Seladelpar Treatment Resulted in Correlated Decreases in Serum IL-31 and Pruritus in Patients with Primary Biliary Cholangitis (PBC)

Post-Hoc Results from the Phase 3 Randomized, Placebo-Controlled ENHANCE Study

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Disclosure

Andreas E. Kremer

I disclose the following financial relationship(s) with a commercial interest:

- Abbvie, AstraZenca, AOP Orphan, Bayer, CymaBay, Escient, Eisai, Falk, FMC, Gilead, GSK, Intercept, Mirum, Medscape, MSD, Myr, Newbridge, Novartis, Lilly, Roche, Viofor

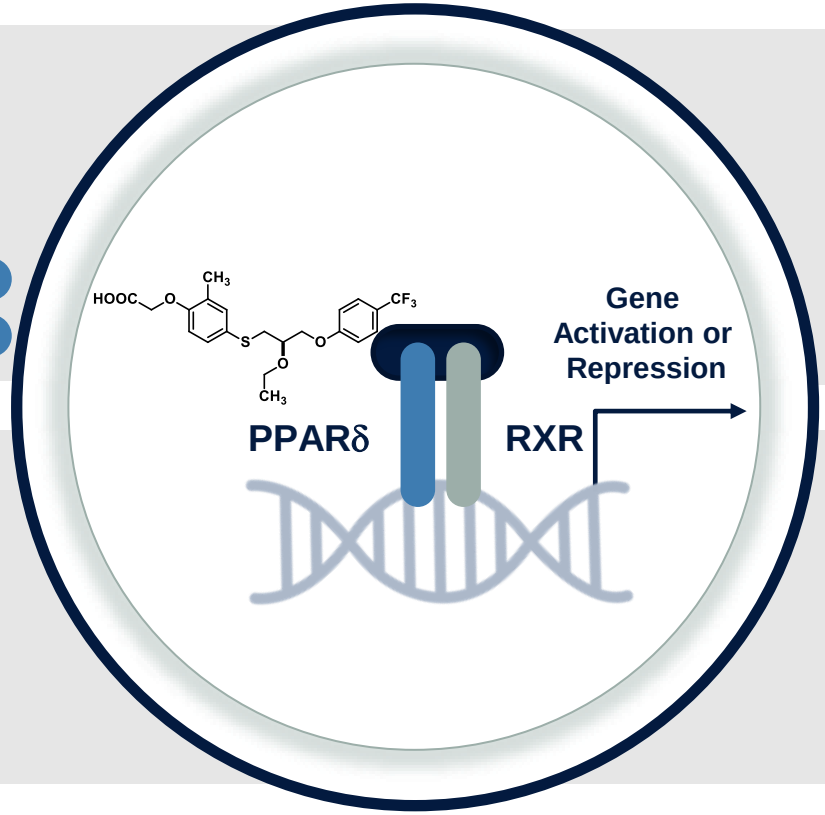
Seladelpar

Targets all important cell types in liver disease

Decrease Bile Acids

- ↓ Cholesterol synthesis
- ↓ Bile acid synthesis (C4)
- ↑ Transport

Hepatocyte
Cholangiocyte



Anti-Inflammatory

- ↓ NFκB-dependent gene activation
- ↓ Inflammatory cytokines
- ↓ hs-C-Reactive Protein

Kupffer Cell
Macrophage

Anti-Fibrotic

- ↓ Profibrotic genes
- ↓ Stellate cell activation
- ↓ Collagen synthesis/deposition

Stellate Cell

Increase Lipid Metabolism

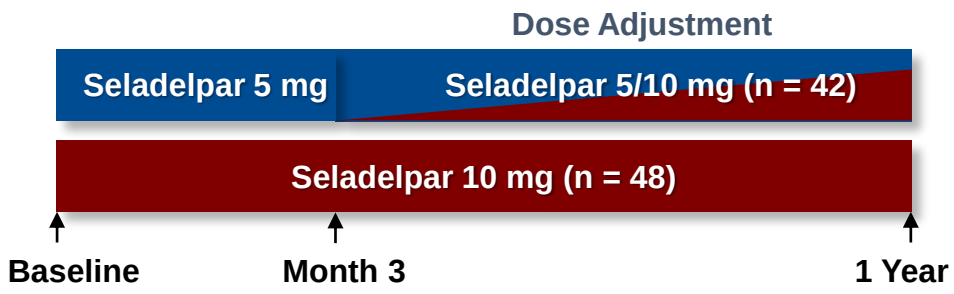
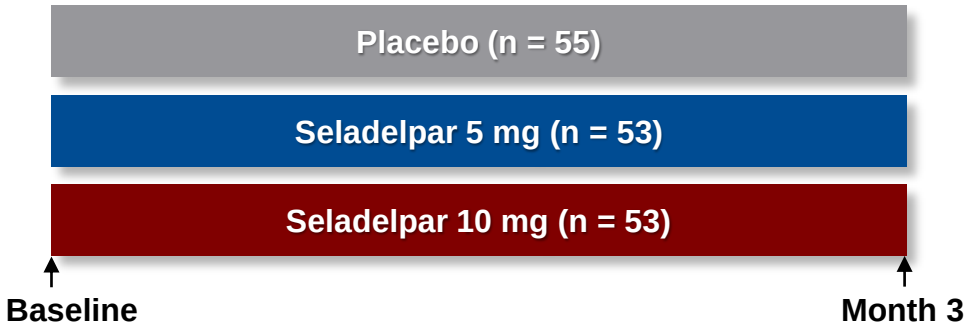
- ↓ Cholesterol/LDL-C
- ↑ Fatty acid oxidation

Hepatocyte
Myocyte
Adipocyte
Enterocyte

Regulates Genes That Control Pathways in Liver Health and Disease

Seladelpar Studies with PBC Patients

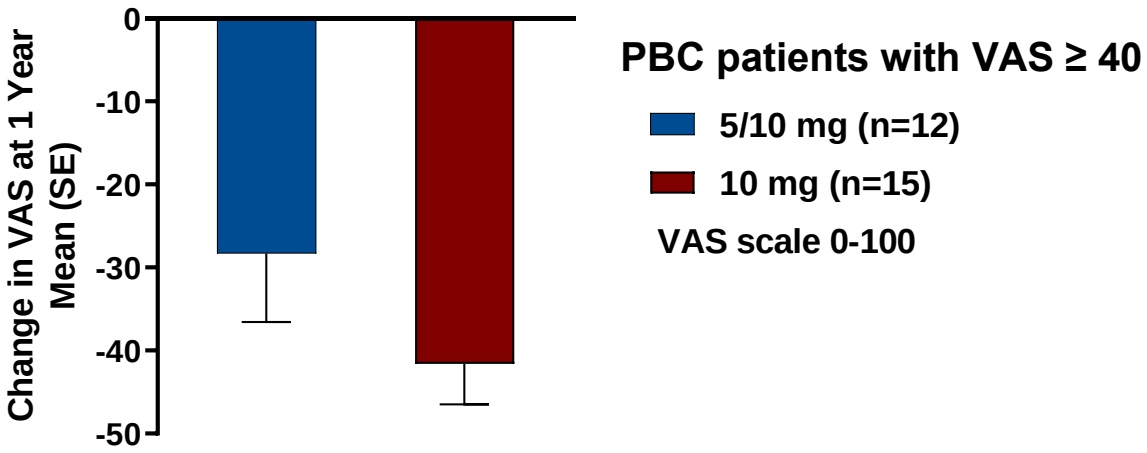
Daily oral add-on to UDCA dose, or as monotherapy when intolerant

