Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis Previously Treated With Fibrates or Obeticholic Acid

THU-274

Alejandra Villamil[1], Daniel Pratt[2], Andreas E. Kremer[3], Vincenza Calvaruso[4], Elena Gómez Dominguez[5], Xin Qi[6], Sarah Proehl[6], William T. Barchuk[6], Timothy R. Watkins[6], Stuart C. Gordon[7,8]

[1]The Liver Autoimmunity Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [2]Autoimmune and Cholestatic Liver Center, Massachusetts General Hospital, Boston, MA, USA; [3]Department of Gastroenterology and Hepatology, University Hospital Zürich, University of Zürich, Zürich, Switzerland; [4]Gastroenterology and Hepatology Unit, University of Palermo, Palermo, Italy; [5]Hepatology Unit, University Hospital 12 de Octubre, Madrid, Spain; [6]Gilead Sciences, Inc., Foster City, CA, USA; [7]Division of Hepatology, Henry Ford Hospital, Wayne State University School of Medicine, Detroit, MI, USA; [8]Michigan State University College of Medicine, East Lansing, MI, USA

Conclusions

- Seladelpar demonstrated consistent biochemical response rates in patients with primary biliary cholangitis (PBC) over 18 months of treatment in the RESPONSE and ASSURE trials, regardless of previous exposure to fibrates or obeticholic acid (OCA)
- A sustained reduction of pruritus in patients with PBC who had moderate to severe itch at baseline was observed with seladelpar treatment regardless of prior fibrate/OCA use
- Seladelpar had a safety profile similar to placebo, irrespective of prior fibrate/OCA use

Plain Language Summary

- Primary biliary cholangitis (PBC) is a long-term liver disease that gets worse over time
- The first choice of treatment for PBC is normally ursodeoxycholic acid (UDCA)
- Some people with PBC are treated with fibrates or obeticholic acid (OCA) if UDCA does not work for them
- Seladelpar is a treatment for people with PBC whose disease does not get sufficiently better with UDCA or who cannot tolerate UDCA
- This analysis reports on how well seladelpar worked and how safe it was in people with PBC who had previously used fibrates or OCA
- Seladelpar helped to improve disease measures of PBC similarly in both people who had previously used fibrates or OCA and people who had not
- Safety results were similar between people who had previously used fibrates or OCA and those who had not

References: **1.** European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-72. **2.** Invernezzi P, et al. *Dig Liver Dis*. 2017; 49(2017):841-46. **3.** Ocaliva. US prescribing information. Intercept Pharmaceuticals; 2016. **4.** Corpechot C. *Curr Hepatology Rep*. 2019;18:107-14. **5.** Lindor KD, et al. *Hepatology*. 2019;69(1):294-419. **6.** Livdezi. US prescribing information. Gilead Sciences, Inc.; 2024. **7.** Livdezi. UK Summary of Product Characteristics. Gilead Sciences, Inc.; 2024. **8.** Seladelpar Gilead. EMA prescribing information. Gilead Sciences, Inc.; 2025. **9.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-94. **10.** Lawitz EJ, et al. Poster presented at: The Liver Meeting, AASLD 2024; November 15–19, 2024; San Diego, CA; Poster 5044. **11.** NCT03301506. https://clinicaltrials.gov/study/NCT03301506. Accessed September 24, 2024.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. These studies were funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Jake Wilmot, PhD, of Red Nucleus, and funded by Gilead Sciences, Inc.

