Mirum Pharmaceuticals Updates: Fibrosis and Bile Acid

PSC FORUM 8

November 14, 2024

Disclosure

I am a full-time employee and shareholder of Mirum Pharmaceuticals.

No additional relationships to disclose.

IBAT Inhibition In Cholestatic Liver Disease

Targeting IBAT Removes Circulating Bile Acids Addressing Toxic Bile Acid Accumulation

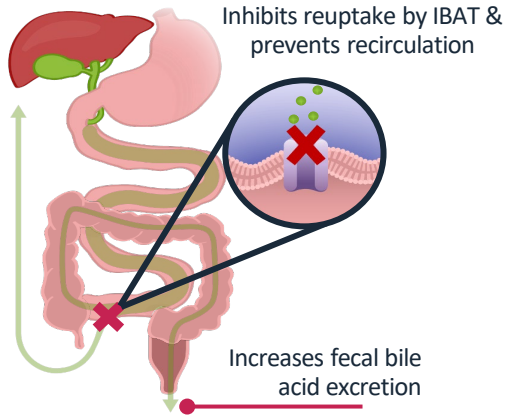
Cholestatic Liver Disease

Defined by impaired bile flow &
Hepatotoxic build-up of bile acids

- **Severe Pruritus**
- **Cellular damage**
- **Poor outcomes**

Targeting IBAT Lowers Bile Acids

Mechanism directly addressing bile acid accumulation



IBAT Inhibition Clinical Benefits[1-5]

- Transplant-free survival
- Quality of Life
- Growth

- Pruritus
- Bilirubin (PFIC)
- Xanthomas (ALGS)

1. Gonzales E et al. *Lancet*. 2021;398:1581-1592. 2. Loomes KM et al. *Hepatol Commun*. 2022;6(9):2379-2390. 3. Thompson R. Serum bile acid control in long-term maralixibat-treated patients is associated with native liver survival in children with progressive familial intrahepatic cholestasis due to bile salt export pump deficiency. Presented at: EASL 2020; August 2020. Accessed April 29, 2021. https://linkinghub.elsevier.com/retrieve/pii/S0168827820307571 4. van Wessel DBE et al. *J Hepatol*. 2021;73(1):84-93.
5. Sokol J, Gonzales E, Kamath BM, et al. Predictors of 6-year event-free survival in patients with Alagille syndrome treated with maralixibat, an IBAT inhibitor. Paper presented at: European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN): Annual Meeting; June 22-25, 2022; Copenhagen, Denmark.