PBC studies	Phase 2 open-label study	ENHANCE Phase 3 study
Key Eligibility	▪ Diagnosis of PBC ▪ ALT/AST ≤ 3 x ULN ▪ Prior UDCA ≥ 12 months or intolerant	▪ ALP ≥ 1.67 x ULN ▪ Total Bilirubin ≤ 2 x ULN
Study Design		
Measurements	▪ Pruritus Visual Analog Scale (VAS, 0-100) ▪ Serum total bile acids ▪ Serum IL-31	▪ Pruritus Numerical Rating Scale (NRS, 0-10) ▪ Serum total bile acids ▪ Serum IL-31 ▪ Serum autotaxin ▪ Other cytokines (IL-4, IL-13 and IL-33)

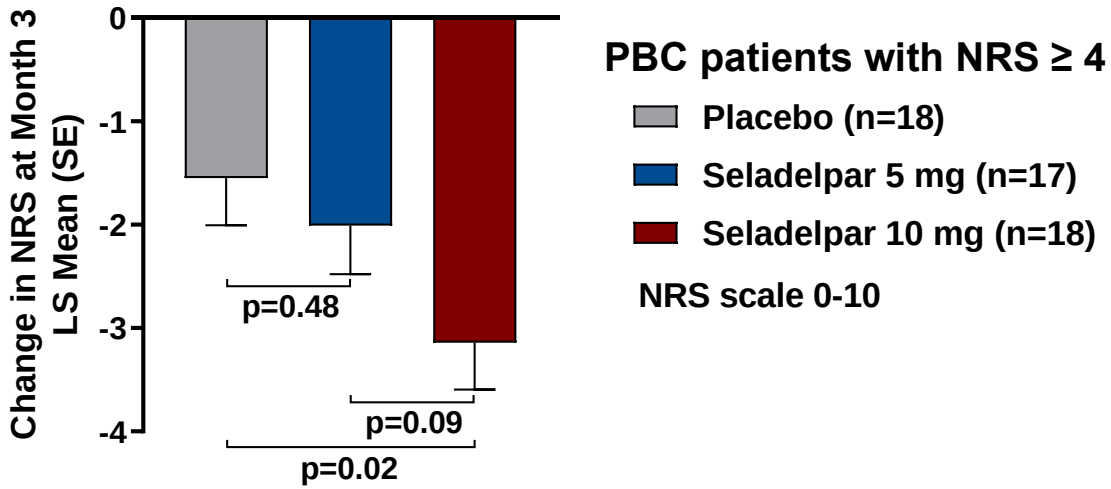
Seladelpar Improved Pruritus in Patients with PBC

