Seladelpar Leads to Decrease in Serum Proteins Associated With PBC Disease Severity: Proteomic Analysis From the RESPONSE Trial

LBP-037

Michael Trauner[1], Yan Liang[2], Peyvand Amini[2], Grant Budas[2], Kyung min Kwon[2], Daria B. Crittenden[2], Anna Zagorska[2]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Gilead Sciences, Inc., Foster City, USA

Late Breaker Posters

Conclusions

- Seladelpar treatment led to marked and sustained reductions in serum proteins associated with cholestasis, pruritus, and fibrosis, consistent with known seladelpar-associated biochemical and symptomatic improvements experienced by patients with primary biliary cholangitis
- Seladelpar treatment led to increases in serum levels of canonical peroxisome proliferator-activated receptor delta targets involved in improving lipid metabolism and high-density lipid biosynthesis
- The largest number of significant changes in abundance occurred at Month 12 of seladelpar treatment, which is suggestive of progressive impact on biological pathways
- Seladelpar's effect on serum proteins correlated with decreased alkaline phosphatase at Month 12 in patients in the RESPONSE trial

Plain Language Summary

- In this study, researchers examined changes in proteins in the blood from people with primary biliary cholangitis (PBC) who received seladelpar treatment in the Phase 3 RESPONSE clinical trial
- Over 12 months of seladelpar treatment, there were changes in protein levels that related to liver health, itching, and inflammation
- These changes in protein levels might explain how seladelpar treatment works in the body to help reduce symptoms in people living with PBC

References: **1.** European Association for the Study of the Liver. *J Hepatol.* 2017;67(1):145-72. **2.** Lyvdelzi. EMA prescribing information. Gilead Sciences, Inc.; 2025. **3.** Hirschfield GM, et al. *N Eng J Med.* 2024;290(9):783-94. **4.** Schattenberg JM, et al. *Aliment Pharmacol Ther.* 2026;63:1215-35. **5.** SomaLogic Operating Co., Inc. SomaScan® 11K Assay v5.0 Technical Note. SL00000919 Rev 1: 2023-12. **6.** Friedman, LS. UpToDate. Mar 2026. **7.** Li Y, et al. *eBioMedicine.* 2025;108:105344. **8.** Li Q, et al. *Biology.* 2021;10:119. **9.** Zhang X, et al. *Front Allergy.* 2025;6:1686370. **10.** Bähler L, et al. *J Allergy Clin Immunol.* 2025;156(5):1160-72. **11.** Wu W, et al. *Arch Dermatol Res.* 2024;316(8):521. **12.** Trinh-Minh T, et al. *J Clin Invest.* 2024;134(10):e159884. **13.** Nakasaki M, et al. *Nat Comm.* 2015;6:8574. **14.** Yasui Y, et al. *Gastro Hep Advances.* 2026;5:100827. **15.** Rifkin D, et al. *Dev Dyn.* 2022;251(1):95-104. **16.** Mantovani A, Garlanda, C. *N Engl J Med.* 2023;388(5):439-52. **17.** Sun Z, et al. *J Cell Mol Med.* 2019;23:887-97. **18.** Marin V, et al. *J Hepatol.* 2017;67(5):1018-25. **19.** Wu, et al. *Journal of Hepatology.* 2024;80:S1. Poster SAT-175. S300. **20.** Kouno T, et al. *J Biol Chem.* 2022;298(7):102056. **21.** Olson EJ, et al. *Arterioscler Thromb Vasc Biol.* 2012;32(9):2289-94.

Acknowledgements: SomaScan assay was run by SomaLogic. This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Allison Yankey, PhD, CMPP, 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.

