ΣΥΝΟΨΗ AASLD 2023

ΣΑΒΒΑΤΟ 2 ΔΕΚΕΜΒΡΙΟΥ 2023

Αυτοάνοσα – Χολοστατικά νοσήματα ήπατος

Προεδρείο: Μ. Ντόιτς

Ομιλητής: Ν. Μάθου

AASLD
The Liver Meeting®
Nov. 10-14, 2023

80 Countries

7000+ Attendees

5 Days Event

255 Exhibitors

339 Speakers

Cholestasis Debrief

Gideon Hirschfield

Stronger Together

AASLD The Liver Meeting®

Nov. 10-14, 2023

Goal-driven care

1. Prompt and clear diagnosis
2. Personalise therapy to the individual
3. Prevent end-stage liver disease: target normal
4. Manage symptoms
5. Challenge inequity
6. Champion innovation and excellence

G. Hirschfield. Cholestasis debrief, TLM 2023

1

Oral

Effectiveness and Safety of Second-Line therapy in Primary Biliary Cholangitis (PBC). A prospective Real-World Cohort.

Conrado Fernández-Rodríguez

• On behalf of the IBER-PBC Cooperative Group.

1. About 30% of patients with PBC have a suboptimal response to ursodeoxycholic acid (UDCA), leading to a worse prognosis.

2. In the phase III POISE trial, response to Obeticholic Acid (OCA) was assessed by using the POISE score.

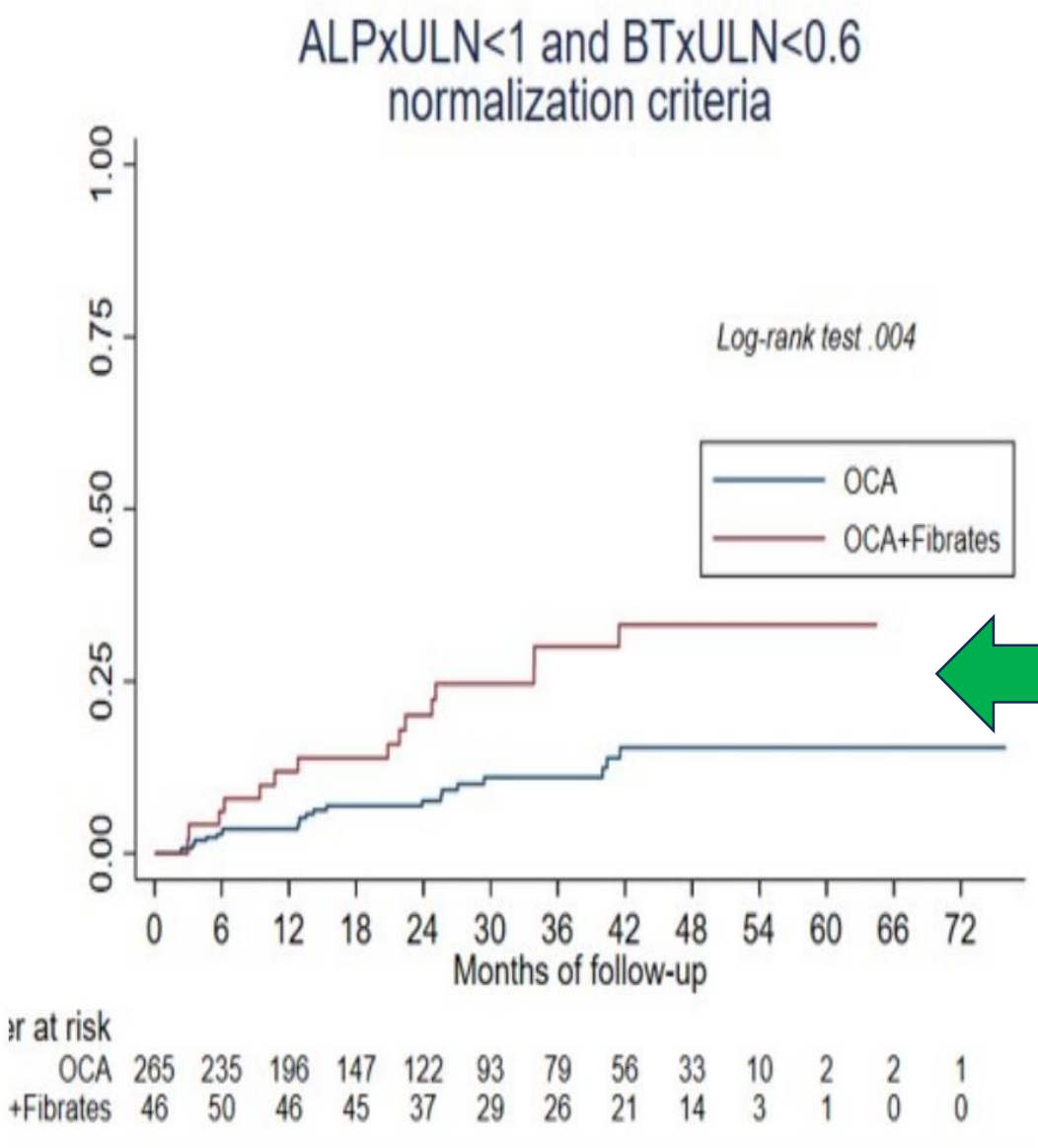
   ALP<1.67 ULN, REDUCTION OF ALP AT LEAST 15% FROM BASELINE, NORMALIZATION BILIRUBIN