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

Introduction

- PBC is a chronic, progressive, cholestatic liver disease[1]
  - UDCA is the first-line treatment for people with PBC, but up to 40% of people have an inadequate response to UDCA and up to 5% are intolerant[2]
- Fibrates and OCA have been used as second-line treatments for PBC, but are associated with safety concerns that limit their use[3–5]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA[6–8]
- In the Phase 3, randomised, placebo-controlled RESPONSE (NCT04620733) study and the ongoing, open-label, long-term, Phase 3 ASSURE (NCT03301506) safety study, seladelpar led to a rapid and sustained biochemical response, and significant improvement in pruritus, in patients with PBC[9,10]
- Patients completing RESPONSE were eligible to enroll in ASSURE[11]

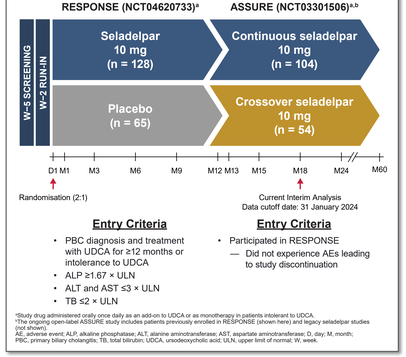
Objective

- To describe the efficacy and safety of seladelpar in the RESPONSE and ongoing ASSURE clinical trials in the subgroups of patients with and without prior use of fibrates or OCA

Methods

- Patients received seladelpar 10 mg or matching placebo orally once daily (QD) in the RESPONSE trial (**Figure 1**)
- Patients received seladelpar 10 mg QD in the open-label ASSURE trial
- Fibrates and OCA were prohibited in both trials, and a 6-week washout period was required prior to entry in the RESPONSE trial
- Data for patients in the ongoing ASSURE trial (as of 31 January 2024) were presented according to the treatment received in the RESPONSE trial: seladelpar (continuous seladelpar patients) or placebo (crossover seladelpar patients)
- Efficacy endpoints included the percentage of patients achieving a composite biochemical response (alkaline phosphatase [ALP] <1.67 × upper limit of normal [ULN], ALP decrease ≥15%, and total bilirubin [TB] ≤ULN), other biochemical parameters, and the score on the pruritus Numerical Rating Scale (NRS)
- Safety was assessed by adverse event (AE) rates and laboratory findings

Figure 1. RESPONSE to ASSURE Rollover Study Design



[a]Study drug administered orally once daily as an add-on to UDCA or as monotherapy in patients intolerant to UDCA.
[b]The ongoing open-label ASSURE study includes patients previously enrolled in RESPONSE (shown here) and legacy seladelpar studies (not shown).
AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, day; M, month; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; W, week.

Results

- Among 193 patients in RESPONSE:
  - 33 (17%; seladelpar, n = 20; placebo, n = 13) reported prior fibrate/OCA use
  - 160 (83%; seladelpar, n = 108; placebo, n = 52) reported no prior fibrate/OCA use
- 27 patients with prior fibrate/OCA use and 131 without prior use rolled over from RESPONSE to ASSURE as of the data cutoff
- Baseline ALP was higher among patients with prior fibrate/OCA use than those without prior use (**Table 1**)

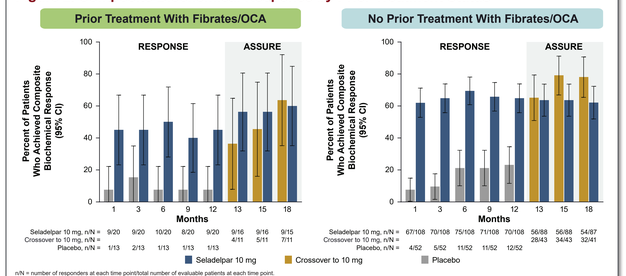
Results

Table 1. Demographics and Baseline Clinical Characteristics by Prior Treatment Status

