Therapeutic Advances in PBC? Real World Cohort and Treatment

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Disclosures

- Advisory Board – ENDRA Life Sciences

Standard of Care

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis

Frederik Nevens, M.D., Ph.D., Pietro Andreone, M.D., Giuseppe Mazzella, M.D., Simone I. Strasser, M.B., B.S., M.D., Christopher Bowlus, M.D., Pietro Invernizzi, M.D., Ph.D., Joost P.H. Drenth, M.D., Ph.D., Paul J. Pockros, M.D., Jaroslaw Regula, M.D., Ph.D., Ulrich Beuers, M.D., Michael Trauner, M.D., David E. Jones, M.B., B.Chir., Ph.D., et al., for the POISE Study Group*

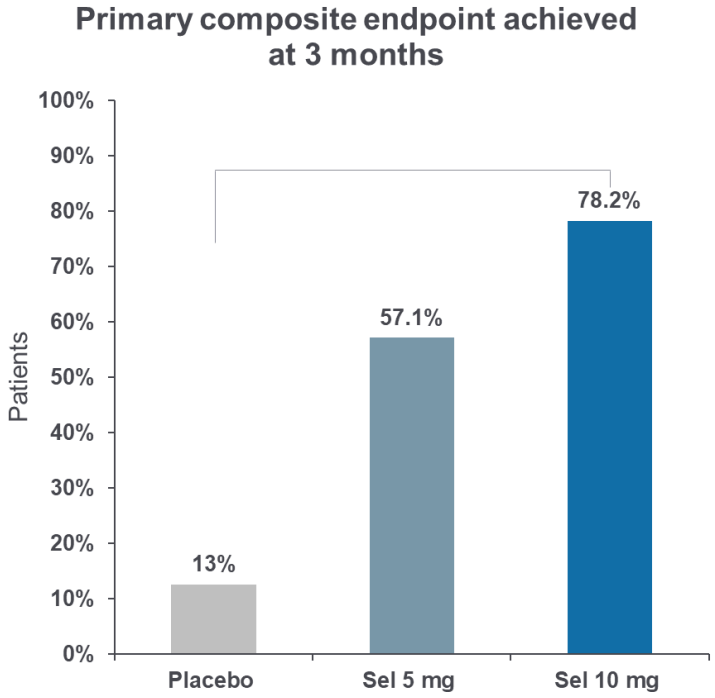
August 18, 2016
N Engl J Med 2016; 375:631-643
DOI: 10.1056/NEJMoa1509840

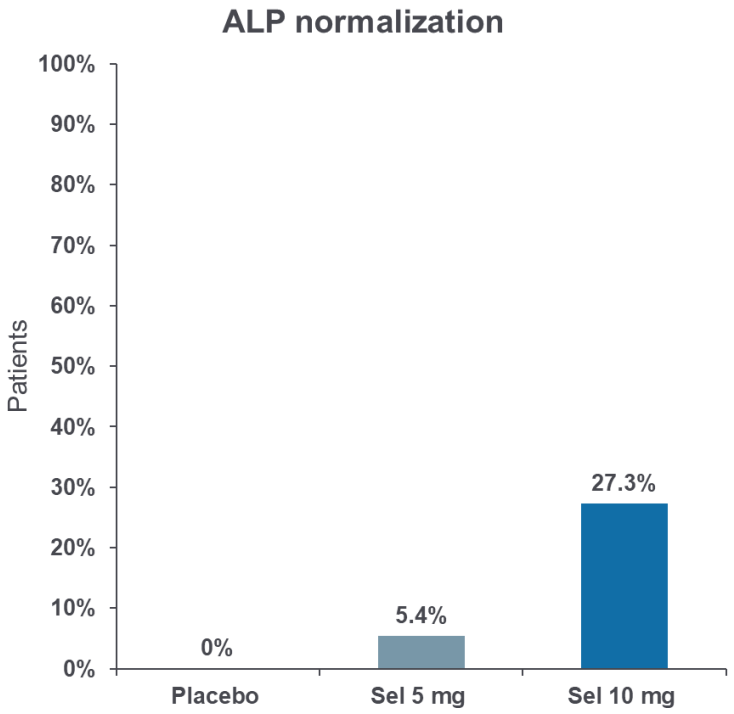
Current FDA Approved Treatment for PBC

- OCALIVA® is indicated for the treatment of adult patients with primary biliary cholangitis (PBC)
  - Without cirrhosis or with compensated cirrhosis (Childs A who do not have evidence of portal hypertension)
- Either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

Response, defined as an ALP less than 1.67xULN, total bilirubin within the normal range, and an ALP decrease of at least 15%.

