Seladelpar and Reductions in Lipids in Patients With Primary Biliary Cholangitis With and Without Statin Use in the Phase 3, Placebo-Controlled RESPONSE Study

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Conclusions

- In the Phase 3, placebo-controlled RESPONSE study (NCT04620733) in patients with primary biliary cholangitis (PBC), 22% of patients in the seladelpar group (28/128) and 26% of patients in the placebo group (17/65) reported statin use at baseline
- Seladelpar resulted in reductions in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, regardless of statin use at baseline
- Concomitant use of seladelpar and statins was overall well tolerated, with no safety concerns identified
  - There were no adverse events associated with creatine kinase elevations regardless of statin use
- This analysis supports that seladelpar can be administered safely to patients with PBC who are also on a statin, and suggests that lipid levels may be further improved with seladelpar use in these patients

Plain Language Summary

- Some patients with primary biliary cholangitis receiving seladelpar in the Phase 3 RESPONSE trial were also taking statins to control their cholesterol levels at the start of the trial
- Statins are medications that can help lower cholesterol levels, which may reduce a patient's risk of heart disease and stroke
- Seladelpar led to lower cholesterol levels in patients who were not on statins as well as in those who were on statins, and seladelpar appeared to be safe in all patients regardless of statin use

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **2.** Sorokin A, et al. *Atherosclerosis*. 2007;194(2):293-9. **3.** Carey EJ, et al. *Lancet*. 2015;386(10003):1565-75. **4.** Wah-Suarez MI, et al. *Frontline Gastroenterol*. 2019;10(4):401-8. **5.** Gungabissoon U, et al. *BMJ Open Gastroenterol*. 2022;9(1):e000857. **6.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-94. **7.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **8.** Kouno T, et al. *J Bio Chem*. 2022;298(7):102056. **9.** Steinberg S, et al. Presented at: 2017 CDDW; March 3–6, 2017; Alberta, Canada. Poster A203. **10.** Jones D, et al. *Lancet Gastroenterol Hepatol*. 2017;2(10):716-26.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by CymaBay Therapeutics, a Gilead Sciences, Inc., company. We extend our gratitude to Shuqiong Zhuo for her contributions to this poster. Medical writing and editorial support were provided by Allison Yankey, PhD, and Ellie Manca, MPH, of Red Nucleus, and funded by Gilead Sciences, Inc.

Disclosures: **CLB** reports receiving grants or contracts to his institution from Boston Scientific; Bristol Myers Squibb; Calliditas Therapeutics; Cara Therapeutics; Chemomab; COUR Pharmaceuticals; CymaBay Therapeutics; Gilead Sciences, Inc.; GSK; and Harmi Pharmaceuticals; and consulting fees from Alnylam Pharmaceuticals; Chemomab; CymaBay Therapeutics; Gilead Sciences, Inc.; GSK; Ipsen; and NGM Bio. **YY** reports receiving consulting fees from CymaBay Therapeutics and Zydus Pharmaceuticals. **EZ**, **MH**, and **PA** report nothing to disclose. **EJ** reports receiving grants or contracts from Calliditas Therapeutics; CymaBay Therapeutics; Dr. Falk; and Gilead Sciences, Inc. **VV** reports participation in an advisory board with Ipsen and receiving speaker fees from Orphalan. **AD-G** reports receiving consulting fees from GSK and Ipsen; honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Advanz Pharma, Eisai, and GSK; and congress support from Advanz Pharma. **AEK** reports receiving grants or contracts from Gilead Sciences, Inc., and Intercept Pharmaceuticals; consulting fees from AbbVie; Advanz Pharma; Alentis Therapeutics; Alfasigma; AstraZeneca; Avior; Bayer; Bristol Myers Squibb; CymaBay Therapeutics; Escient Pharmaceuticals; Falk; Gilead Sciences, Inc.; GSK; Guidepoint; Intercept Pharmaceuticals; Ipsen; Mirum Pharma; Merck Sharp & Dohme; Novo Nordisk; Roche; and Takeda; and a leadership or fiduciary role (paid or unpaid) with PBC Foundation, Swiss Association for the Study of the Liver (SASL), Swiss Gastroenterology Society (SGG), Swiss Hepa, and Swiss Transplant Society (STS). **S-HJ** reports receiving institutional fees for seladelpar clinical trial participation from CymaBay Therapeutics, a Gilead Sciences, Inc., company. **EP** reports receiving grants or contracts from CymaBay Therapeutics and Intercept Pharmaceuticals. **AV** reports receiving speaker fees from Intercept Pharmaceuticals and participation in an advisory board with Novartis. **ALdGC** reports receiving grants or contracts from AstraZeneca, Akero Therapeutics, Eli Lilly, Galectin Therapeutics, GSK, Inventiva Pharma, Madrigal Pharmaceuticals, Merck Sharp & Dohme, Novo Nordisk, and Viking Therapeutics. **MJM** reports receiving grants or contracts from CymaBay Therapeutics; Genfit; Gilead Sciences, Inc.; GSK; Ipsen; and Mirum Pharma; consulting fees from CymaBay Therapeutics, GSK, Intra-Sana Laboratories, Ipsen, Ironwood Pharmaceuticals, Mallinckrodt Pharmaceuticals, and Mirum Pharma; and support for attending meetings and/or travel from CymaBay Therapeutics, GSK, Ipsen, and Mallinckrodt Pharmaceuticals. **SP**, **KY**, and **DBC** report employment and stock options with Gilead Sciences, Inc. **CAM** reports former employment with CymaBay Therapeutics, a Gilead Sciences, Inc., company, from 2007 to 2024; receiving consulting fees from Gilead Sciences, Inc.; being listed as an inventor on seladelpar patents; and a leadership or fiduciary role (paid or unpaid) with 89Bio (independent director). **DP** reports receiving consulting fees from Mediar Therapeutics.