3. Complete biochemical response (CBR) (Normal ALP and bilirubin ≤ 0.6 ULN) improves liver-related and overall survival. However, the effectiveness of long-term second-line therapy for this target is uncertain.

Multicenter cohort (24 hospitals from Spain and Portugal) of PBC patients, non-responders to UDCA.

Prospective F-U with periodic retrospective analysis every 6 monts.

- Inclusion: Suboptimal response to UDCA at 12 months (Paris II Criteria), receiving obeticholic acid (OCA) with or without fibrates as second-line treatment.
- Exclusion: Decompensated patients at baseline, previously transplanted patients, or pregnancy.



316pts
f/u: 26.3m (13.3-43.3)

ALP,GGT, TRANSA, BIL decrease ($p<0.01$)
GLOBE PBC & UK-PBC improved ($p<0.01$)

12m: 41.7% POISE response (ITT)

Triple tx more likely to achieve a CBR compared to dual tx

36m: liver related survival 97.3%
OCA discontinuation: 18.2% (5% pruritus)
16/72 cirrhotics decompensate
(all with APRI>0.75)

Conclusions

In this real-world PBC cohort, long-term OCA-based treatment positive outcomes included:

1. Significant biochemical response, improvement in liver function and on the GLOBE and UK-PBC continuous scores.
2. Cumulative POISE score response (more pronounced in non-cirrhotic patients). cumulative biochemical remission, all associated with triple therapy and lower degree of cholestasis.
3. Treatment seems safe in early stages of cirrhosis.

LATE BREAKING ABSTRACTS

Efficacy and safety of elafibranor in primary biliary cholangitis: Results from the ELATIVE™ double-blind, randomized, placebo-controlled phase 3 trial

Christopher L. Bowlus,[1] Kris V. Kowdley,[2,3] Cynthia Levy,[4] Ulus Akarca,[5] Mario Reis Alvares-da-Silva,[6] Pietro Andreone,[7] Marco Arrese,[8] Christophe Corpechot,[9] Sven Francque,[10,11] Michael A. Heneghan,[12] Pietro Invernizzi,[13,14] David Jones,[15] Frederik C. Kruger,[16,17] Eric Lawitz,[18] Marlyn J. Mayo,[19] Mitchell L. Shiffman,[20] Mark G. Swain,[21] José Miguel Valera,[22] Victor Vargas,[23] John M. Vierling,[24] Alejandra Villamil,[25] Carol Addy,[26] Julie Dietrich,[26] Jean-Michel Germain,[27] Sarah Mazain,[28] Dragutin Rafailovic,[27] Bachirou Taddé,[27] Benjamin Miller,[29] Jianfen Shu,[29] Claudia O. Zein,[29] Jörn M. Schattenberg,[30] and the ELATIVE™ Study Group