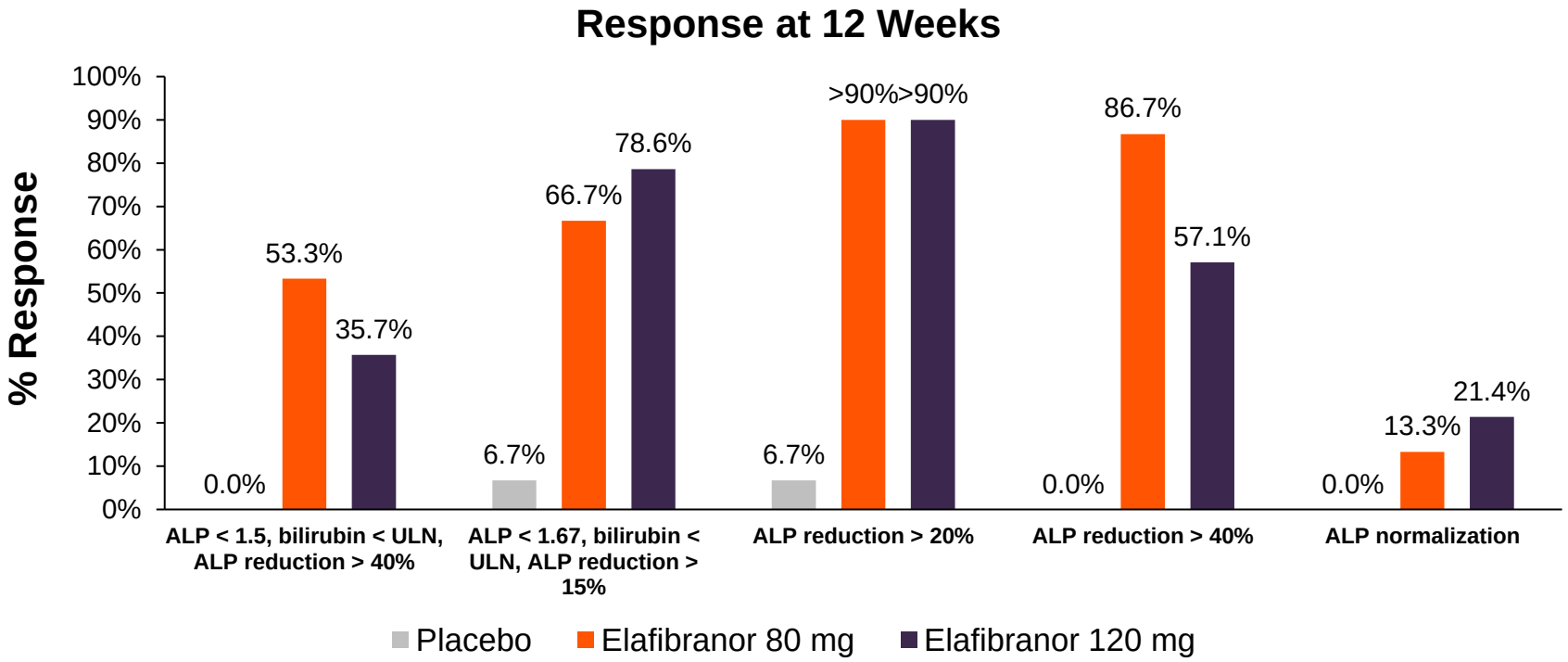
Clinical Trials: Seladelpar – PPAR agonist (δ)





Hirschfield GM et al. [AASLD abstract LO11]. *Hepatology*. 2020;72(suppl 1).

Clinical Trials: Elafibranor – PPAR Agonist (α and δ)



Schattenberg JM et al. *J Hepatol*. 2021;74:1344-1354.