Phase 2b Study of Volixibat in PSC Patients with Cholestatic Pruritus

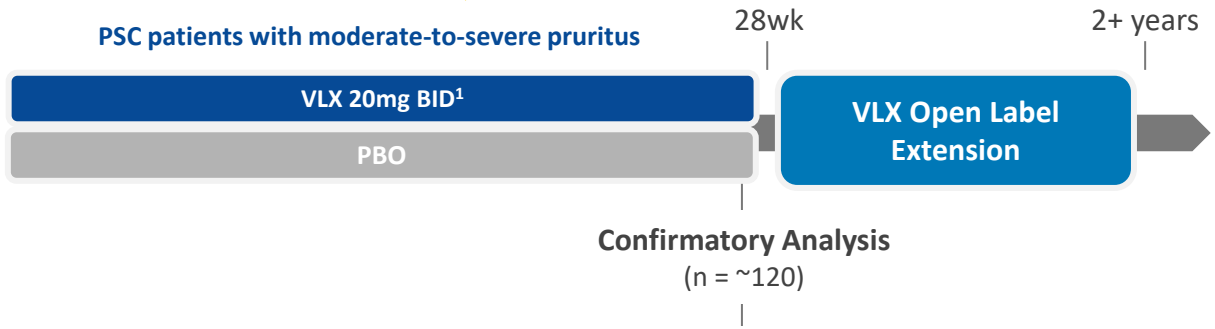
Positive Interim Analysis

Exceeded prespecified efficacy and safety thresholds for continuation

20 mg BID dose selected

VISTAS continues with no changes

vistas
EFFICACY & SAFETY OF VOLIXIBAT IN THE TREATMENT OF CHOLESTATIC PRURITUS IN PATIENTS WITH PSC



Primary Endpoint
Change in pruritus from baseline to 28wk

Enrollment Completion Expected H2 2025