Full *NEJM* publication now available

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis

K.V. Kowdley, C.L. Bowlus, C. Levy, U.S. Akarca, M.R. Alvares-da-Silva, P. Andreone, M. Arrese, C. Corpechot, S.M. Francque, M.A. Heneghan, P. Invernizzi, D. Jones, F.C. Kruger, E. Lawitz, M.J. Mayo, M.L. Shiffman, M.G. Swain, J.M. Valera, V. Vargas, J.M. Vierling, A. Villamil, C. Addy, J. Dietrich, J.-M. Germain, S. Mazain, D. Rafailovic, B. Taddé, B. Miller, J. Shu, C.O. Zein, and J.M. Schattenberg

USA
Ana Corregidor, Victor Ankoma-Sey, Walid Ayoub, **Christopher Bowlus**, Stephen Caldwell, Hany Elbeshbeshy, Lisa Forman, Michael Galambos, Reem Ghalib, Richard Gilroy, Stuart Gordon, Ira Jacobson, Saro Khemichian, **Kris Kowdley**, Karen Krok, Marcelo Kugelmas, Sonal Kumar, **Eric Lawitz**, **Cynthia Levy**, **Marlyn Mayo**, Ashwini Mehta, Abdullah Mubarak, Andrew Muir, Anthony Post, Daniel Pratt, Mordechai Rabinovitz, Ravi Ravinuthala, Don Rockey, Peter Ruane, Mark Russo, David Sass, Andrew Scanga, **Mitchell Shiffman**, Marina Silveira, Dharmendra Verma, **John Vierling**, Kidist Yimam

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Nabiha Faisal, **Mark Swain**, Catherine Vincent

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Laura Ladron De Guevara

Brazil
Mario Reis Alvares-da-Silva, Eduardo Cancado

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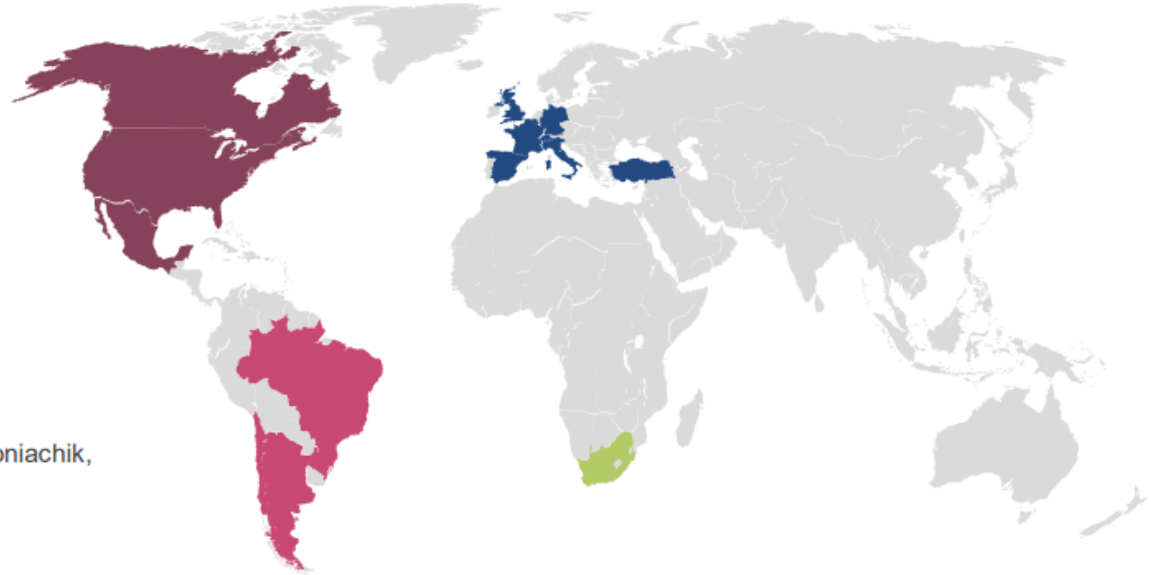
Marco Arrese, Gabriel Mezzano, Teller Jaime Poniachik, **José Miguel Valera**

Argentina
Raul Adrover, Fernando Bessone, Luis Colombato, Adrian Gadano, Omar Galdame, **Alejandra Villamil**