PBC Clinical Endpoints Outlined by FDA

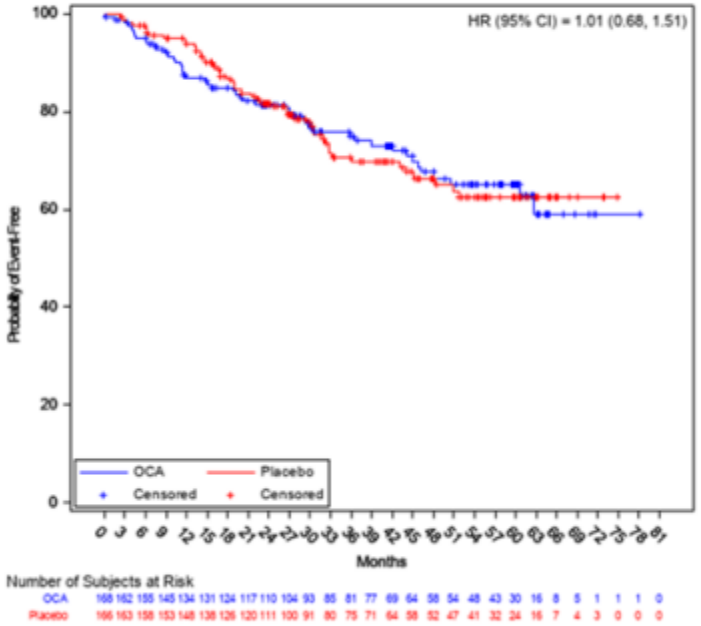
The **FDA expanded composite endpoint** was time to first occurrence of:

- Death (all-cause)
- Liver transplant
- If decompensation prior to index:
  - Hospitalization for new onset or recurrence of:
    - Variceal bleed
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
  - Uncontrolled or refractory ascites requiring hospitalization and/or
    - ≥2 paracentesis per month for ≥2 months
    - TIPS procedure
  - Portal hypertension syndromes
    - Hepatorenal syndrome
    - Hepatopulmonary syndrome
- If without decompensation at index: progression to decompensated liver disease
- If without decompensation or portal hypertension at index: progression to decompensation or portal hypertension

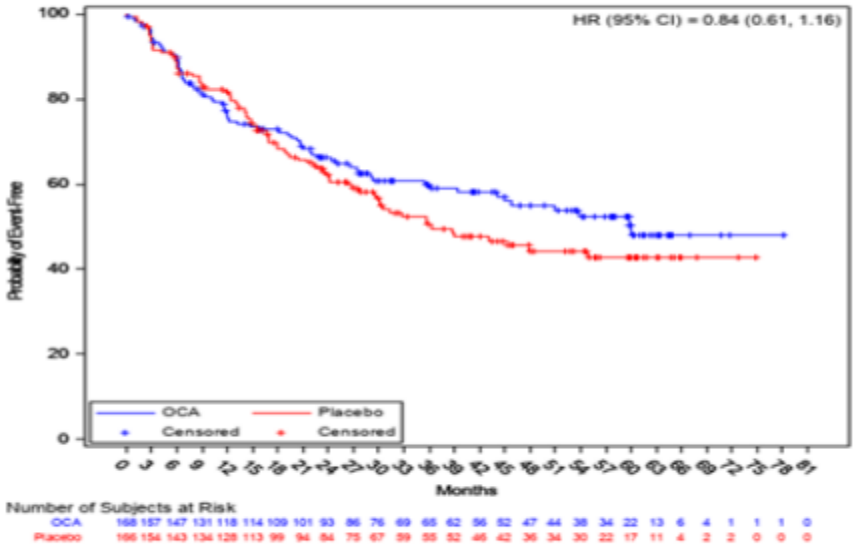
- COBALT was a Phase 3b/4 randomized, double-blind, placebo controlled confirmatory trial aimed to assess efficacy and safety of OCA in patients with advanced PBC