Patients with moderate to severe pruritus

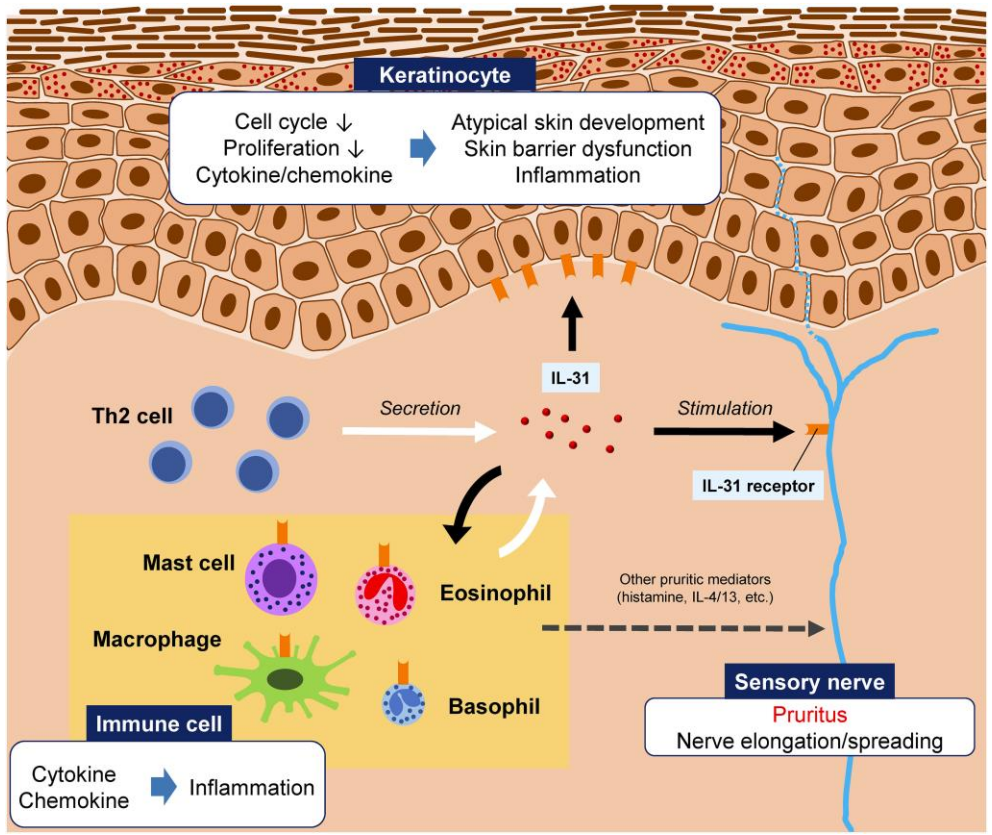
Phase 2 open-label study



ENHANCE phase 3 study



IL-31 in Pruritic Skin Diseases

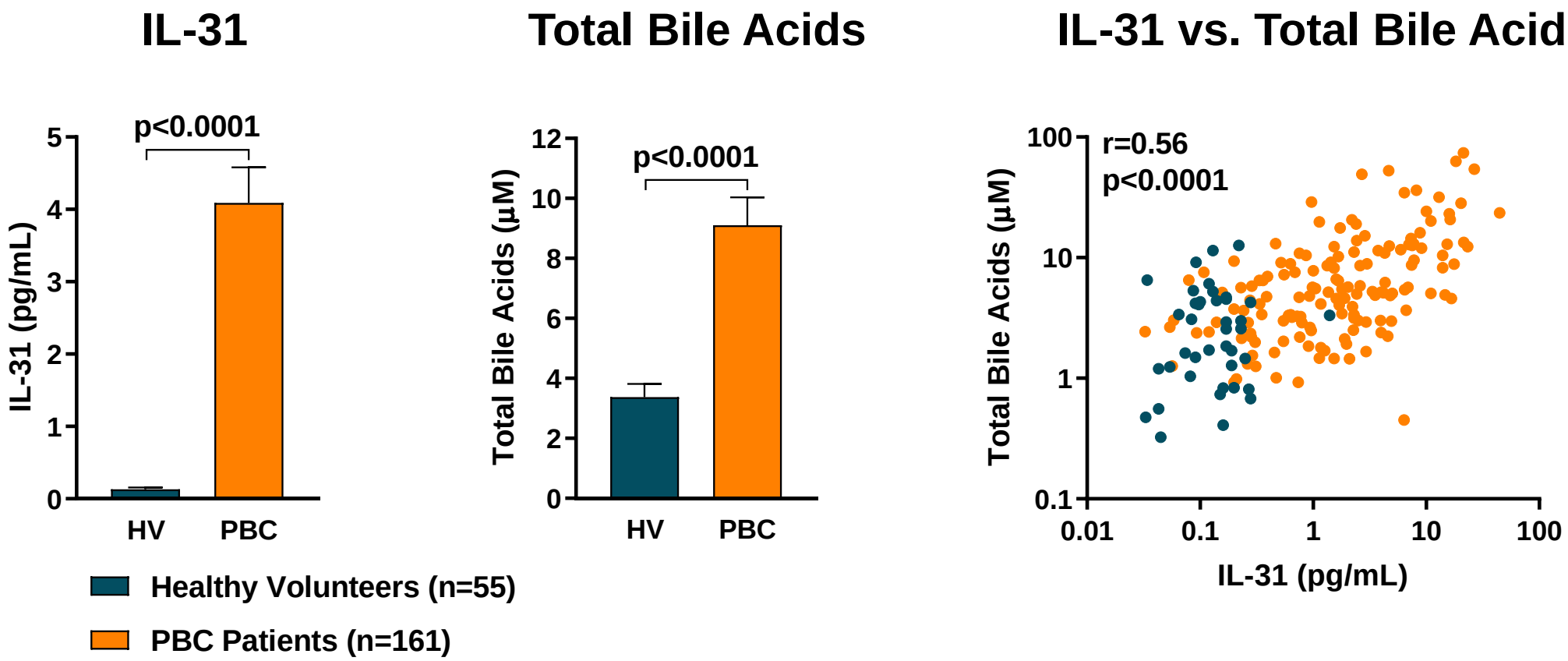


- **IL-31 is elevated** in tissue or serum of patients with **pruritic skin diseases** (atopic dermatitis, prurigo nodularis).
- IL-31 is primarily produced by **T helper 2 (Th2) cells**, although other innate immune cells can also produce IL-31.
- The **dimeric IL-31 receptor** is expressed by various cell types, including peripheral **sensory nerves,** epidermal **keratinocytes,** and **immune cells.**
- **Animals** (mouse, dog, monkey and human) treated with **IL-31** exhibited **increased scratching behavior,** and treatments targeting IL-31 reduced scratching.
- **Nemolizumab,** a human monoclonal **anti-IL-31 RA antibody,** significantly **reduced pruritus** in patients with **atopic dermatitis in phase III trial.**

Kabashima *et al*, Front Med, 2021
Arai *et al*, Exp Dermatol, 2013
Pearson *et al*, Vet Sci, 2023
Lewis *et al*, J Eur Acad Dermatol Venereol, 2017
Hawro *et al*, Allergy, 2014
Kabashima *et al*, N Engl J Med, 2020

Serum IL-31: PBC Patients vs. Healthy Volunteers (HV)

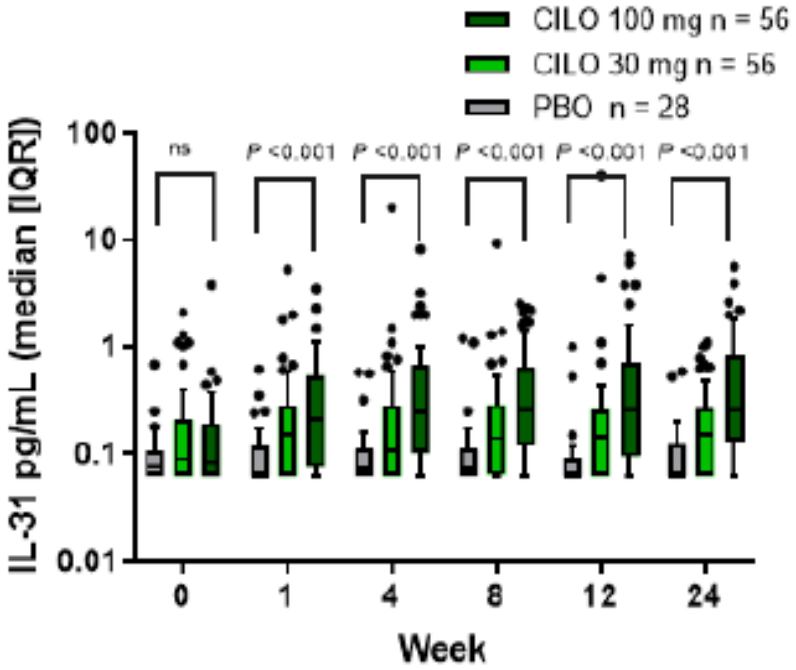
Healthy volunteers: age, sex and BMI matched with PBC patients (ENHANCE)