	Prior Treatment With Fibrates/OCA (n = 33)		No Prior Treatment With Fibrates/OCA (n = 160)	
	Seladelpar 10 mg (n = 20)	Placebo (n = 13)	Seladelpar 10 mg (n = 108)	Placebo (n = 52)
Age, years, mean (SD)	55.8 (9.3)	55.4 (11.1)	56.7 (10.2)	57.4 (8.7)
Female, n (%)	18 (90)	12 (92)	105 (97)	48 (92)
Duration of PBC, years, mean (SD)	9.5 (6.3)	12.3 (7.9)	7.9 (6.8)	7.7 (5.8)
Prior use of fibrates, n (%)	7 (35)	5 (38)	–	–
Prior use of OCA, n (%)	15 (75)	10 (77)	–	–
Duration of treatment with fibrates/OCA, years, mean (SD)	2.7 (2.4)	2.0 (1.4)	–	–
Duration of fibrates/OCA washout prior to study entry, years, mean (SD)	0.9 (0.8)	0.8 (0.8)	–	–
Patients with cirrhosis at baseline, n (%)	2 (10)	0	16 (15)	9 (17)
Child-Pugh Class A, n (% of patients with cirrhosis)	2 (100)	0	16 (100)	9 (100)
ALP, U/L, mean (SD)	371.0 (145.0)	348.6 (141.9)	304.1 (116.2)	305.1 (110.7)
TB, mg/dL, mean (SD)	0.8 (0.2)	0.6 (0.2)	0.8 (0.3)	0.8 (0.3)

Demographics and baseline clinical characteristics were captured at baseline in the RESPONSE trial.
ALP, alkaline phosphatase; OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, total bilirubin.

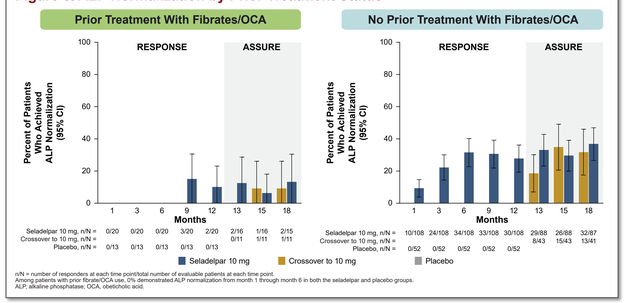
Figure 2. Composite Biochemical Response by Prior Treatment Status



n/N = number of responders at each time point/total number of evaluable patients at each time point.
Composite biochemical response defined as ALP <1.67 × ULN, ALP decrease ≥15%, and TB ≤ULN.
ALP, alkaline phosphatase; OCA, obeticholic acid; TB, total bilirubin; ULN, upper limit of normal..

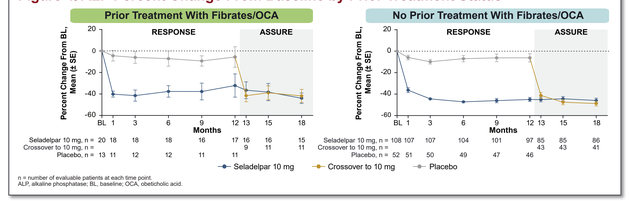
- Seladelpar led to a composite biochemical response in a substantial proportion of patients with PBC regardless of prior use of fibrates/OCA
- At month 12 of the RESPONSE trial:
  - Among patients receiving seladelpar, 9/20 (45%) patients with prior fibrate/OCA use achieved a composite biochemical response vs 70/108 (65%) patients without prior use (**Figure 2**)
  - Among patients receiving placebo, 1/13 (8%) patients with prior fibrate/OCA use achieved a composite biochemical response vs 12/52 (23%) patients without prior use
- At month 6 of the ASSURE study (month 18 of seladelpar treatment for the continuous seladelpar group and month 6 of treatment for the crossover seladelpar group), generally similar proportions of patients with vs without prior fibrate/OCA use achieved a composite biochemical response (60–78% of patients)
- Fewer patients with prior fibrate/OCA use achieved ALP normalization (**Figure 3**) in the setting of higher baseline ALP. However, ALP percent change (**Figure 4**) was similar between the groups, as were declines in alanine aminotransferase (ALT; **Figure 6**), gamma-glutamyl transferase (GGT; **Figure 7**), and pruritus NRS (**Figure 8**)
- TB was generally stable with some variation in the setting of small sample sizes (**Figure 5**)