Introduction

- Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune, cholestatic liver disease that affects approximately 1 in 1000 women over 40 years of age[1]
- Hypercholesterolemia is common in patients with PBC,[2-4] and many patients (approximately 25%) with PBC are taking concomitant statins[5]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) targeting multiple cell types and processes in PBC[6]
  - In August 2024, seladelpar was granted accelerated approval in the United States for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a monotherapy in patients unable to tolerate UDCA[7]
- PPARδ agonism by seladelpar reduces bile acid synthesis, decreases cholesterol synthesis, and alters cholesterol metabolism[8-10]
- In the Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar treatment was associated with decreases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, with no concerns in regard to muscle safety[6]

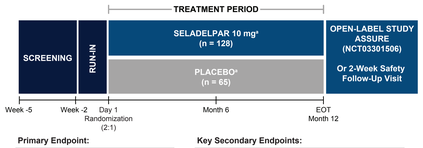
Objective

- To analyze changes in lipids in patients with or without statin use at baseline among those randomized to seladelpar or placebo in the Phase 3 RESPONSE study

Methods

- RESPONSE was a Phase 3, placebo-controlled study of seladelpar 10 mg in patients with PBC who had an inadequate response or intolerance to UDCA (**Figure 1**)
  - Key entry criteria: Alkaline phosphatase ≥1.67 × upper limit of normal (ULN), alanine aminotransferase/aspartate aminotransferase ≤3 × ULN, and total bilirubin ≤2 × ULN
- Total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured at baseline and every 3 months thereafter
- Change from baseline in lipids was summarized for patients receiving seladelpar or placebo by baseline statin subgroup
- Safety of concomitant seladelpar and statin use was assessed by examining overall adverse events (AEs) and muscle-related AEs by baseline statin subgroup

Figure 1. Phase 3 RESPONSE Study in Patients With PBC



Primary Endpoint:

Composite response at month 12 (ALP <1.67 × ULN, ≥15% decrease in ALP, total bilirubin ≤ULN)

Key Secondary Endpoints:

- ALP normalization at month 12[b]
- Change from baseline in pruritus NRS at 6 months in patients with baseline NRS ≥4[c]

RESPONSE study; NCT04620733. Seladelpar was administered orally once daily.
[a]Study drug given as an add-on to UDCA in patients on UDCA for at least 12 months, or as monotherapy in patients intolerant to UDCA. [b]ALP normalization defined as ALP ≤1.0 × ULN. [c]Pruritus data collected daily through the first 6 months, then monthly for 7 consecutive days each month until EOT.
ALP, alkaline phosphatase; EOT, end of treatment; NRS, numerical rating scale; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Results