COBALT Trial Primary Endpoint Kaplan Meier

2A: COBALT ITT OCA-Treated vs. Placebo



2B: COBALT ITT OCA-Treated vs. Placebo



Clinicaltrials.gov (NCT02308111); The Liver Meeting oral presentation 2022

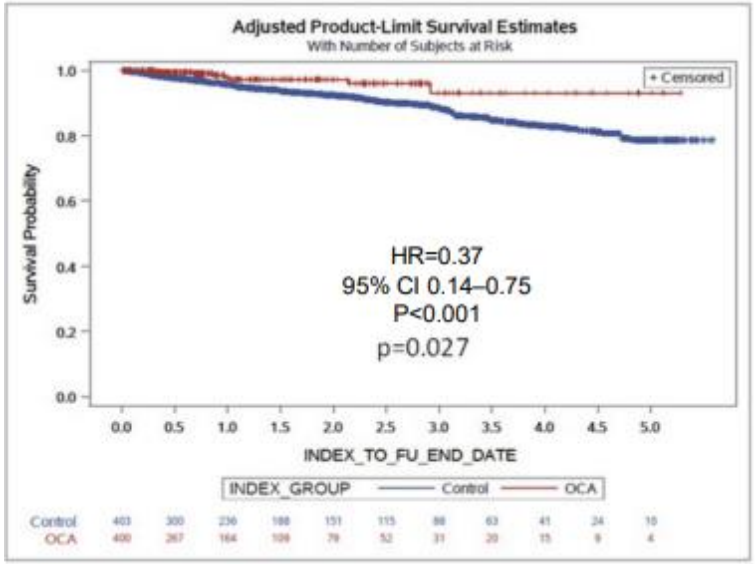
HEROES: Treatment Efficacy of OCA on Hepatic Real-World Outcomes in PBC

- Komodo Health Database
  - Inpatient, outpatient, pharmaceutical dataset
- Treatment effect of obeticholic acid (OCA) on time of first occurrence of death, liver transplant, and/or hepatic decompensation

Hirschfield et al, The Liver Meeting oral presentation 2022

HEROES Study

- 4,535 control patients and 431 OCA treated patients met the inclusion/exclusion criteria (contributing 12,399 and 431 indexes, respectively)
  - OCA treatment resulted in 63% reduction in relative risk of death, liver transplant or hepatic decompensation



Key takeaways

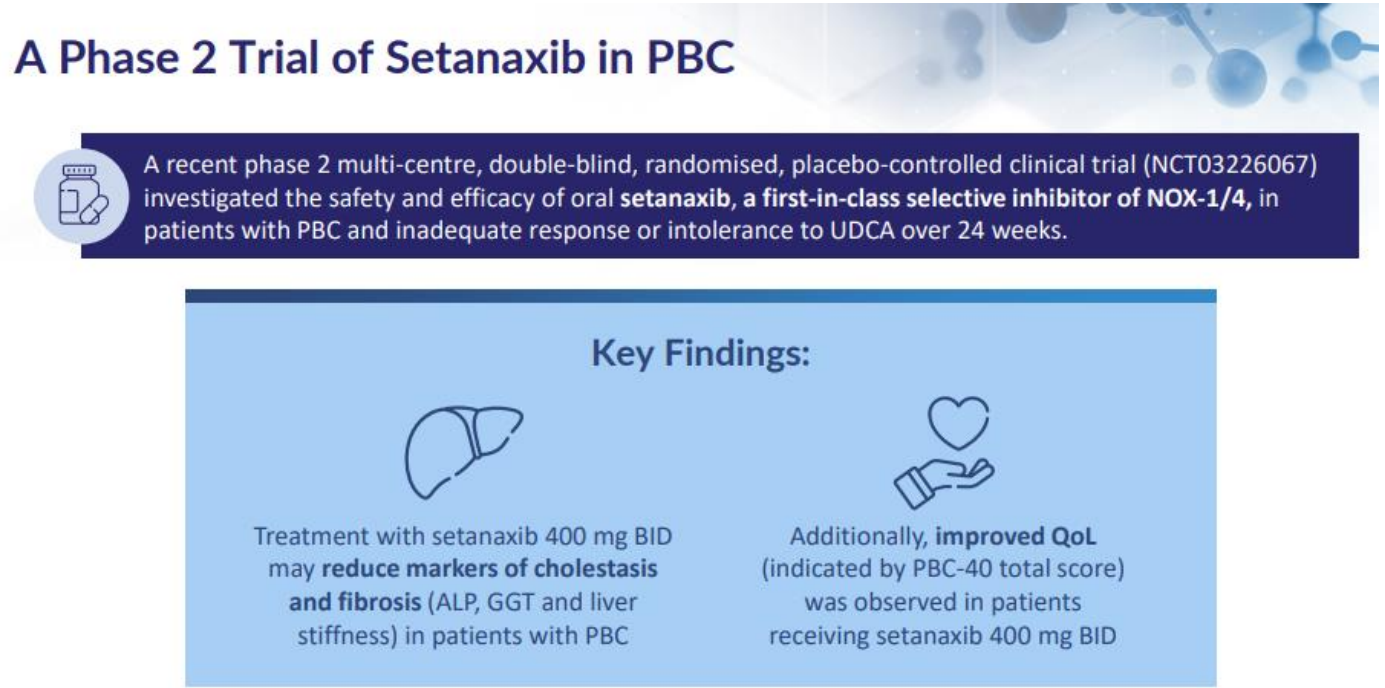
- OCA treatment led to a statistically significant and clinically meaningful 63% reduction in risk for hospitalization for hepatic decompensation, liver transplant, or death compared to non-OCA-treated controls in the real world.
- Real world data with OCA is consistent with the effects in POISE open-label extension and Global PBC Registry external controls.