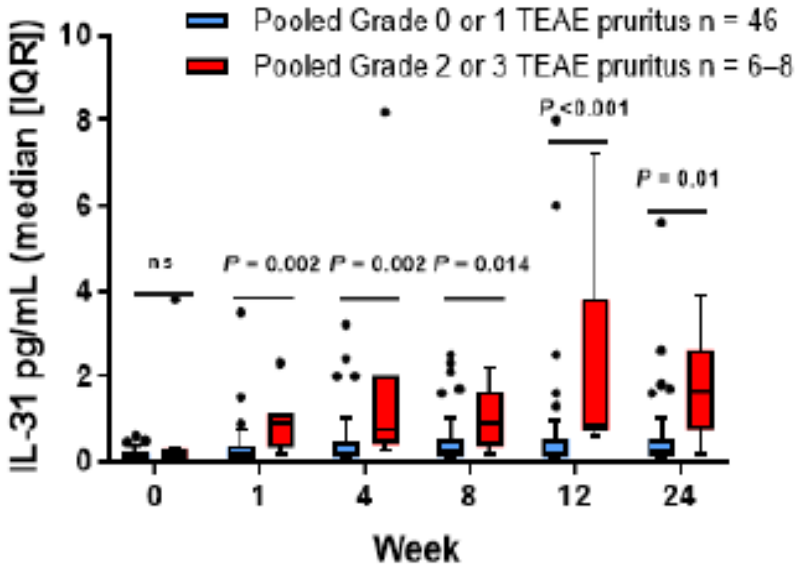


- IL-31 was elevated in previous studies (Mu *et al*, Immunological Investigations, 2021; Xu *et al*, Hepatology, 2023)

FXR Agonist Increased Serum IL-31 Levels

- FXR agonist, cilofexor, dose-dependently increased serum IL-31 levels in noncirrhotic NASH patients
- Significantly higher IL-31 levels in cilofexor-treated NASH patients with severe pruritus
- FXR agonist OCA elevated serum human IL-31 levels in PXB mice with humanized liver



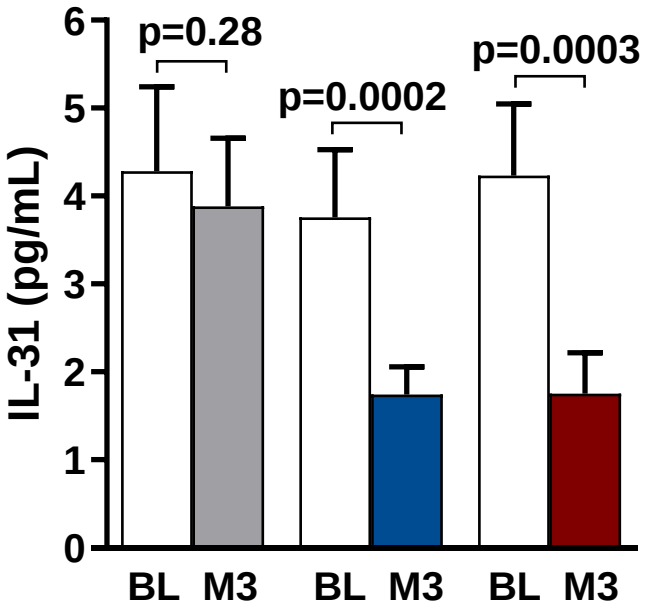


Xu *et al*, Hepatology, 2023

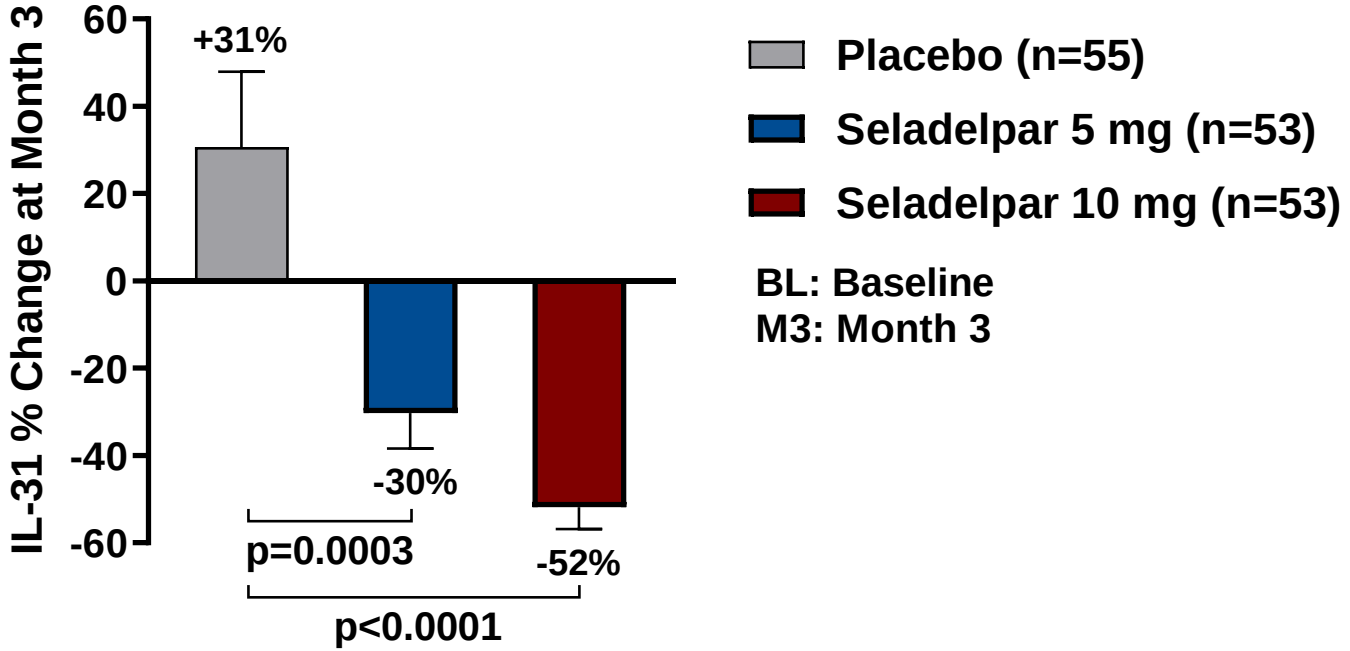
Substantial Reduction of Serum IL-31 by Seladelpar After 3 Months

