Seladelpar Effect on Lipids and Muscle Safety With Concomitant Statin Use in Patients With Primary Biliary Cholangitis: Interim Results From the Open-Label ASSURE Study With up to 4 Years of Treatment

SAT-254

Christopher L. Bowlus[1], Yusuf Yilmaz[2], Ehud Zigmond[3], Victor Vargas[4], Christophe Corpechot[5], Alvaro Diaz-Gonzalez[6], Sarah Proehl[7], Johnny Chew[7], Kyung Min Kwon[7], Xiangyu Liu[7], Robert P. Kustra[7], John M. Vierling[8]

[1]Division of Gastroenterology and Hepatology, University of California Davis School of Medicine, Sacramento, CA, USA; [2]Department of Gastroenterology, School of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey; [3]Liver Health Center, Cheba Medical Center, Ramat-Gan, Israel; [4]Universitat Autònoma Barcelona, Barcelona, Spain; [5]Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, French Network for Rare Liver Disease in Children and Adults (FILFOIE), European Reference Network RARE-LIVER, Saint-Antoine Hospital and Research Center, Assistance Publique-Hôpitaux de Paris, Sorbonne University, Paris, France; [6]Hospital Universitario Marqués de Valdecilla, Instituto de Investigación Valdecilla (IDIVAL), Santander, Spain; [7]Gilead Sciences, Inc., Foster City, CA, USA; [8]Baylor College of Medicine, Houston, TX, USA

Immune-Mediated and Cholestatic Disease: Clinical Aspects

Conclusions

- Statin use at baseline was common (26%) among patients with primary biliary cholangitis in the Phase 3, open-label ASSURE study (NCT03301506)
- Regardless of baseline statin use, seladelpar treatment resulted in clinically meaningful and sustained improvements in lipid profiles through 36 months
- Concomitant statin and seladelpar use appeared overall safe, with no increase in muscle-related adverse events or muscle toxicity for up to 48 months

Plain Language Summary

- High cholesterol levels are common in patients with primary biliary cholangitis (PBC)
- Statins are a group of medications that are used to lower cholesterol levels
- In total, 26% of patients with PBC in the ASSURE study were taking statins at the time of seladelpar initiation
- In this long-term follow-up study, patient cholesterol and triglyceride levels were reduced with seladelpar treatment, and seladelpar was safe with up to 4 years 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.** Wah-Suarez MI, et al. *Frontline Gastroenterol*. 2019;10(4):401-8. **4.** Gungabissoon U, et al. *BMJ Open Gastroenterol*. 2022;9(1):e000857. **5.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **6.** Livdelzi. UK summary of product characteristics. Gilead Sciences, Inc.; 2024. **7.** Lyvdelzi. EMA prescribing information. Gilead Sciences, Inc.; 2025. **8.** Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-94. **9.** Bowlus C, et al. Presented at 2024 AASLD; November 15–19, 2024; San Diego, CA, USA. Poster #4342. **10.** Levy C, et al. *Am J Gastroenterol*. 2025; doi: 10.14309/ajg.0000000000003603.

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Correspondence: Christopher L. Bowlus, clbowlus@UCDAVIS.EDU

Introduction

- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease associated with progressive liver injury and significant symptom burden[1]
- Dyslipidaemia is common in patients with PBC; approximately 25% of patients with PBC are currently taking statins[2-4]
- 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[5-7]
- In the pivotal Phase 3, placebo-controlled RESPONSE study (NCT04620733), seladelpar treatment was associated with reductions in triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) at Month 12 vs placebo, regardless of statin use[8,9]
- In RESPONSE, muscle-related adverse events (AEs) and creatinine kinase elevations were similar between seladelpar and placebo groups, regardless of statin use[8,9]
- The ongoing, open-label ASSURE Phase 3 study (NCT03301506) enrolled patients with PBC from the RESPONSE study and legacy seladelpar studies[10]