Hirschfield et al, The Liver Meeting oral presentation 2022

Clinical Endpoints in PBC

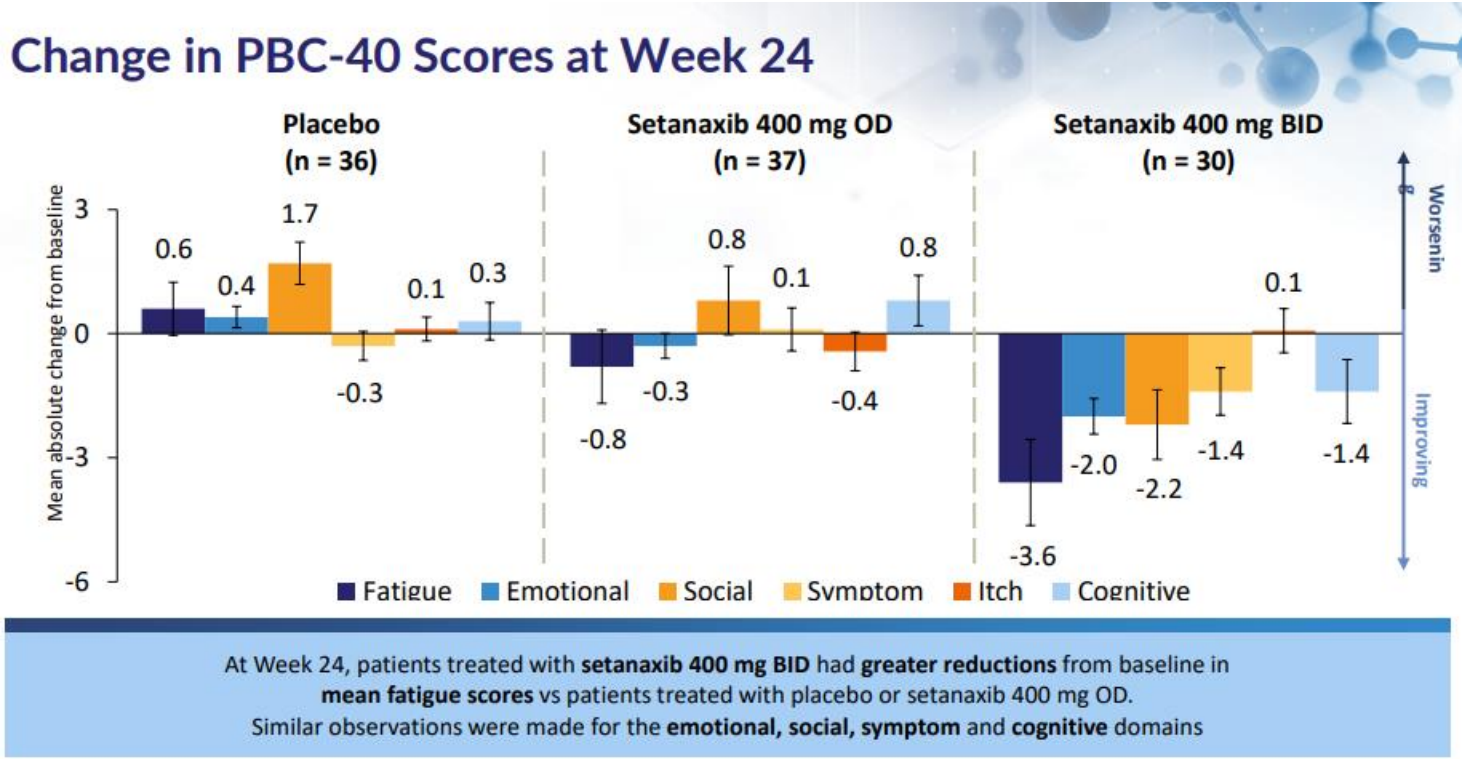
- Liver
  - ALP, Bili, other LFTs, MELD, portal hypertension, hepatic decompensation, liver transplant, death
- Extra-hepatic
  - Fatigue, cognitive, emotional, social

Clinical Trials: NOX-1/4 Selective Inhibitor Trials



Huang JC et al. *Hepatology.* 2019; 70: 777–779.