UK
Kuldeep Cheent, Lindsey Corless, **Michael Heneghan**, **David Jones**, Roger McCorry, George Mells, David Sheridan

France
Christophe Corpechot, Alexandra Heurgue, Marie-Noelle Hilleret, Vlad Ratziu, Philippe Sogni



South Africa
Frederik Kruger, Naayil Rajabally, Mark Sonderup

Belgium
Sven Francque, Christophe Moreno, Xavier Verhelst

Germany
Heike Bantel, Holger Hinrichsen, Wolf-Peter Hofmann, Tobias Müller, **Jörn Schattenberg**, Ingolf Schiefke, Kathrin Sprinzl

Switzerland
Susana Gomes Rodrigues, Benedetta Terziroli Beretta-Piccoli

Spain
Javier Ampuero, Jose Luis Calleja Panero, Alvaro Diaz Gonzalez, Maria Carlota Londono-Hurtado, Antonio Olveira Martin, Magdalena Salcedo Plaza, Juan Turnes, **Victor Vargas**

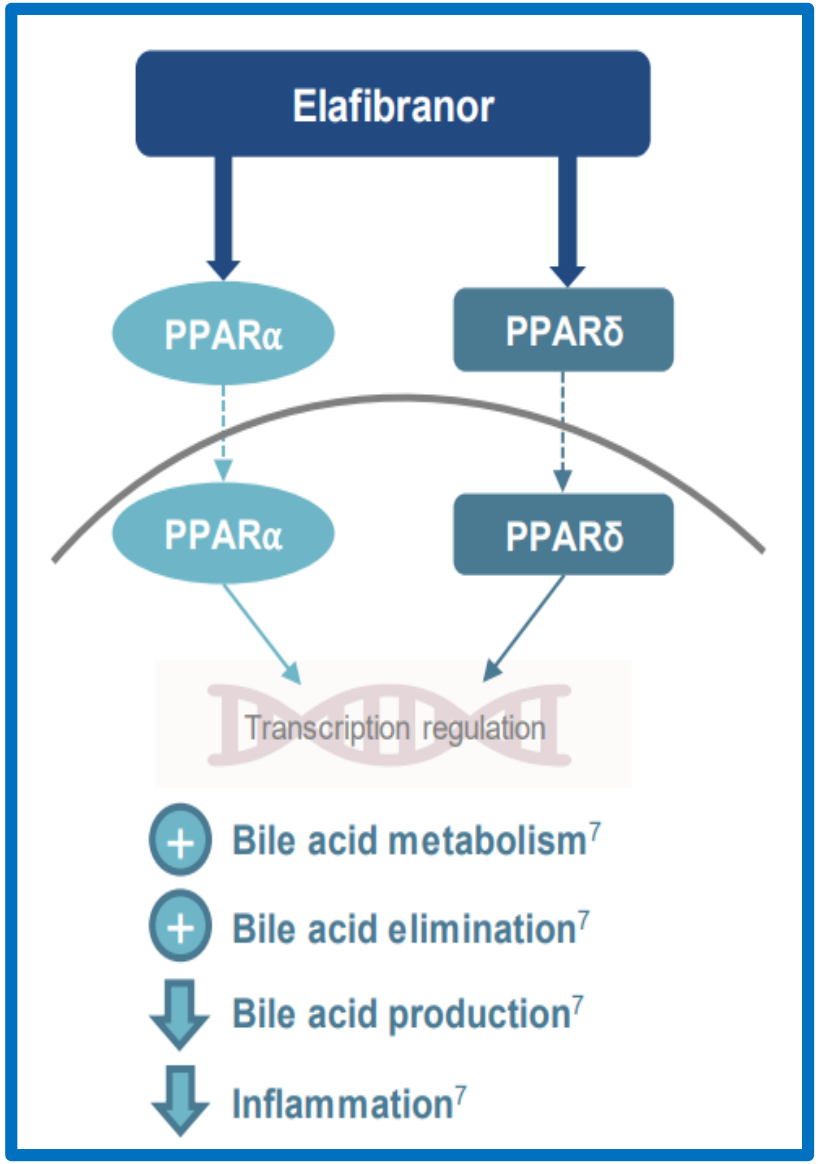
Italy
Pietro Andreone, Vincenza Calvaruso, **Pietro Invernizzi**, Luigi Muratori