Figure 3. ALP Normalization by Prior Treatment Status



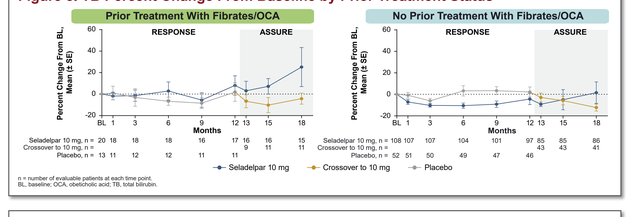
n/N = number of responders at each time point/total number of evaluable patients at each time point.
Among patients with prior fibrate/OCA use, 0% demonstrated ALP normalization from month 1 through month 6 in both the seladelpar and placebo groups.
ALP, alkaline phosphatase; OCA, obeticholic acid.

Figure 4. ALP Percent Change From Baseline by Prior Treatment Status



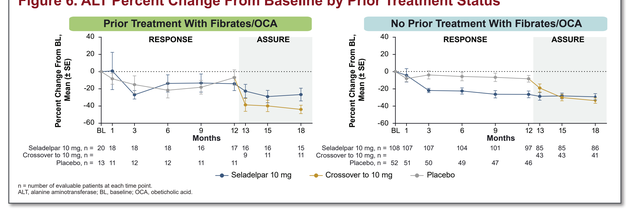
n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; BL, baseline; OCA, obeticholic acid.

Figure 5. TB Percent Change From Baseline by Prior Treatment Status



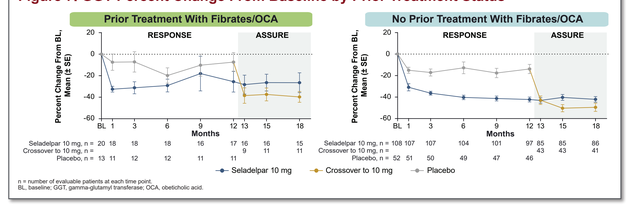
n = number of evaluable patients at each time point.
BL, baseline; OCA, obeticholic acid; TB, total bilirubin.

Figure 6. ALT Percent Change From Baseline by Prior Treatment Status



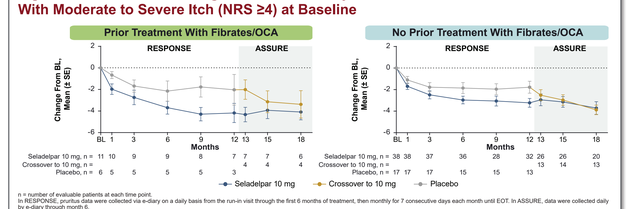
n = number of evaluable patients at each time point.
ALT, alanine aminotransferase; BL, baseline; OCA, obeticholic acid.

Figure 7. GGT Percent Change From Baseline by Prior Treatment Status



n = number of evaluable patients at each time point.
BL, baseline; GGT, gamma-glutamyl transferase; OCA, obeticholic acid.

Figure 8. Pruritus NRS Change From Baseline by Prior Treatment Status in Patients With Moderate to Severe Itch (NRS ≥4) at Baseline



n = number of evaluable patients at each time point.
In RESPONSE, pruritus data were collected via e-diary on a daily basis from the run-in visit through the first 6 months of treatment, then monthly for 7 consecutive days each month until EOT. In ASSURE, data were collected daily by e-diary through month 6.
Pruritus NRS scores range from 0 to 10, with higher scores indicating worse itch.
BL, baseline; EOT, end of treatment; NRS, numerical rating scale; OCA, obeticholic acid.