Clinical Trials: NOX-1/4 Selective Inhibitor Trials

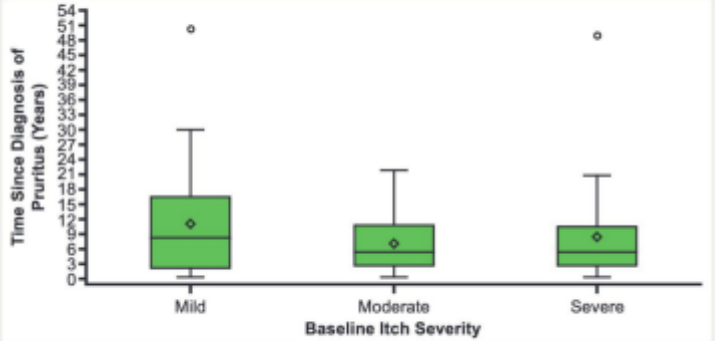


Huang JC et al. *Hepatology.* 2019; 70: 777–779.

Clinical Trials: Treatment of Pruritus in Patients With PBC: Phase 2b GLIMMER Trial

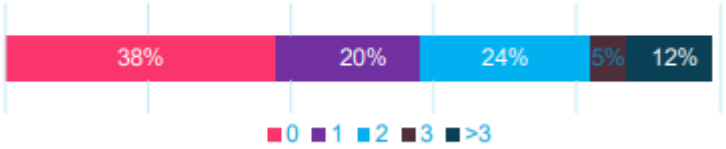
Results:

Figure 1. Duration of pruritus by baseline pruritus severity*

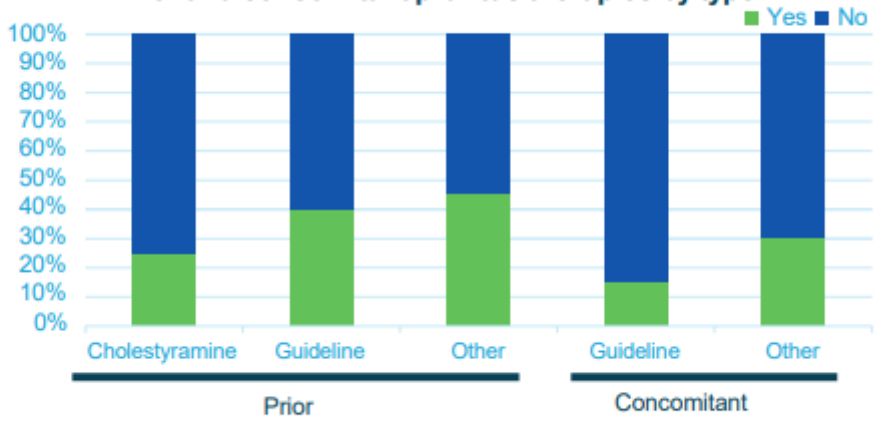


*From the time since diagnosis to the first dose of linerixibat or placebo, a post hoc analysis. Baseline itch severity is derived from mean worst daily itch score which is the average of the worst daily itch score (recorded morning and evening) in the 7 days prior to the baseline visit and further categorized as Mild: <4, Moderate: >=4 to <7, Severe: >=7 to <=10.

Number of prior pruritus treatments



Prior and concomitant pruritus therapies by type



Conclusions:

- Many patients do no receive treatment despite a long history of pruritus
- Currently available treatments have varying levels of efficacy, as suggested by the low uptake of cholestyramine
- Despite being on concomitant itch medications, many patients still reported moderate to severe pruritus
- There is a high unmet need to effective therapies against itch in PBC

GLIMMER: A Randomized Phase 2b Dose-Ranging Trial of Linerixibat in PBC Patients With Pruritus. *CGH*. 2022 Nov 4 S1542-3565.