[1] Participants are randomized 1:1 between Volixibat 20mg BID and Placebo

Phase 2b Study of Volixibat in PBC Patients with Cholestatic Pruritus

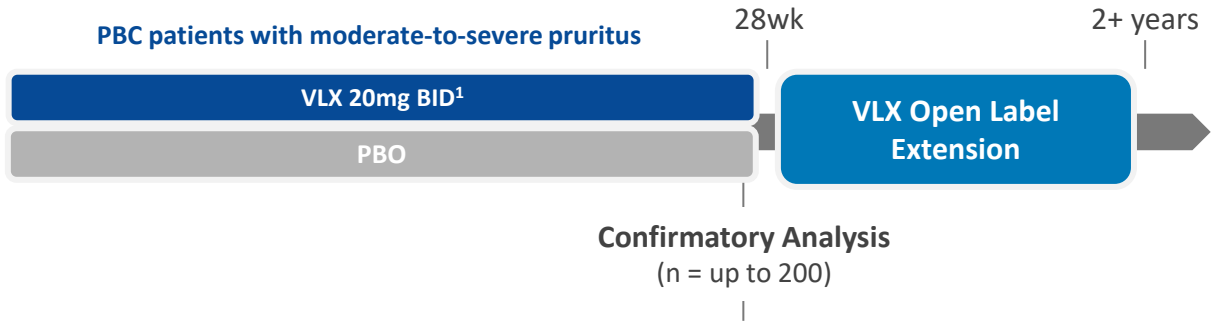
Positive Interim Analysis

Rapid and statistically significant improvement in pruritus

Reductions in sBA and improvements in fatigue

20 mg BID dose selected for confirmatory portion

VANTAGE



Primary Endpoint

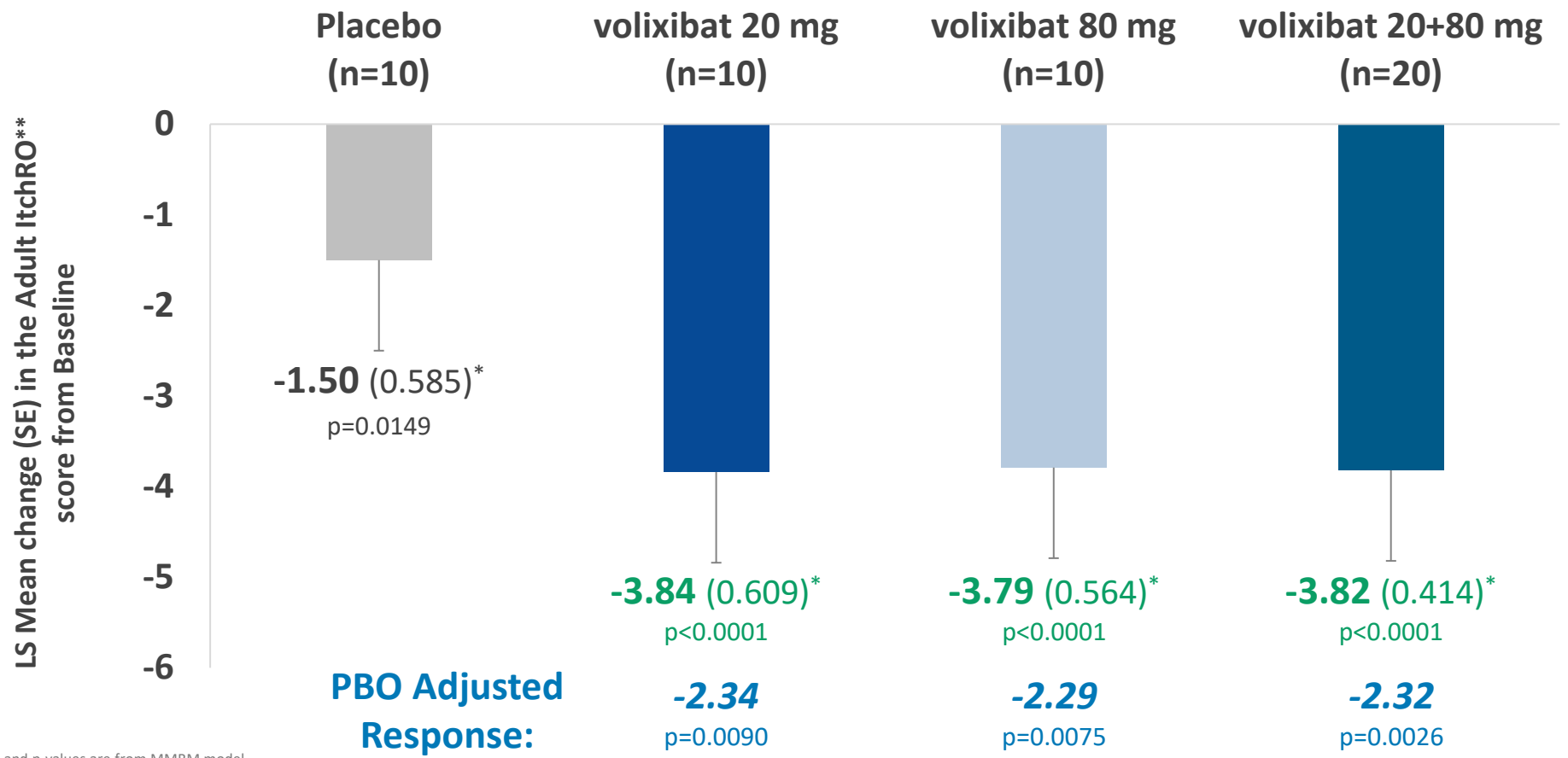
Change in pruritus from baseline to 28wk