Table 1. Statin Use in the RESPONSE Study at Baseline

n (%)	Seladelpar 10 mg (n = 128)	Placebo (n = 65)
Patients on a statin at baseline	28 (22)	17 (26)
Type of statin at baseline[a]		
Atorvastatin	9 (32)	7 (41)
Atorvastatin calcium	4 (14)	2 (12)
Rosuvastatin calcium	4 (14)	2 (12)
Simvastatin	4 (14)	1 (6)
Rosuvastatin	3 (11)	2 (12)
Pravastatin	3 (11)	1 (6)
Ezetimibe/rosuvastatin	1 (4)	0
Ezetimibe/atorvastatin	0	1 (6)
Ezetimibe/simvastatin	0	1 (6)

Terms used to identify statins included atorvastatin, atorvastatin calcium, ezetimibe/atorvastatin, ezetimibe/rosuvastatin, ezetimibe/simvastatin, pravastatin, rosuvastatin, rosuvastatin calcium, and simvastatin.
[a]The percentage of patients on each type of statin is reported with the number of patients on statins at baseline as the denominator.

- In the RESPONSE study, 23% of patients (45/193) were taking concomitant statins at baseline (**Table 1**)

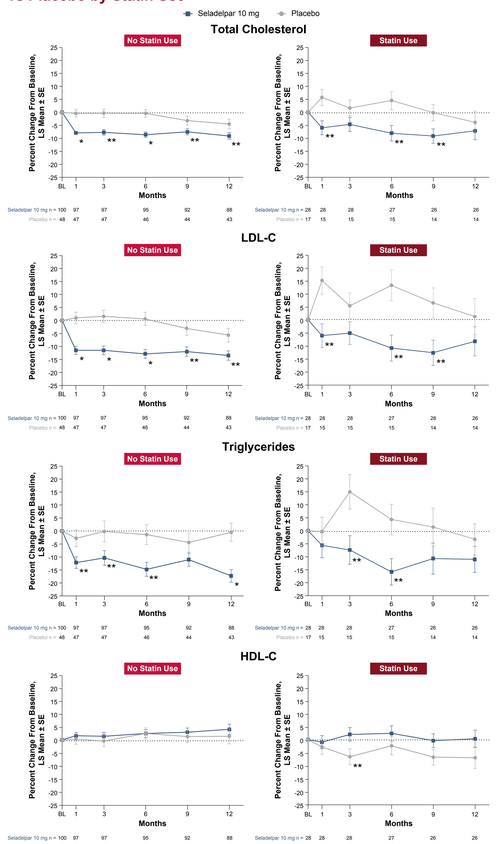
Table 2. Demographics and Baseline Characteristics by Statin Use

	No Statin Use (n = 148)		Statin Use (n = 45)	
	Seladelpar 10 mg (n = 100)	Placebo (n = 48)	Seladelpar 10 mg (n = 28)	Placebo (n = 17)
Age, years, mean (SD)	55.4 (10.1)	56.7 (10.1)	60.8 (8.7)	57.8 (6.0)
Sex, n (%)				
Female	98 (98)	45 (94)	25 (89)	15 (88)
Male	2 (2)	3 (6)	3 (11)	2 (12)
Race, n (%)				
White	90 (90)	42 (88)	24 (86)	14 (82)
Black	2 (2)	1 (2)	0	1 (6)
Asian	4 (4)	2 (4)	3 (11)	2 (12)
American Indian or Alaska Native	2 (2)	3 (6)	1 (4)	0
Missing	2 (2)	0	0	0
Hispanic, n (%)	26 (26)	21 (44)	3 (11)	6 (35)
BMI, kg/m², mean (SD)	27.1 (5.5)	26.6 (4.5)	27.7 (6.0)	27.5 (5.7)
Duration of PBC, years, mean (SD)	7.6 (6.0)	8.2 (6.1)	10.2 (8.5)	9.7 (7.6)
Cirrhosis, n (%)	14 (14)	7 (15)	4 (14)	2 (12)
UDCA intolerance, n (%)	6 (6)	3 (6)	2 (7)	1 (6)
ALP, U/L, mean (SD)	320.3 (121.3)	297.1 (96.9)	294.0 (128.9)	361.1 (156.8)
Total cholesterol, mg/dL, mean (SD)	251.6 (46.9)	247.5 (53.6)	202.3 (48.2)	206.6 (48.9)
HDL-C, mg/dL, mean (SD)	80.9 (21.5)	74.7 (20.9)	79.1 (28.5)	76.2 (26.7)
LDL-C, mg/dL, mean (SD)	146.9 (42.4)	148.4 (50.5)	100.4 (36.6)	106.3 (39.6)
Triglycerides, mg/dL, mean (SD)	118.7 (54.8)	122.3 (44.8)	113.0 (40.6)	120.6 (39.8)