Turkey
Ulus Akarca, Yasemin Balaban, Yusuf Yilmaz

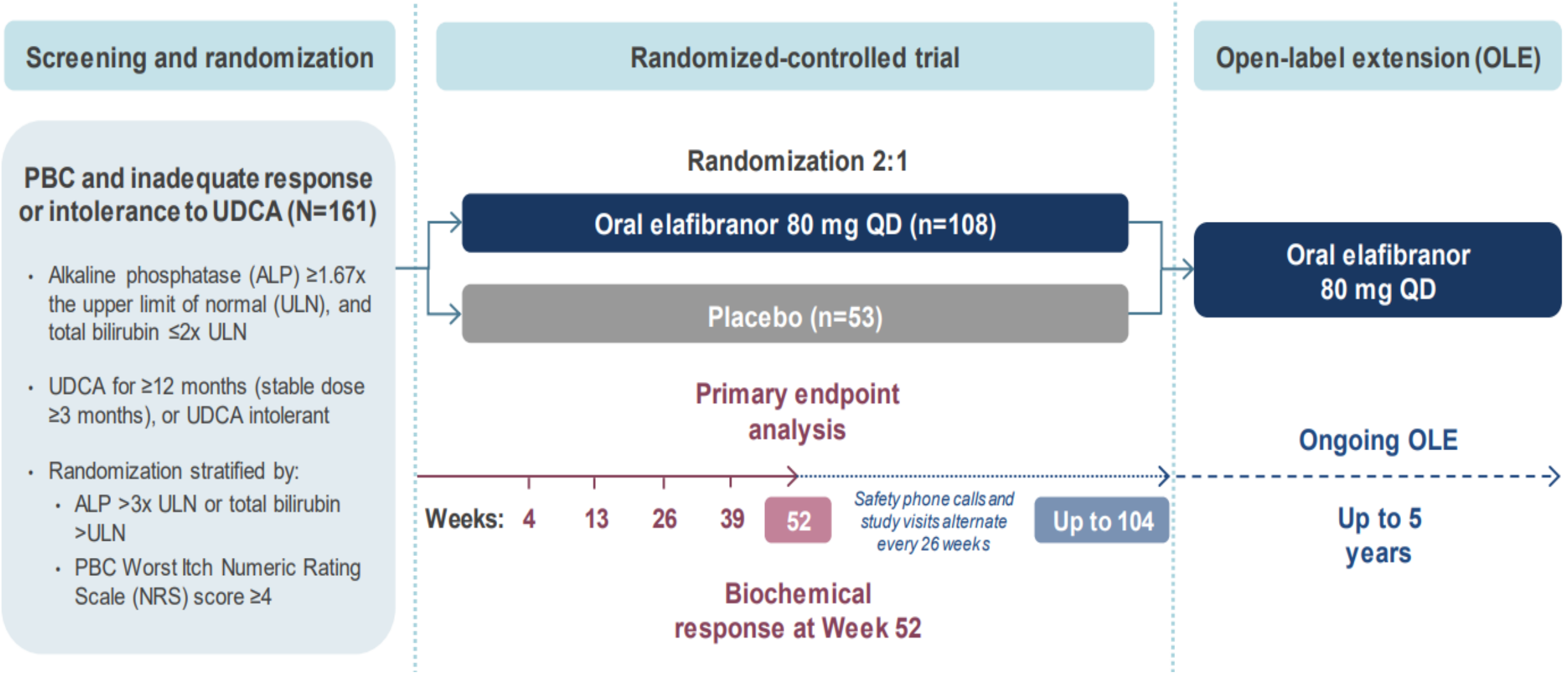
Background

First-line: UDCA	Second-line: OCA
Up to **40%** of patients have an inadequate response[4]	Over **50%** of patients have an inadequate response[6]
3–5% are intolerant[5]	**Pruritus** may be exacerbated[6]