Enrollment Completion Expected 2026

[1] Participants are randomized 1:1 between Volixibat 20mg BID and Placebo

VANTAGE Interim Analysis: Reduction in Pruritus from Baseline

RAPID AND STATISTICALLY SIGNIFICANT REDUCTIONS IN PRURITUS

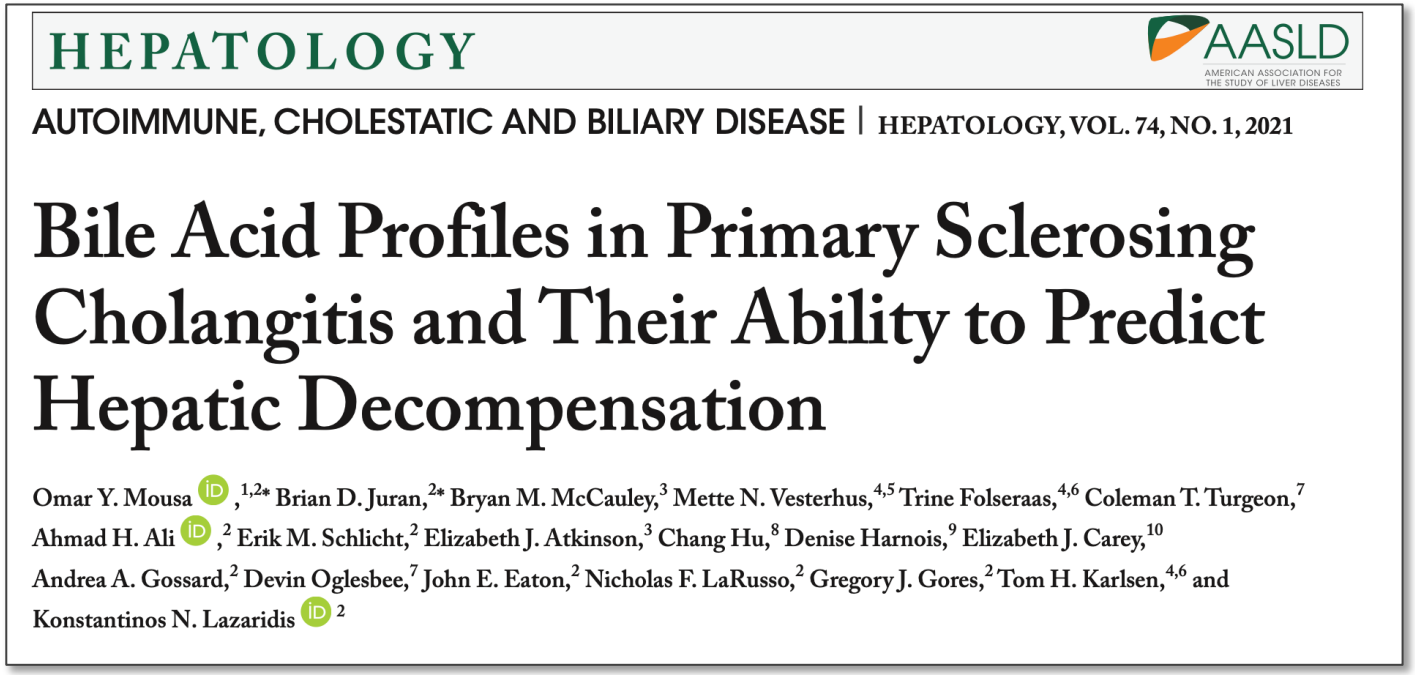


* LS Means (SE), LSMean, SE and p-values are from MMRM model
**Adult ItchRO is a 0-10 numerical rating scale

VANTAGE Interim Analysis: Key Observations

- Significant reduction in pruritus as early as Week 1
- Significant improvements in fatigue at Week 16
- 75% of patients on volixibat achieved >50% reduction in sBA
- No new safety signals:
  - No clinically meaningful changes in liver laboratory tests for patients on volixibat
  - 77% of patients on volixibat experienced diarrhea, all mild to moderate
    - One patient discontinued due to diarrhea
  - 4 patients experienced SAEs, including one in the placebo arm