ENHANCE phase 3 study with seladelpar in patients with PBC

IL-31



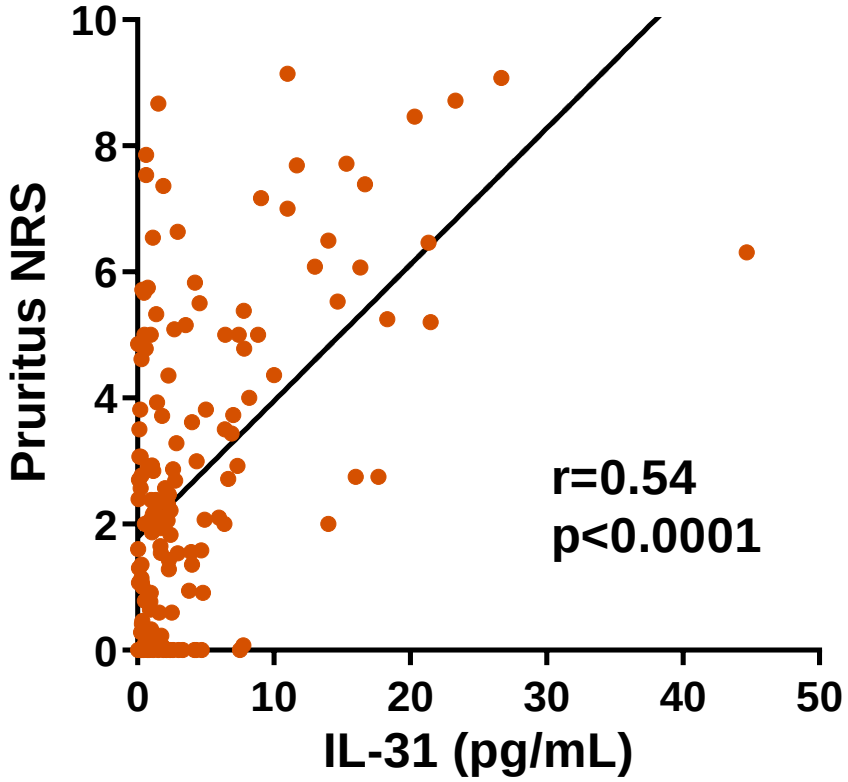
IL-31 % Change



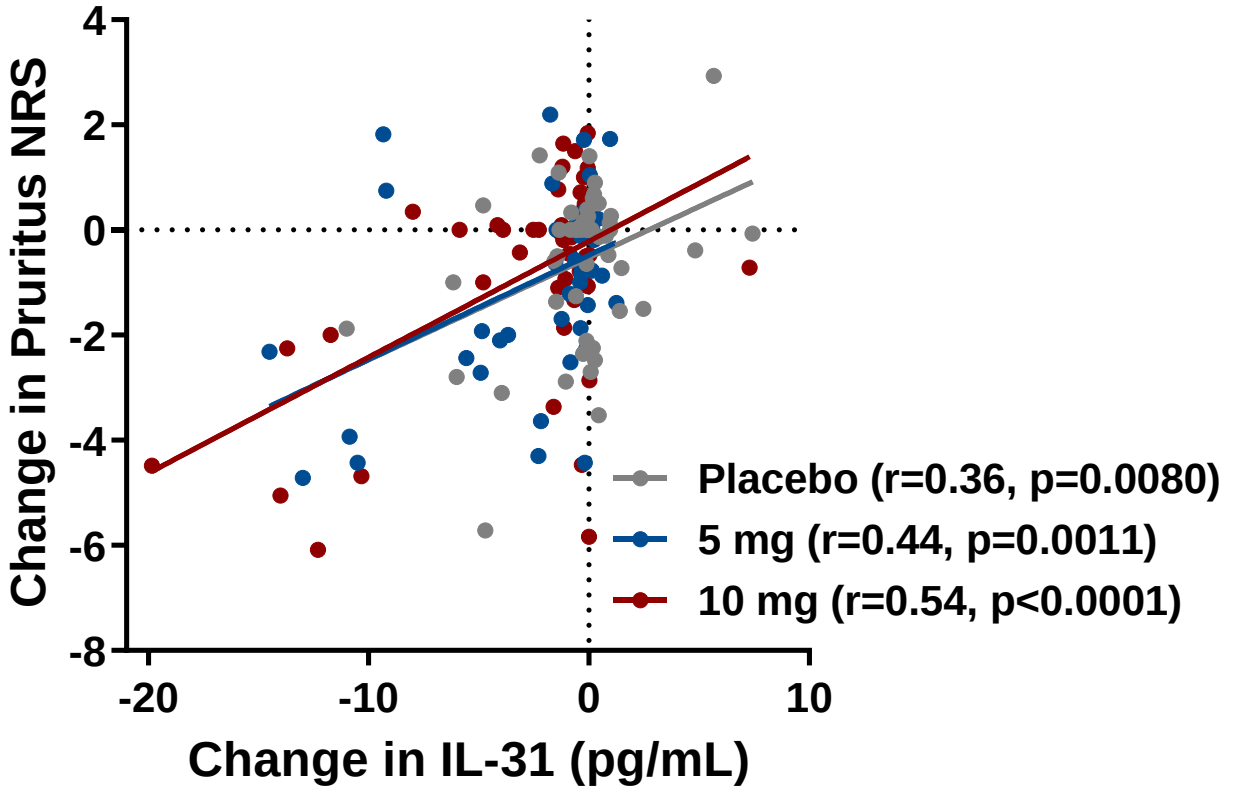
Serum IL-31 Correlates with Pruritus NRS