Correspondence: Michael Trauner, michael.trauner@meduniwien.ac.at

Introduction

- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease that is associated with progressive liver injury and significant symptom burden[1]
- Seladelpar, a first-in-class delpar (selective peroxisome proliferator-activated receptor delta [PPARδ] agonist), is approved for second-line treatment of PBC and significantly improved cholestasis and pruritus in the pivotal, placebo-controlled RESPONSE study (NCT04620733)[2,3]
- This proteomic analysis of the RESPONSE study builds upon the established PPARδ-mediated mechanism of action of seladelpar and its clinical impact on PBC by evaluating longitudinal effects of seladelpar on proteome biomarkers of disease[4]

Objective

- To evaluate the effects of seladelpar on longitudinal changes in the abundance of serum proteins associated with PBC disease severity
- To expand on the known impacts of seladelpar's activity through PPARδ using highly sensitive proteomic profiling with SomaScan

Methods

- In the RESPONSE study, 193 patients with PBC were randomised 2:1 to receive placebo or seladelpar 10 mg for 12 months[3]
- Serum proteomes from 180 patients (862 samples) were profiled using the SomaScan 11k Assay version 5.0, which quantifies 9852 human proteins
- Data normalisation, calibration, and quality control processes were performed according to the manufacturer's instructions[5]
- Baseline correlations between protein levels and markers of PBC, including clinically relevant metrics and circulating biomarkers associated with PBC, were evaluated using Spearman's rank correlation (**Table 1**)
- The association between protein percent change from baseline and alkaline phosphatase (ALP) percent change from baseline was evaluated using Spearman's rank correlation
- Longitudinal changes in protein levels at Months 1, 3, 6, and 12 were analysed using mixed-effects models that estimated placebo-adjusted changes from baseline at each post-baseline time point
  - Treatment, time, treatment-time interaction, age, sex, baseline disease severity, and plate ID were treated as fixed effects; patients were treated as random effects
- For Figures 3–5, proteins previously associated with cholestasis, pruritus, fibrosis, inflammation and PPARδ-agonism were identified among proteins with significant, placebo-adjusted longitudinal change with seladelpar (adjusted *P* <.1) in patients who achieved the composite biochemical response previously described in the RESPONSE study (ALP <1.67 × upper limit of normal [ULN], total bilirubin ≤1 × ULN, and ALP reduction ≥15% from baseline)[3]

Table 1. Clinically Relevant Metrics and Circulating Biomarkers Related to Symptoms of PBC Used for Correlations With SomaScan

	Cholestasis	Pruritus	Fibrosis
Clinically Relevant Metrics	• ALP • GGT	• Pruritus NRS • PBC-40 Itch Score	• Liver stiffness
Circulating Biomarkers	• Total bile acids[a]	• IL-31[b] • Autotaxin[c]	• P3NP and ELF score

Circulating biomarkers measured by [a]mass spectrometry (excluding UDCA and its conjugates), [b]Simoa, and [c]ELISA.
ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; ELISA, enzyme-linked immunosorbent assay; GGT, gamma glutamyl transferase; IL-31, interleukin-31; NRS, Numerical Rating Score; P3NP, procollagen-3 N-terminal peptide; PBC, primary biliary cholangitis; ursodeoxycholic acid. UDCA.

Results

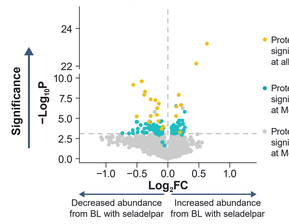
- Seladelpar treatment resulted in sustained and significant changes in the serum proteome over time (**Figure 1A**)
  - Seladelpar-associated changes in protein abundance were sustained over time; the number of proteins with seladelpar-modulated changes increased over time
  - At Month 12, 71/158 proteins were upregulated and 87/158 were downregulated (adjusted *P* <.05; **Figure 1B**)
  - Across all time points, 22 proteins showed significant changes with seladelpar treatment

Figure 1. Proteins With a Significant Placebo-Adjusted Change From Baseline With Seladelpar Treatment

A The Number of Proteins Significantly Upregulated or Downregulated by Seladelpar vs Placebo Increased Over Time[a]

	Month 1	Month 3	Month 6	Month 12
Upregulated	11	9	18	71
Downregulated	26	31	24	87

B Volcano Plot Showing Placebo-Adjusted Changes in Protein Abundance at Month 12



Proteins above the dotted line had significant change in abundance from BL with seladelpar treatment compared to placebo at Month 12 (adjusted *P* <.05).
[a]Adjusted *P* <.05.
BL, baseline; FC, fold change.

