	90.7 (13.9)	73.0 (5.6)	49.6 (9.2)	23.7 (8.5)

BMI, body mass index; eGFR, estimated glomerular filtration rate.

- Of 36 participants who completed the study, 12 had normal renal function and 8 each had mild, moderate, or severe renal impairment (**Table 1**)

Figure 2. Comparisons of Seladelpar Plasma Concentration-Time Profiles in the Mild (A), Moderate (B), and Severe (C) Renal Impairment Groups vs the Normal Renal Function Group



The same pool of 12 patients with normal renal function were matched by age, sex, and body mass index to each of the patients with renal impairment; therefore, patients with normal renal function may be included in more than 1 group.

Table 2. Seladelpar PK Parameters by Renal Function Group With Assignment Based on Body Surface Area Indexed eGFR

	Mild Renal Impairment vs Matched Normal			Moderate Renal Impairment vs Matched Normal			Severe Renal Impairment vs Matched Normal		
	Normal Renal Function (n = 8)	Mild Renal Impairment (n = 8)	GLSM Ratio (90% CI)	Normal Renal Function (n = 8)	Moderate Renal Impairment (n = 8)	GLSM Ratio (90% CI)	Normal Renal Function (n = 8)	Severe Renal Impairment (n = 8)	GLSM Ratio (90% CI)
AUC_{0-t}, h*ng/mL, mean (SD)	628.7 (277.87)	689.5 (203.80)	1.13 (0.82, 1.57)	567.8 (151.30)	961.4 (511.29)	1.59 (1.15, 2.20)	605.2 (126.74)	645.5 (422.05)	0.95 (0.69, 1.31)
AUC_{0-inf}, h*ng/mL, mean (SD)	670.6 (267.36)	725.6 (219.95)	1.10 (0.81, 1.49)	606.3 (132.48)	1005.8 (556.88)[a]	1.52 (1.08, 2.14)	637.1 (120.44)[a]	693.8 (427.38)	1.01 (0.71, 1.44)
C_{max}, ng/mL, mean (SD)	69.3 (14.65)	85.6 (33.37)	1.17 (0.85, 1.63)	83.8 (36.10)	85.8 (40.74)	0.99 (0.69, 1.44)	82.0 (37.64)	86.8 (45.07)	1.01 (0.66,1.55)
T_{max}, h, median (range)	2.8 (1.0, 4.0)	2.0 (0.5, 6.0)	–	2.6 (1.0, 4.0)	2.8 (1.0, 10.0)	–	2.8 (1.0, 10.0)	3.3 (1.0, 6.0)	–
$T_{1/2}$, h, mean (SD)	5.1 (1.47)	4.8 (1.18)	–	4.7 (0.60)	7.9 (3.04)	–	4.8 (0.60)[a]	5.8 (3.52)	–
Ae_{0-t}, ng, mean (SD)	3068.3 (2340.39)[b]	2113.6 (774.17)	–	3068.3 (2340.39)[b]	2583.7 (2701.77)[a]	–	2052.5 (863.86)[b]	1409.1 (1154.96)[b]	–
CL_R, L/h, mean (SD)	0.006 (0.0056)[b]	0.003 (0.0016)	–	0.006 (0.0056)[b]	0.004 (0.0050)[a]	–	0.003 (0.0014)[b]	0.002 (0.0016)[b]	–

[a]n = 7, [b]n = 4.
Arithmetic means are presented.
The same pool of 12 patients with normal renal function were matched by age, sex, and body mass index to each of the patients with renal impairment; therefore, patients with normal renal function may be included in more than 1 group.
Ae_{0-t}, cumulative urinary excretion from time zero to time t; AUC_{0-inf}, area under the curve extrapolated to infinity; AUC_{0-t}, area under the curve from time 0 to time of last non-zero concentration; CL_R, renal clearance; C_{max}, maximum concentration; eGFR, estimated glomerular filtration rate; GLSM, geometric least squares mean; PK, pharmacokinetic; $T_{1/2}$, terminal half-life; T_{max}, time of observed C_{max}.

- There was no consistent change in seladelpar PK with increasing degrees of renal impairment (**Figure 2**; **Table 2**)
- The observed differences between the renal impairment groups and the normal renal function group were within the PK variability of seladelpar (CV of 44% for AUC and 42.5% for C_{max})
- Overall, the changes were not considered clinically meaningful, and dose adjustment is not needed