ENHANCE phase 3 study with seladelpar in patients with PBC

Baseline IL-31 vs. Baseline NRS

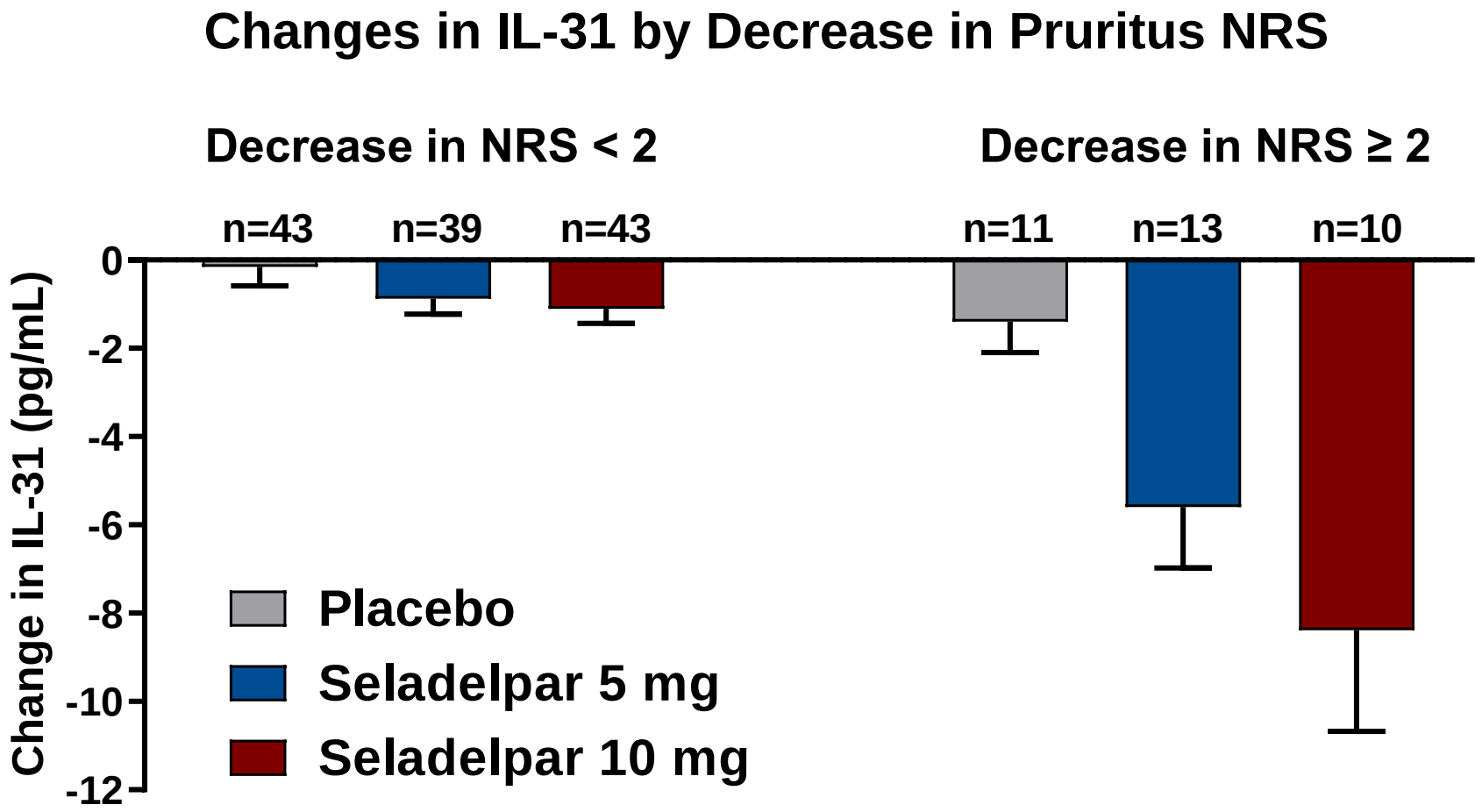


Changes in IL-31 vs. Change in NRS



Patients with Pruritus Improvement Showed Greater Decrease in Serum IL-31 Levels

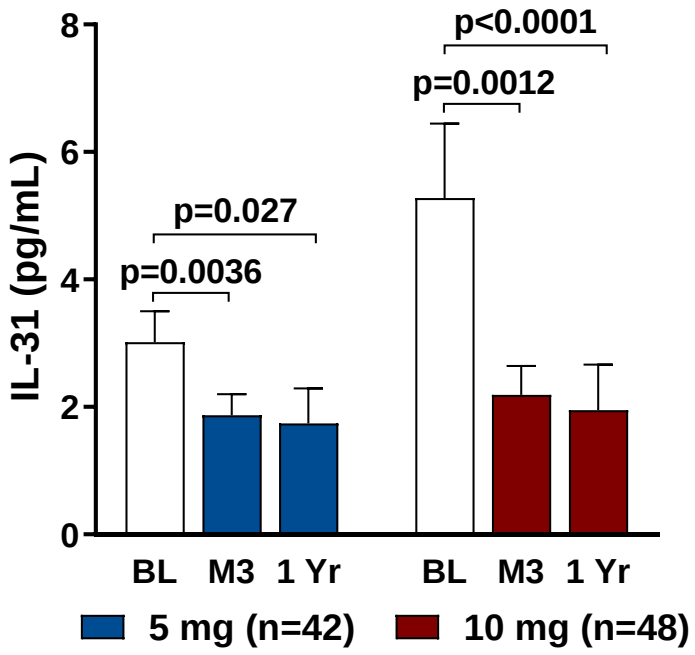
ENHANCE phase 3 study with seladelpar in patients with PBC



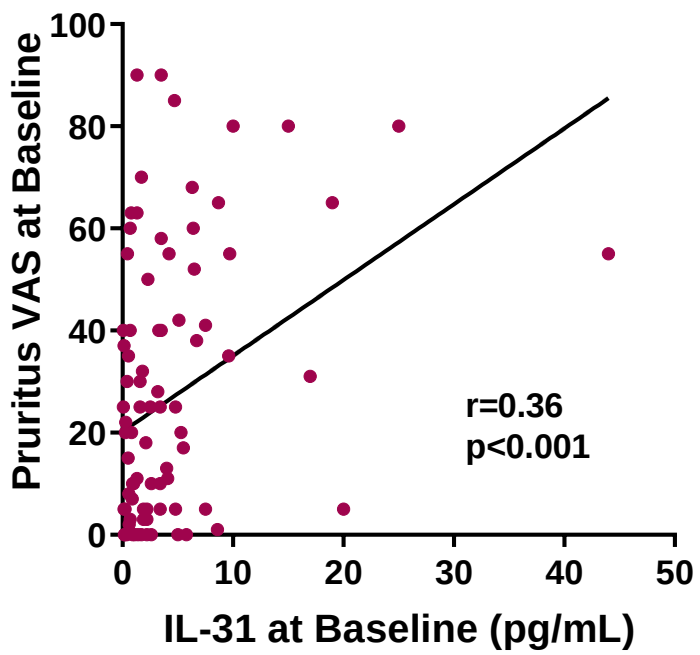
Phase 2 Study Confirms IL-31 and Pruritus Results