Potential Role for Bile Acids in Pathogenesis of PSC



HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

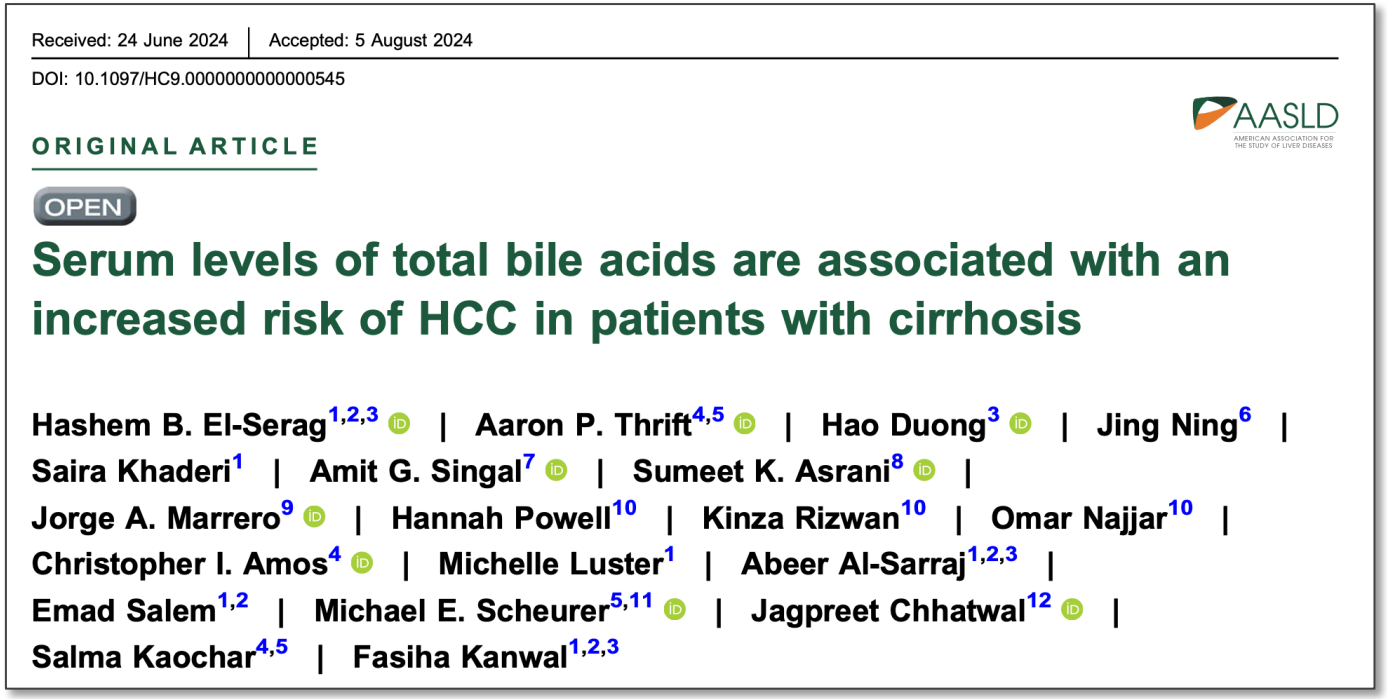
AUTOIMMUNE, CHOLESTATIC AND BILIARY DISEASE | HEPATOLOGY, VOL. 74, NO. 1, 2021

Bile Acid Profiles in Primary Sclerosing Cholangitis and Their Ability to Predict Hepatic Decompensation

Omar Y. Mousa [1,2*] Brian D. Juran,[2*] Bryan M. McCauley,[3] Mette N. Vesterhus,[4,5] Trine Folseraas,[4,6] Coleman T. Turgeon,[7] Ahmad H. Ali [2] Erik M. Schlicht,[2] Elizabeth J. Atkinson,[3] Chang Hu,[8] Denise Harnois,[9] Elizabeth J. Carey,[10] Andrea A. Gossard,[2] Devin Oglesbee,[7] John E. Eaton,[2] Nicholas F. LaRusso,[2] Gregory J. Gores,[2] Tom H. Karlsen,[4,6] and Konstantinos N. Lazaridis [2]

- Looked at 5 year risk of hepatic decompensation (HD) in 400 patients with PSC and 302 controls (derivation cohort) and then validated in 108 patients
- Concentration of total bile acids (C-statistic: 0.80), and specific subspecies was predictive of HD, outperforming cirrhosis, bilirubin and AlkPhos

Bile Acids and HCC



Received: 24 June 2024 | Accepted: 5 August 2024

DOI: 10.1097/HC9.0000000000000545

ORIGINAL ARTICLE

OPEN

Serum levels of total bile acids are associated with an increased risk of HCC in patients with cirrhosis

