INTRO AND SCIENTIFIC OBJECTIVES
Cholangiocytes, epithelial cells lining bile ducts, play a crucial role as the primary site of injury in primary biliary cholangitis (PBC). The Phase 3 RESPONSE trial in patients with PBC demonstrated that the selective PPARδ agonist seladelpar effectively reduced bile acid pools, improved cholestatic and liver injury markers (ALP, GGT and ALT), and decreased the pruriticogenic cytokine IL-31, leading to an accompanying alleviation of patient-reported pruritus. Given the central role of cholangiocytes in PBC pathobiology, we investigated the response to seladelpar treatment of human cholangiocyte cells as a potential translational model to understand its observed clinical profile.

METHODS
H69 human cholangiocytes were cultured and exposed to varying concentrations and durations of seladelpar treatment. Inflammatory PBC mediators like IL-17 were used in addition to seladelpar. Gene expression changes were analyzed by bulk RNAseq and qPCR assays. Secreted cytokines in culture media were analyzed with Meso Scale Discovery (MSD) assays.

WORKING HYPOTHESIS
Seladelpar MOA in regulation of inflammatory response

(1) Direct PPARδ target

(2) PPARδ Transrepression

RESULTS
Seladelpar induces concerted gene changes in human cholangiocyte cells

Pro-inflammatory reagents that induced inflammatory responses in cholangiocytes

Seladelpar reduced type I and type III interferons in cholangiocytes in inflammatory conditions

CONCLUSIONS
- Seladelpar induces pathway-level gene changes in human cholangiocyte cells.
- TNFα, IL-1β, IFN-α2a and IL-17A are most effective to induce inflammatory response in cholangiocytes.
- Seladelpar reduced type I and type III interferons in cholangiocytes in inflammatory conditions.
- Seladelpar reduced a group of chemokines in cholangiocytes.
- Seladelpar reduced expression of HLA-ABC in cholangiocytes.

REFERENCES