Open-label phase 2 study with seladelpar in patients with PBC

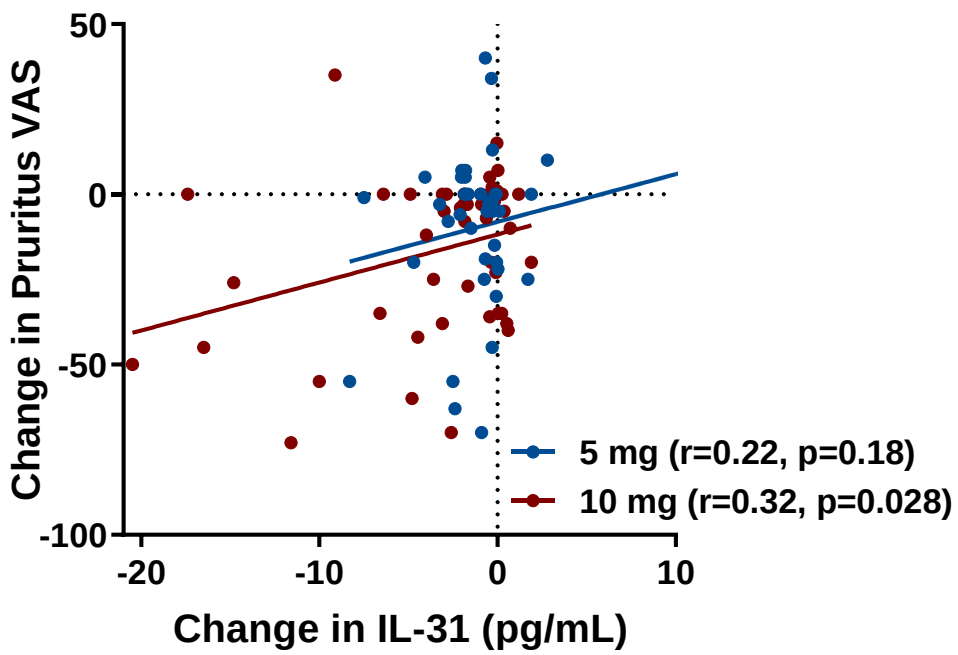
IL-31



Baseline IL-31 vs. VAS



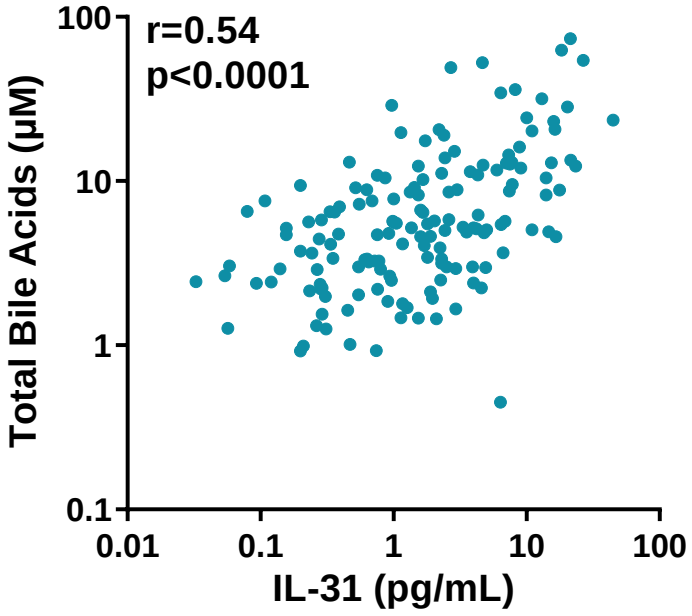
Changes in IL-31 vs. VAS at 1 Year



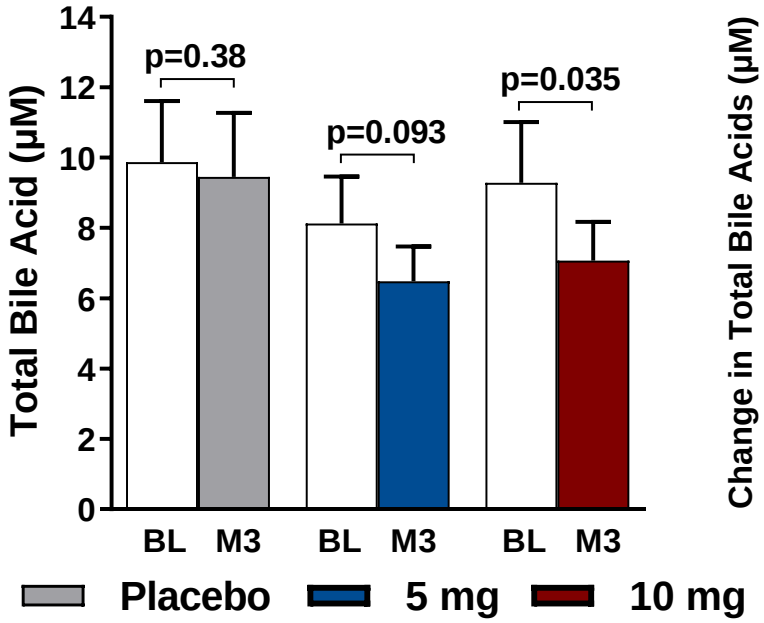
IL-31 is Correlated with Total Bile Acids