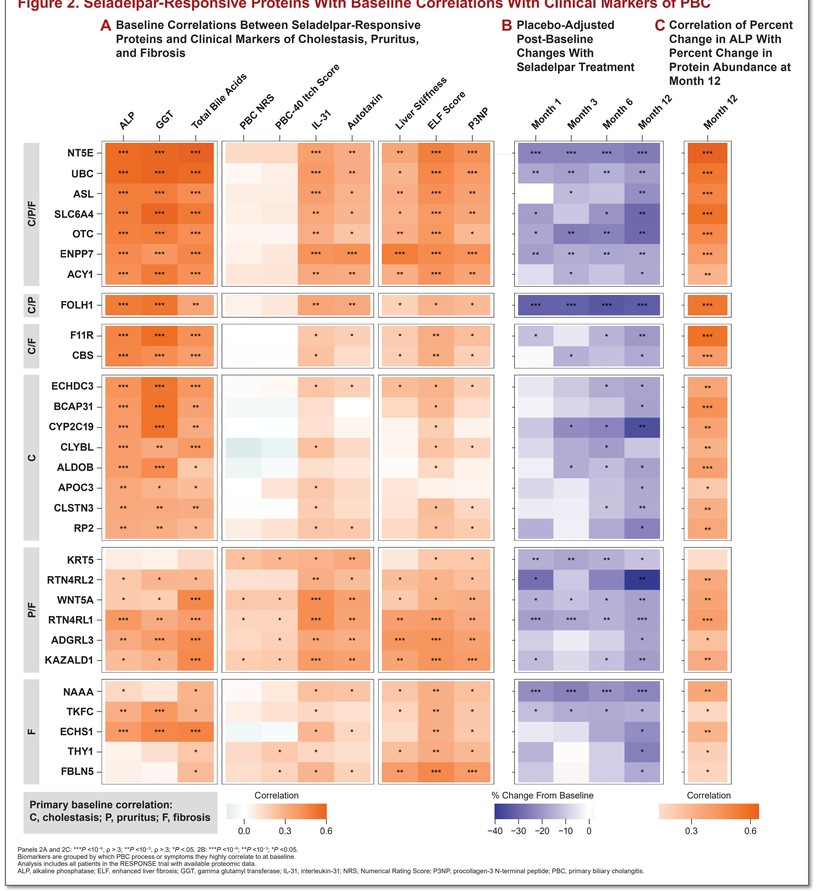
- Using a stepwise approach, 29 seladelpar-responsive proteins were identified based on the following stringent criteria:
  - Baseline correlations (ρ >.3; adjusted *P* <.05) with ≥1 clinical markers of PBC
  - Significant placebo-adjusted change in abundance with seladelpar treatment at any post-baseline time point (*P* <.05, absolute log_2FC >.25)
- Most of the identified proteins were simultaneously associated with multiple clinical markers of cholestasis, pruritus, and fibrosis (**Figure 2A**)
- The greatest placebo-adjusted change in abundance was seen at Month 12, indicating seladelpar-associated results are significant, sustained, and increase over time (**Figure 2B**)
- A strong correlation was observed at Month 12 for a majority of seladelpar-reponsive proteins between the percent change in abundance and the change in ALP from baseline (**Figure 2C**)

Figure 2. Seladelpar-Responsive Proteins With Baseline Correlations With Clinical Markers of PBC

A Baseline Correlations Between Seladelpar-Responsive Proteins and Clinical Markers of Cholestasis, Pruritus, and Fibrosis

B Placebo-Adjusted Post-Baseline Changes With Seladelpar Treatment

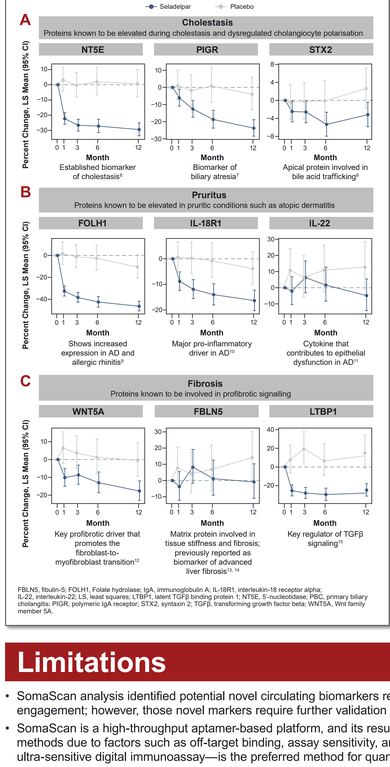
C Correlation of Percent Change in ALP With Percent Change in Protein Abundance at Month 12