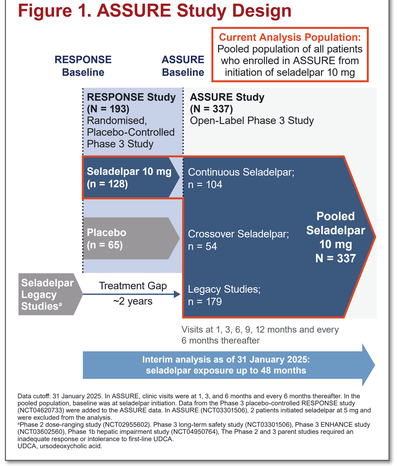
Objective

- To assess long-term changes in lipids and muscle-related safety in patients with PBC treated with seladelpar, with and without concomitant statin use, in the ongoing open-label Phase 3 ASSURE study

Methods

- Patients from RESPONSE and legacy seladelpar studies enrolled in ASSURE and received open-label seladelpar 10 mg once daily (**Figure 1**)
- This interim, post hoc, pooled analysis includes all patients enrolled in ASSURE (N = 337; data cutoff date: 31 January 2025)
- Baseline was defined as the time of seladelpar initiation in RESPONSE or ASSURE
- Changes from baseline in lipids (triglycerides, total cholesterol, LDL-C, and high-density lipoprotein cholesterol [HDL-C]) were reported by baseline statin use through 36 months
- Exposure-adjusted safety was assessed by examining overall AEs and muscle-related AEs by baseline statin use through Month 48 (or longest exposure)

Figure 1. ASSURE Study Design



Data cutoff: 31 January 2025. In ASSURE, clinic visits were at 1, 3, and 6 months and every 6 months thereafter. In the pooled population, baseline was at seladelpar initiation. Data from the Phase 3 placebo–controlled RESPONSE study (NCT04620733) were added to the ASSURE data. In ASSURE (NCT03301506), 2 patients initiated seladelpar at 5 mg and were excluded from the analysis.
[a]Phase 2 dose-ranging study (NCT02955602). Phase 3 long-term safety study (NCT03301506). Phase 3 ENHANCE study (NCT03602560). Phase 1b hepatic impairment study (NCT04950764). The Phase 2 and 3 parent studies required an inadequate response or intolerance to first-line UDCA.
UDCA, ursodeoxycholic acid.

Results

- Key baseline demographics and clinical characteristics for patients with PBC in the ASSURE study are shown in **Table 1**
- In ASSURE, 87/337 (26%) patients were taking concomitant statins at baseline
  - The most commonly used statins were atorvastatin (51%) and rosuvastatin (26%), followed by simvastatin, pravastatin, lovastatin, and combination statin treatments (each <10%)
  - Mean total cholesterol and LDL-C were higher in patients with no statin use (241.3 mg/dL and 140.2 mg/dL, respectively) than in patients with statin use at baseline (198.6 mg/dL and 101.0 mg/dL, respectively)
  - Patients had similar mean HDL-C and triglyceride levels at baseline, regardless of statin use

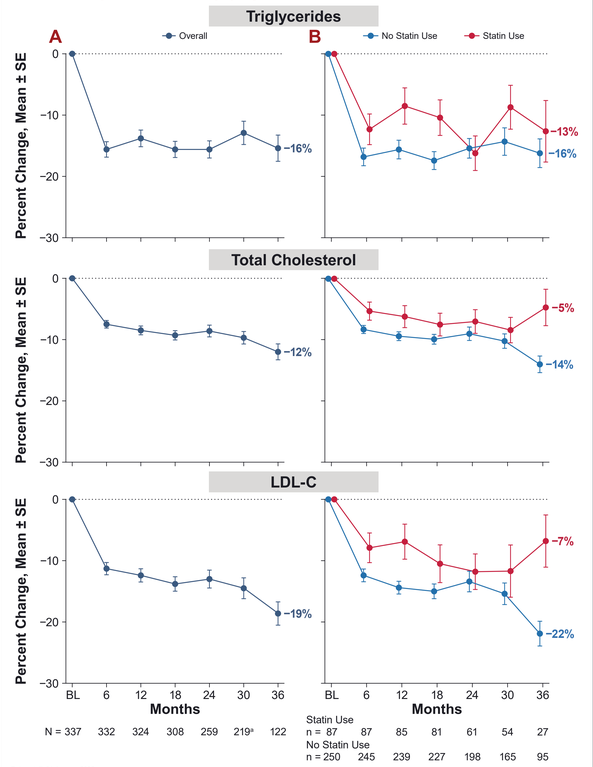
Table 1. Demographics and Baseline Characteristics in the Overall Population With and Without Statin Use