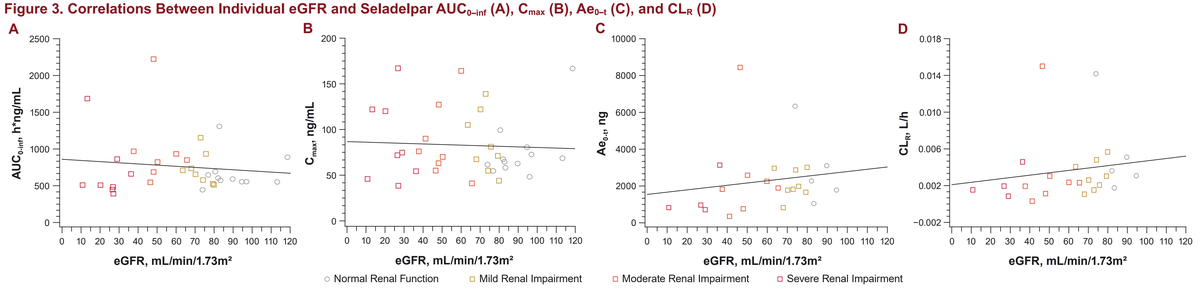
Table 3. Comparisons of Seladelpar PK Parameters by Renal Function Group With Assignment Based on Absolute eGFR

	Mild Renal Impairment vs Matched Normal	Moderate Renal Impairment vs Matched Normal	Severe Renal Impairment vs Matched Normal
AUC_{0-t}, h*ng/mL, GLSM ratio (90% CI)	1.54 (1.38, 1.72)	1.34 (0.90, 2.00)	0.97 (0.62, 1.51)
AUC_{0-inf}, h*ng/mL, GLSM ratio (90% CI)	1.48 (1.36, 1.61)	1.33 (0.77, 2.31)	1.03 (0.60, 1.78)
C_{max}, ng/mL, GLSM ratio (90% CI)	1.17 (0.69, 1.99)	0.95 (0.70, 1.30)	1.05 (0.58, 1.89)

AUC_{0-inf}, area under the curve extrapolated to infinity; AUC_{0-t}, area under the curve from time 0 to time of last non-zero concentration; C_{max}, maximum concentration; eGFR, estimated glomerular filtration rate; GLSM, geometric least squares mean; PK, pharmacokinetic.

- Results of the post hoc analysis conducted after regrouping participants based on absolute eGFR were consistent with those using body surface area indexed eGFR (**Table 3**)

Figure 3. Correlations Between Individual eGFR and Seladelpar AUC_{0-inf} (A), C_{max} (B), Ae_{0-t} (C), and CL_R (D)



Ae_{0-t}, cumulative urinary excretion from time zero to time t; AUC_{0-inf}, area under the plasma concentration curve extrapolated to infinity; CL_R, renal clearance; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate.

- There was no apparent correlation between eGFR and seladelpar AUC_{0-inf} (R^2 = 0.014), C_{max} (R^2 = 0.002), Ae_{0-t} (R^2 = 0.023), or CL_R (R^2 = 0.025; **Figure 3**)

Table 4. Seladelpar Plasma Protein Binding by Renal Function Group

	Mild Renal Impairment vs Matched Normal		Moderate Renal Impairment vs Matched Normal		Severe Renal Impairment vs Matched Normal	
	Normal Renal Function (n = 8)	Mild Renal Impairment (n = 8)	Normal Renal Function (n = 8)	Moderate Renal Impairment (n = 8)	Normal Renal Function (n = 8)	Severe Renal Impairment (n = 8)
Fu, %, mean (SD)	0.215 (0.0373)	0.246 (0.0299)	0.189 (0.0451)	0.343 (0.1519)	0.187 (0.0430)	0.290 (0.0795)

Arithmetic means are presented.
The same pool of 12 patients with normal renal function were matched by age, sex, and body mass index to each of the patients with renal impairment; therefore, patients with normal renal function may be included in more than 1 group.
Fu, fraction unbound.

- The mean percentage fraction of unbound seladelpar across the renal impairment groups ranged from 0.246% to 0.343% compared with 0.187% to 0.215% in the matched normal participants (**Table 4**)
  - These values were consistent with previously reported *ex vivo* protein binding using human plasma, suggesting renal impairment does not have a meaningful impact on the protein binding of seladelpar

Table 5. AEs by Renal Function Group

Patient Incidence, n (%)	Normal Renal Function (n = 12)	Mild Renal Impairment (n = 8)	Moderate Renal Impairment (n = 8)	Severe Renal Impairment (n = 8)
Any AE	2 (17)	1 (13)	3 (38)	0
Grade ≥3 AEs	0	0	0	0
SAEs	0	0	0	0
AEs related to the study drug[a]	0	0	0	0
AEs leading to study discontinuation	0	0	0	0
AEs leading to death	0	0	0	0

All AEs were treatment emergent unless otherwise stated.
[a]AEs related to the study drug are defined as AEs judged as possibly, probably, or definitely related to the study drug.
AE, adverse event; SAE, serious adverse event.

- In this study, seladelpar was well tolerated, with only mild AEs reported (Grade 1, unrelated to seladelpar; **Table 5**)
- There was no notable trend in AEs by renal impairment status. The moderate renal impairment group had the highest number of AEs, while no AEs were reported in the severe renal impairment group
- No clinically relevant differences in clinical laboratory values over time, vital signs, or electrocardiograms were observed across renal function groups