ENHANCE phase 3 study with seladelpar in patients with PBC

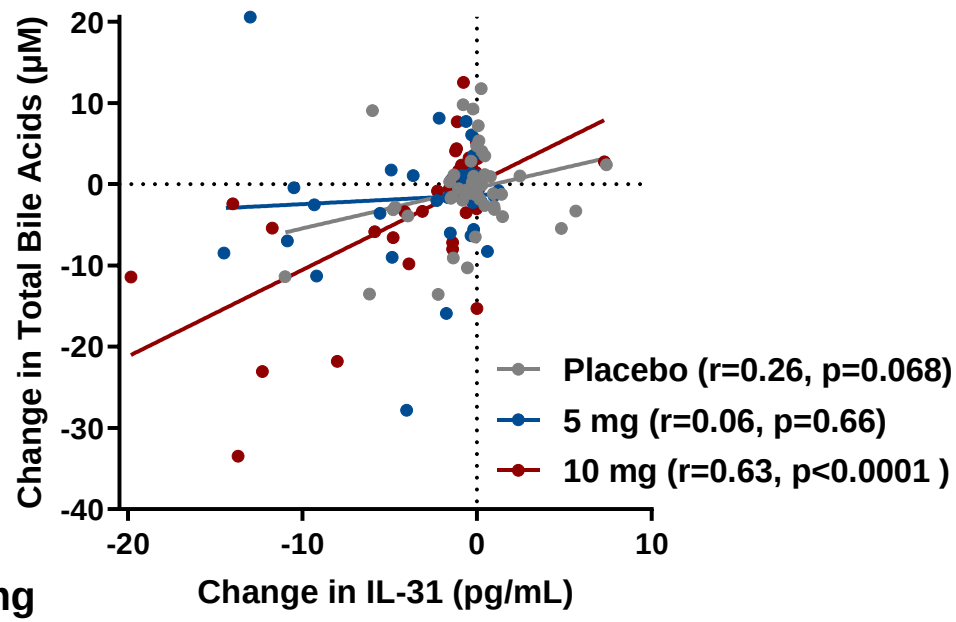
Baseline IL-31 vs. Total Bile Acids



Total Bile Acids

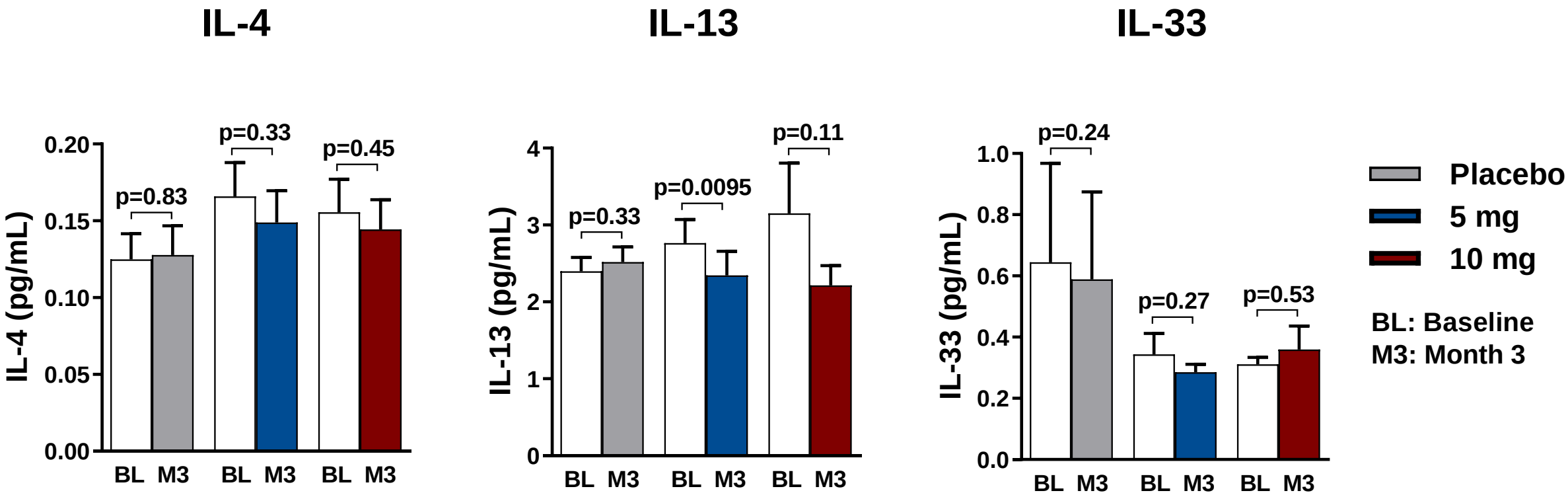


Changes in IL-31 and Total Bile Acids



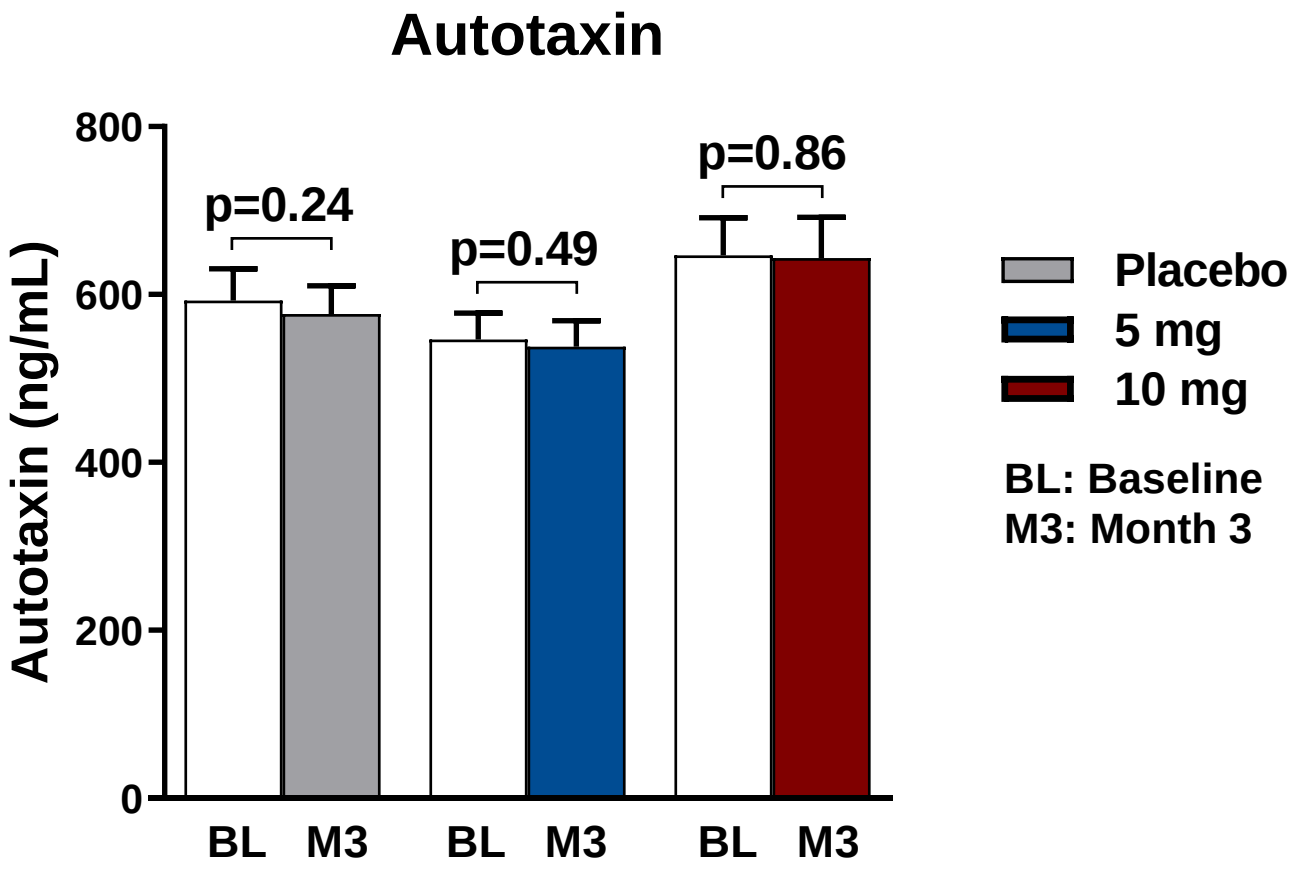
No Effect of Seladelpar on Other Cytokines Known to Be Associated with IL-31 and Pruritus

ENHANCE phase 3 study with seladelpar in patients with PBC



No Effect of Seladelpar on Autotaxin Levels

ENHANCE phase 3 study with seladelpar in patients with PBC



Conclusions

- IL-31 levels were increased over 30-fold in PBC patients compared to healthy volunteers.
- Baseline IL-31 level is correlated with pruritus NRS and bile acid levels.
- Seladelpar treatment for 3 month and up to 1 year led to significant and substantial reductions in IL-31.
- Greater reduction in IL-31 was observed in patients with a significant improvement in pruritus (NRS ≥ 2).
- Decreases in IL-31 levels were associated with improvements in pruritus and decreases in total bile acids.