	Overall (N = 337)	No Statin Use (n = 250)	Statin Use (n = 87)
Age, years, mean (SD)	58.1 (9.70)	57.0 (9.88)	61.3 (8.44)
Sex, n (%)			
Female	318 (94)	243 (97)	75 (86)
Male	19 (6)	7 (3)	12 (14)
Race[a], n (%)			
White	289 (86)	219 (88)	70 (81)
Black	7 (2)	5 (2)	2 (2)
Asian	24 (7)	15 (6)	9 (10)
American Indian or Alaska Native	11 (3)	9 (4)	2 (2)
Missing/Declined to Answer	6 (2)	2 (1)	4 (5)
Hispanic, n (%)	72 (21)	60 (24)	12 (14)
Duration of PBC[b], years, mean (SD)	10.1 (6.33)	9.8 (5.90)	11.0 (7.41)
BMI, kg/m², mean (SD)	27.3 (5.82)	27.4 (6.00)	27.0 (5.30)
Cirrhosis, n (%)	53 (16)	39 (16)	14 (16)
ALP, U/L, mean (SD)	287.5 (128.39)	284.3 (127.70)	296.9 (130.63)
Creatine kinase, U/L, mean (SD)	79.6 (63.03)	80.2 (68.75)	77.6 (42.80)
Total cholesterol, mg/dL, mean (SD)	230.2 (51.62)	241.3 (48.98)	198.6 (45.81)
HDL-C, mg/dL, mean (SD)	77.1 (23.89)	78.2 (23.16)	74.0 (25.78)
LDL-C, mg/dL, mean (SD)	130.1 (43.84)	140.2 (41.61)	101.0 (36.68)
Triglycerides, mg/dL, mean (SD)	115.6 (50.38)	114.9 (51.62)	117.7 (46.85)

[a]Options not shown included Native Hawaiian or Other Pacific Islander (0) and Other (0). [b]Time from diagnosis date to the informed consent date.
ALP, alkaline phosphatase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBC, primary biliary cholangitis.

- A reduction in lipids was observed with seladelpar use, regardless of statin use at baseline (**Figure 2**)
- In 122 patients evaluable at Month 36 of treatment, mean percent change from baseline was −15.4% for triglycerides, −12.0% for total cholesterol, and −18.6% for LDL-C
- There were no meaningful changes in HDL-C

Figure 2. Percent Change in Lipids With Seladelpar in (A) the Overall Population and (B) by Statin Use



Data cutoff: 31 January 2025.
[a]At Month 30, 218 patients had evaluable LDL-C data.
BL, baseline; LDL-C, low-density lipoprotein cholesterol.