Table 2. Overall Safety by Prior Treatment Status

Patient Incidence, n (%)	Prior Treatment With Fibrates/OCA (n = 33)		No Prior Treatment With Fibrates/OCA (n = 160)	
RESPONSE through month 12	Seladelpar 10 mg (n = 20)	Placebo (n = 13)	Seladelpar 10 mg (n = 108)	Placebo (n = 52)
Any AE	17 (85)	11 (85)	94 (87)	44 (85)
Grade ≥3 AEs	1 (5)	1 (8)	13 (12)	4 (8)
SAEs	1 (5)	1 (8)	8 (7)	3 (6)
Treatment-related SAEs	0	0	0	0
AEs leading to permanent withdrawal of the study drug	1 (5)	1 (8)	3 (3)	2 (4)
AEs leading to study discontinuation	1 (5)	1 (8)	2 (2)	2 (4)
AEs leading to death	0	0	0	0
Liver-related AEs[a]	2 (10)	1 (8)	6 (6)	5 (10)
ASSURE through month 6 (month 18 overall)	**Continuous Seladelpar (n = 16)**	**Crossover Seladelpar (n = 11)**	**Continuous Seladelpar (n = 88)**	**Crossover Seladelpar (n = 43)**
Any AE	12 (75)	8 (73)	59 (67)	31 (72)
Grade ≥3 AEs	2 (13)	1 (9)	6 (7)	2 (5)
SAEs	2 (13)	1 (9)	3 (3)	4 (9)
Treatment-related SAEs	0	0	0	0
AEs leading to permanent withdrawal of the study drug	1 (6)	0	0	0
AEs leading to study discontinuation	0	0	0	0
AEs leading to death	0	0	0	0
Liver-related AEs[a]	2 (13)	0	3 (3)	0

All AEs listed are treatment emergent unless otherwise stated.
[a]Liver-related AEs were identified by a predefined search strategy.
AE, adverse event; OCA, obeticholic acid; SAE, serious adverse event.

- Incidence of AEs was similar between treatment groups regardless of prior fibrate/OCA use (**Table 2**; **Table 3**); no treatment-related SAEs were reported
- The incidence of liver-related AEs was similar between patients with and without prior fibrate/OCA use

Table 3. Common AEs by Prior Treatment Status (>10% in Any Group)

Patient Incidence, n (%)	Prior Treatment With Fibrates/OCA (n = 33)		No Prior Treatment With Fibrates/OCA (n = 160)	
RESPONSE through month 12	Seladelpar 10 mg (n = 20)	Placebo (n = 13)	Seladelpar 10 mg (n = 108)	Placebo (n = 52)
COVID-19	8 (40)	3 (23)	15 (14)	7 (13)
Pruritus	2 (10)	2 (15)	4 (4)	8 (15)
Asthenia	0	3 (23)	5 (5)	1(2)
Arthralgia	0	2 (15)	8 (7)	2 (4)
Gastroenteritis	0	2 (15)	0	1 (2)
Hypercholesterolemia	0	2 (15)	1 (1)	0
Nasopharyngitis	0	2 (15)	7 (6)	3 (6)
ASSURE through month 6 (month 18 overall)	**Continuous Seladelpar (n = 16)**	**Crossover Seladelpar (n = 11)**	**Continuous Seladelpar (n = 88)**	**Crossover Seladelpar (n = 43)**
Diarrhea	0	2 (18)	1 (1)	3 (7)
Hematuria	0	2 (18)	0	0
Pruritus	2 (13)	0	7 (8)	0
Anemia	2 (13)	0	2 (2)	2 (5)
Herpes zoster	2 (13)	0	2 (2)	0
Headache	1 (6)	0	1 (1)	5 (12)

AE, adverse event; OCA, obeticholic acid.

- In RESPONSE, the incidence of ALT or aspartate aminotransferase (AST) >3 × ULN was similar between the seladelpar and placebo groups regardless of prior fibrate/OCA use (seladelpar: prior fibrates/OCA, 4/20 [20%]; no prior fibrates/OCA, 5/108 [5%]; placebo: prior fibrates/OCA, 2/13 [15%]; no prior fibrates/OCA, 5/52 [10%])
- In ASSURE, through month 6, incidence of ALT or AST >3 × ULN was infrequent and patient incidence was overall similar between seladelpar and placebo, regardless of prior OCA/fibrate use (continuous seladelpar: prior fibrates/OCA, 1/16 [6%]; no prior fibrates/OCA, 1/88 [1%]; crossover seladelpar: 0)