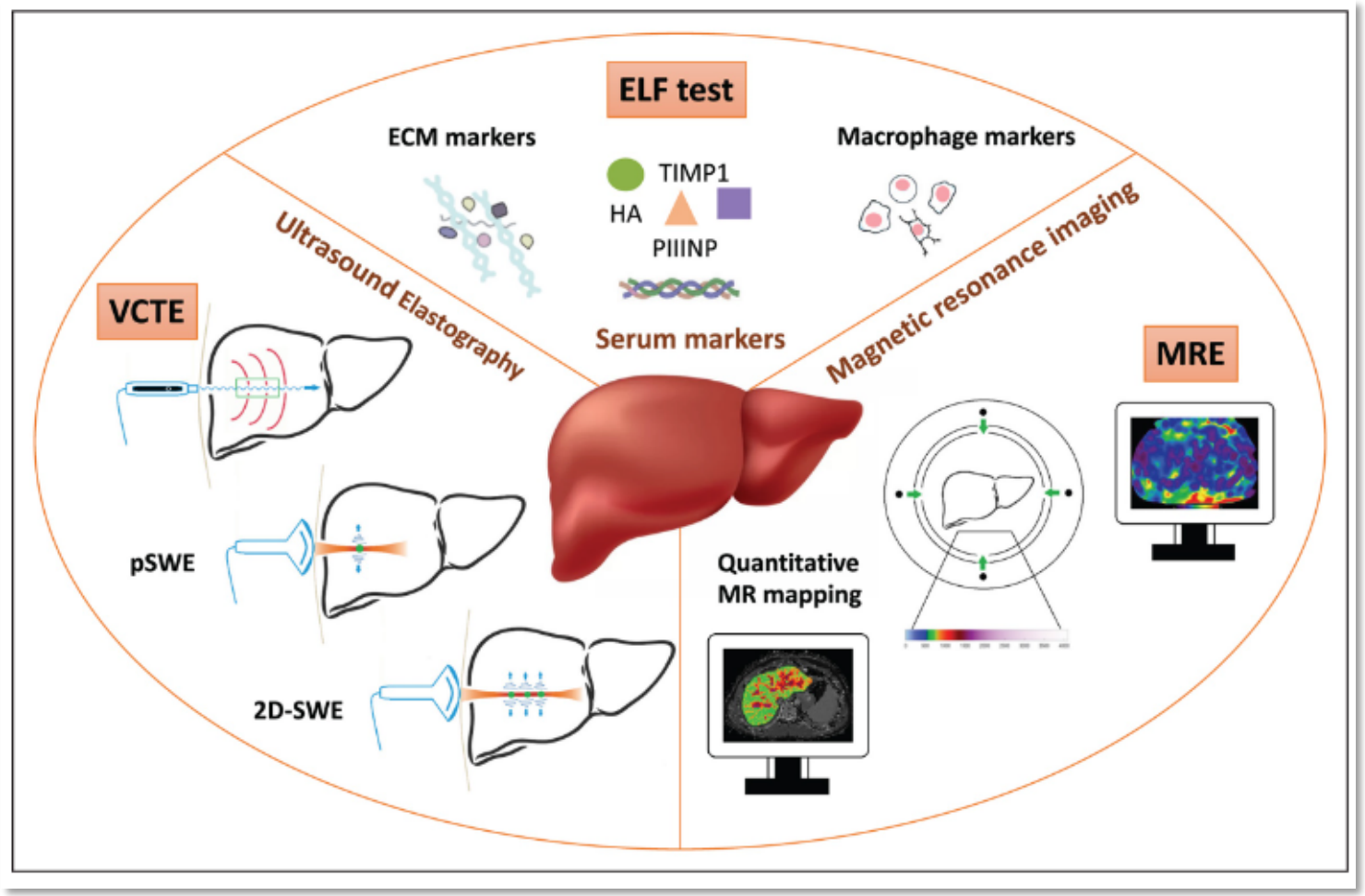
Hashem B. El-Serag[1,2,3] | Aaron P. Thrift[4,5] | Hao Duong[3] | Jing Ning[6] | Saira Khaderi[1] | Amit G. Singal[7] | Sumeet K. Asrani[8] | Jorge A. Marrero[9] | Hannah Powell[10] | Kinza Rizwan[10] | Omar Najjar[10] | Christopher I. Amos[4] | Michelle Luster[1] | Abeer Al-Sarraj[1,2,3] | Emad Salem[1,2] | Michael E. Scheurer[5,11] | Jagpreet Chhatwal[12] | Salma Kaochar[4,5] | Fasiha Kanwal[1,2,3]

- A cohort of 940 patients with cirrhosis (predominantly MASLD, HCV, or alcoholic LD) were followed and incident HCC was determined.
- Higher baseline serum TBA level was significantly associated with an increased risk of developing HCC with an adjusted HR of 3.69 (95% CI = 1.85–7.37) for the highest versus lowest tertile.
- TBA levels significantly increased predictive ability for progression to HCC at 2 years of follow-up; the c statistic increased from 0.74 to 0.80 ($p < 0.001$).