ALP, alkaline phosphatase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

- Key baseline characteristics were overall similar in patients on statins vs not on statins at baseline (**Table 2**)
- Total cholesterol and LDL-C levels were lower among patients on statins vs not on statins at baseline, whereas HDL-C and triglyceride levels were similar

Figure 2. Mean Percent Change in Lipids Over Time With Seladelpar vs Placebo by Statin Use



*P <.0001. †P <.05.
BL, baseline; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares.

- Compared with placebo, seladelpar resulted in greater reductions in total cholesterol, LDL-C, and triglyceride levels; similar results were seen between patients who were using statins at baseline and those who were not (**Figure 2**)
- In both the placebo and seladelpar treatment groups, HDL-C remained stable

Table 3. Overall Safety by Statin Use

	No Statin Use (n = 148)		Statin Use (n = 45)	
Patient Incidence, n (%)	Seladelpar 10 mg (n = 100)	Placebo (n = 48)	Seladelpar 10 mg (n = 28)	Placebo (n = 17)
Any AE	84 (84)	41 (85)	27 (96)	14 (82)
Grade ≥3 AEs (per CTCAE)	12 (12)	3 (6)	2 (7)	2 (12)
SAEs	8 (8)	2 (4)	1 (4)	2 (12)
Treatment-related SAEs	0	0	0	0
AEs leading to treatment discontinuation	4 (4)	2 (4)	0	1 (6)
AEs leading to study discontinuation	3 (3)	2 (4)	0	1 (6)
AEs leading to death	0	0	0	0

All AEs listed are treatment emergent unless otherwise stated.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

- Incidence rates of AEs, serious AEs, and Grade ≥3 AEs were similar across treatment groups, regardless of statin use (**Table 3**)

Table 4. Muscle-Related AEs by Statin Use

	No Statin Use (n = 148)		Statin Use (n = 45)	
Patient Incidence, n (%)	Seladelpar 10 mg (n = 100)	Placebo (n = 48)	Seladelpar 10 mg (n = 28)	Placebo (n = 17)
Any muscle-related AE[a]	6 (6)	5 (10)	2 (7)	0
Musculoskeletal pain	0	0	1 (4)	0
Myalgia	2 (2)	2 (4)	1 (4)	0
Fibromyalgia	2 (2)	1 (2)	0	0
Muscle spasms	2 (2)	1 (2)	0	0
Musculoskeletal stiffness	0	1 (2)	0	0

All AEs listed are treatment emergent.
[a]Muscle-related AEs were identified by a predefined search strategy.
AE, adverse event.

- Muscle-related AEs also occurred at similar rates across treatment groups, regardless of statin use, and none led to treatment discontinuation (**Table 4**)
- All muscle-related AEs occurring in the seladelpar group were Grades 1 or 2 in severity; one Grade 3 event of myalgia was reported in the placebo group
- There were no AEs associated with creatine kinase (CK) elevations regardless of statin use
  - No patient using a statin at baseline had CK elevations to >3x ULN in either treatment group

Table 5. Statin Status Changes During Study

	Seladelpar 10 mg (n = 128)	Placebo (n = 65)
Patients not using statins at baseline, n	100	48
Patients who started a statin medication while on study, n (%)	4 (4)	7 (15)
Patients using statins at baseline, n	28	17[a]
Patients who stopped any statin medication while on study, n (%)	1 (4)	0
Patients who had statin dosage increased while on study, n (%)	1 (4)	1 (6)

[a]One patient in the placebo group started a statin at baseline and then had their dose reduced from days 143 to 274 while on study. From day 275 to end of study, this patient then had their statin dose increased to baseline levels. Therefore, this patient was not included in the stopped-medication category or the dosage-change category.

- In general, a higher proportion of patients in the placebo group started or increased their statin dose during the study, compared to the seladelpar group (**Table 5**)