- Through Month 48, incidences of AEs and serious AEs were similar in patients on a statin at baseline compared with those not on a statin (**Table 2**)

Table 2. Overall Safety

Exposure-Adjusted AEs, n (n per 100 PY)	Overall (N = 337) PY = 872.4	No Statin Use (n = 250) PY = 653.8	Statin Use (n = 87) PY = 218.5
Any AE[a]	306 (35.1)	228 (34.9)	78 (35.7)
Grade ≥3 AEs	76 (8.71)	55 (8.41)	21 (9.61)
SAEs	62 (7.11)	45 (6.88)	17 (7.78)
Treatment-related SAEs[b]	1 (0.11)	1 (0.15)	0
AEs leading to treatment discontinuation	30 (3.44)	20 (3.06)	10 (4.58)
AEs leading to study discontinuation	21 (2.41)	15 (2.29)	6 (2.75)
AEs leading to death[c]	1 (0.11)	1 (0.15)	0

All AEs were treatment emergent.
[a]AEs were coded according to MedDRA version 27.1. [b]Grade 3 colitis updated to Grade 2 and assessed as not related to seladelpar by the investigator after the data cut. [c]Autoimmune haemolytic anaemia, assessed as not related to seladelpar by the investigator.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; SAE, serious AE.

- The exposure-adjusted patient incidence (per 100 patient-years) of muscle-related AEs was similar between patients who were taking a statin (3.66) and those who were not (3.52; **Table 3**)
- Among 31 patients with muscle-related AEs, 1 patient (not on a statin) discontinued treatment due to myalgia that was not associated with a creatine kinase elevation
- An event of myositis (grade 1) occurred in 1 patient at approximately Month 16, did not require treatment, was not associated with an elevation in creatine kinase, and was assessed by the investigator as unlikely related to seladelpar

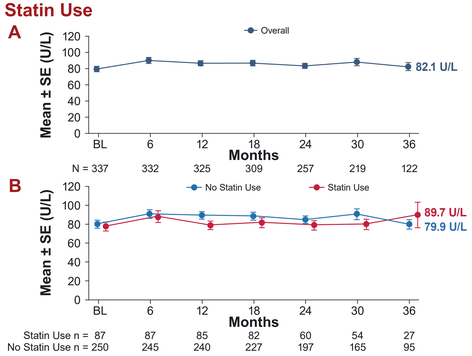
Table 3. Exposure-Adjusted Muscle-Related AEs in the Overall Population and by Statin Use

Exposure-Adjusted AEs, n (n per 100 PY)	Overall (N = 337) PY = 872.4	No Statin Use (n = 250) PY = 653.8	Statin Use (n = 87) PY = 218.5
Any muscle-related AE[a]	31 (3.55)	23 (3.52)	8 (3.66)
Myalgia	11 (1.26)	10 (1.53)	1 (0.46)
Muscle spasms	9 (1.03)	8 (1.22)	1 (0.46)
Fibromyalgia	3 (0.34)	2 (0.31)	1 (0.46)
Musculoskeletal chest pain	3 (0.34)	1 (0.15)	2 (0.92)
Musculoskeletal pain	3 (0.34)	2 (0.31)	1 (0.46)
Muscle tightness	1 (0.11)	1 (0.15)	0
Musculoskeletal discomfort	1 (0.11)	0	1 (0.46)
Myositis	1 (0.11)	1 (0.15)	0
Musculoskeletal stiffness	1 (0.11)	0	1 (0.46)

All AEs were treatment emergent. Some patients experienced more than 1 AE.
[a]AEs were coded according to MedDRA version 27.1; muscle-related AEs were determined based on predefined search strategy.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years.

- Creatine kinase levels remained stable through 36 months of seladelpar treatment, with similar mean values regardless of statin use (**Figure 3**)
- Creatine kinase elevations >3 × upper limit of normal occurred infrequently both in patients on a statin (1%) and not on a statin (1%)
- Statin initiation while on seladelpar was uncommon; 19/250 (8%) of patients without baseline statin use initiated statins while taking seladelpar

Figure 3. Mean Creatine Kinase Over Time With Seladelpar in (A) the Overall Population and (B) by Statin Use



Data cutoff: 31 January 2025. Month 48 data was not included due to insufficient sample size; hence, the data are limited to Month 36.
BL, baseline.

Limitations

- In this open-label study, there were fewer patients who received statins than those who did not
- Findings from this post hoc subgroup analysis are exploratory and should not be interpreted as confirmatory evidence