NORDIC BIOSCIENCE

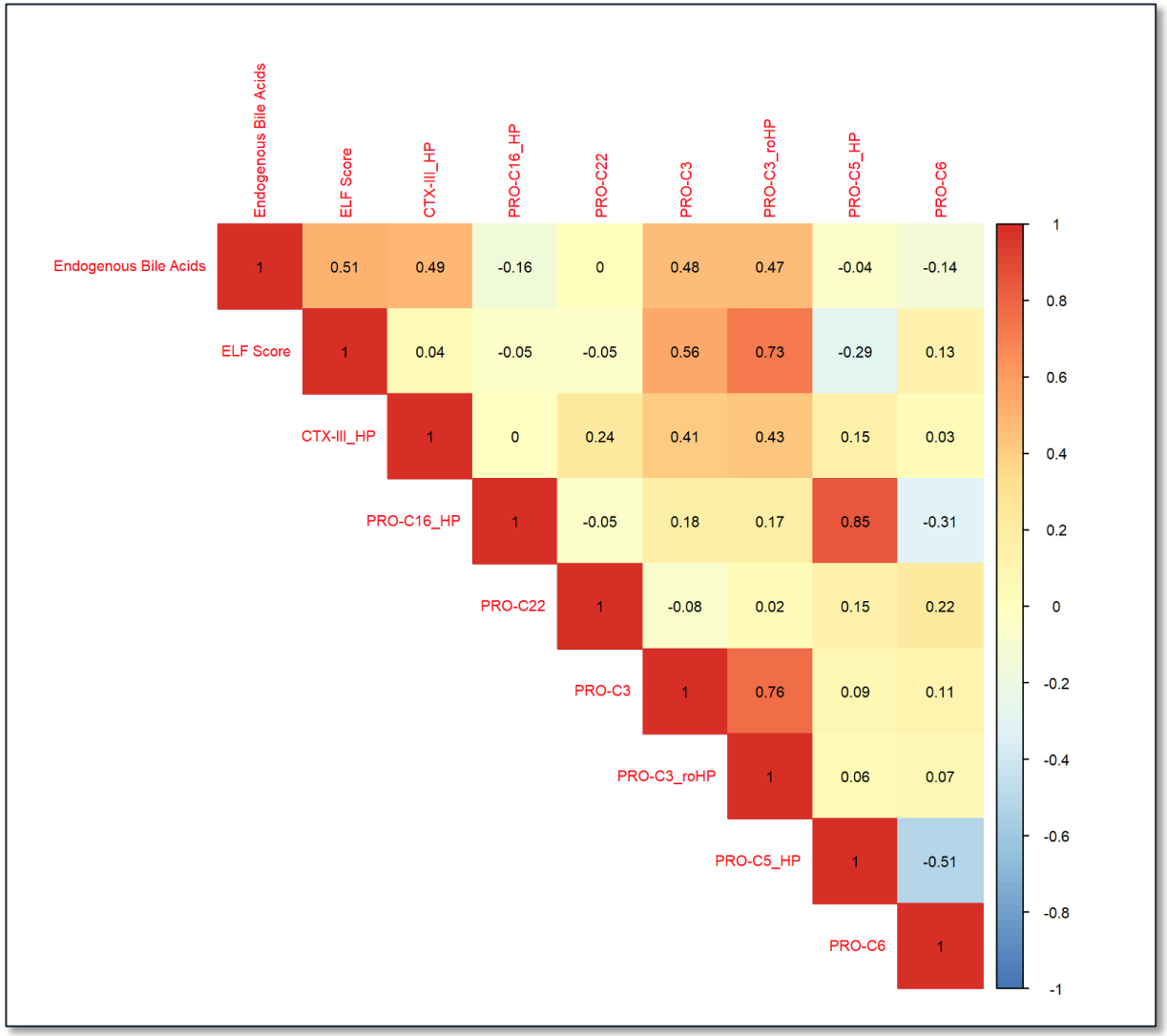
Fibrosis biomarkers

CTX-III_HP
ELF Score
Bile Acids
PRO-C16_HP
PRO-C22
PRO-C3
PRO-C3_roHP
PRO-C5_HP
PRO-C6