Panels 2A and 2C: ***P <10^{-5}, ** p >.3; **P <10^{-3}, * p >.3; *P <.05. 2B: ***P <10^{-5}, **P <10^{-3}, *P <0.05.
Biomarkers are grouped by which PBC process or symptoms they highly correlate to at baseline.
Analysis includes all patients in the RESPONSE trial with available proteomic data.
ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; GGT, gamma glutamyl transferase; IL-31, interleukin-31; NRS, Numerical Rating Score; P3NP, procollagen-3 N-terminal peptide; PBC, primary biliary cholangitis.

- Proteins previously associated with cholestatic conditions, pruritic diseases, and fibrotic pathways were identified among proteins that correlated with clinical markers of PBC and significantly decreased over time with seladelpar treatment (placebo-adjusted; adjusted *P* <.1; **Figure 3**)

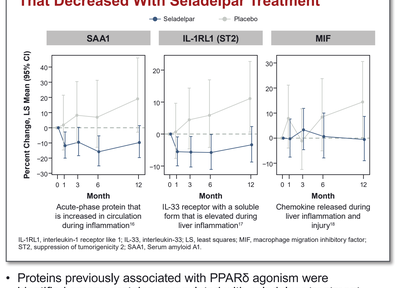
Figure 3. Example Proteins Involved in (A) Cholestasis, (B) Pruritus, and (C) Fibrosis That Change in Abundance With Seladelpar Treatment



FBLN5, fibulin-5; FOLH1, Folate hydrolase; IgA, immunoglobulin A; IL-18R1, interleukin-18 receptor alpha; IL-22, interleukin-22; LS, least squares; LTBP1, latent TGFβ binding protein 1; NT5E, 5′-nucleotidase; PBC, primary biliary cholangitis; PIGR, polymeric IgA receptor; STX2, syntaxin 2; TGFβ, transforming growth factor beta; WNT5A, Wnt family member 5A.

- Markers of inflammation were identified using proteins mapped to the Gene Ontology inflammatory response (GO:0006954) and also significantly decreased over time with seladelpar treatment (placebo-adjusted; adjusted *P* <.1; **Figure 4**)

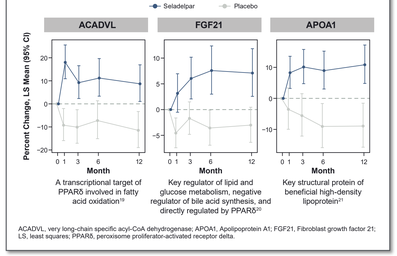
Figure 4. Example Inflammatory Pathway Markers That Decreased With Seladelpar Treatment



IL-1RL1, interleukin-1 receptor like 1; IL-33, interleukin-33; LS, least squares; MIF, macrophage migration inhibitory factor; ST2, suppression of tumorigenicity 2; SAA1, Serum amyloid A1.

- Proteins previously associated with PPARδ agonism were identified among proteins upregulated with seladelpar treatment (placebo-adjusted, adjusted *P* <.1; **Figure 5**)
  - Seladelpar treatment led to significant increases in known targets of PPARδ involved in lipid metabolism

Figure 5. Select PPARδ-Regulated Proteins Involved in Lipid Metabolism That Increased With Seladelpar Treatment



ACADVL, very long-chain specific acyl-CoA dehydrogenase; APOA1, Apolipoprotein A1; FGF21, Fibroblast growth factor 21; LS, least squares; PPARδ, peroxisome proliferator-activated receptor delta.

Limitations

- SomaScan analysis identified potential novel circulating biomarkers reflective of PBC disease severity and markers indicative of PPARδ pathway engagement; however, those novel markers require further validation against other platforms and with long-term patient data
- SomaScan is a high-throughput aptamer-based platform, and its results do not always correlate with measurements obtained using antibody-based methods due to factors such as off-target binding, assay sensitivity, and post-translational modifications; for IL-31 in particular, Simoa—an ultra-sensitive digital immunoassay—is the preferred method for quantitative measurement