Diagnosis/Staging Prognostic for events Endotyping of patients Prediction of Tx effect

Baseline Correlations from Trial of NGM282 in PSC



Biomarker	Output
PRO-C3	Measures the soluble N-terminal (pro-collagen) of Collagen type III, produced during collagen synthesis.
Pro-C5_HP	A fragment of C-terminal type V collagen produced during fibrogenesis.
PRO-C6	A fragment of C-terminal type VI alpha 3 chain, C5 domain collagen
PRO-C8	A fragment of C-terminal type VIII
PRO-C16	A fragment of C-terminal type XVI collagen.
PRO-C18L	N-terminal of type XVIII collagen medium and long isoform of type XVIII collagen.
PRO-C22	A C-terminal fragment of type XXII collagen.
CTX-III (I10)	A crosslinked fragment of collagen type III cleaved by MMP.
C4G	A fragment of type IV collagen released by granzyme-B. Associated with T-cell mediated breakdown of the basement membrane

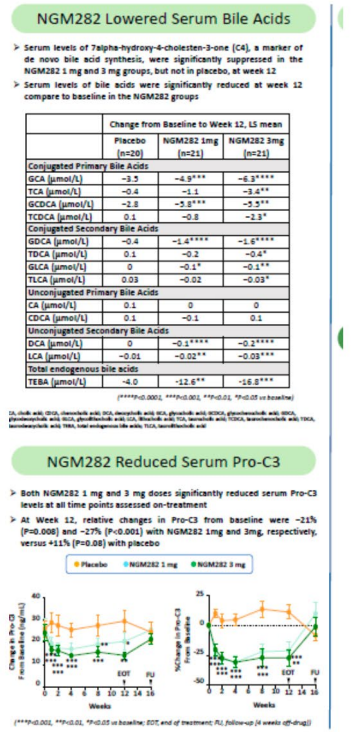
Bile Acids versus Pro-C3 in NGM282

Change in bile acid versus PRO-C3 (PSC)

Serum Bile Acids Correlate with Pro-C3

- Serum concentrations of individual bile acids, and conjugated primary bile acids in particular, significantly correlated with Pro-C3
- The lack of correlation of serum bile acids with C4 likely reflects the adaptive suppression of de novo bile acid synthesis in cholestasis in this patient population

Week 12	Pro-C3		C4	
	P value	P value	r value	P value
Conjugated primary bile acids				
GCA	0.62	<0.0001	−0.03	0.83
TCA	0.52	<0.0001	−0.12	0.37
GCDCA	0.55	<0.0001	−0.25	0.06
TCDCA	0.46	0.0003	−0.28	0.032
Conjugated secondary bile acids				
GDCA	0.31	0.020	0.27	0.038
TDCA	0.28	0.038	0.22	0.09
Unconjugated primary bile acids				
CA	−0.18	0.18	0.09	0.49
CDCA	−0.21	0.12	−0.01	0.92
Unconjugated secondary bile acids				
DCA	−0.06	0.65	0.52	<0.0001



Hirschfield G et al., *J Hepatol*, 2019 Mar;70(3):483-493.

Summary

- Increasing understanding of the role of bile acids as a contributor to cholestatic pruritus in a number of liver disease
- Potential exists for bile acids to contribute to pathogenesis of long-term outcomes in PSC
- Initial evidence suggests possible correlation between bile acids and markers of fibrosis
- Stay tuned…

Thank You