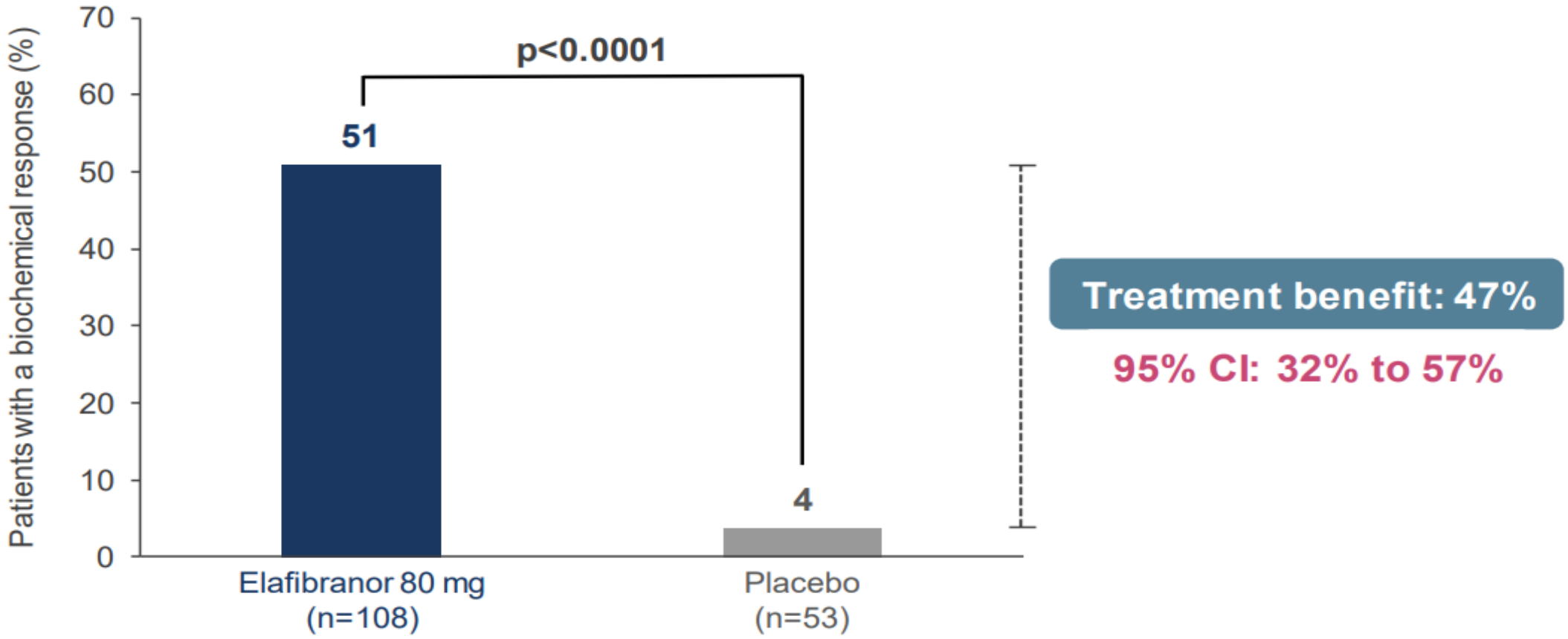
- **Fibrates** (peroxisome proliferator-activated receptor [PPAR] agonists) are also used off-label as second-line treatment[2]



ELATIVE™ aimed to evaluate the **efficacy and safety of elafibranor** in adult patients with PBC with an **inadequate response or intolerance to UDCA**



Treatment with elafibranor led to a significant improvement in biochemical response at Week 52



Biochemical response was defined as a composite of ALP <1.67x ULN, with a reduction of ≥15% from baseline, and total bilirubin at or below the ULN

Conclusions

Treatment with elafibranor led to a **significant improvement in biochemical response** compared with placebo at Week 52 (**51% vs 4%; treatment benefit 47%**)

- Reductions in ALP were **rapid and sustained** through Week 52
- Only patients treated with elafibranor achieved **ALP normalization**

Greater reductions in PBC-40 and 5-D Itch scores suggest that elafibranor may improve moderate-to-severe pruritus in patients with PBC

Elafibranor was generally **well tolerated** with an acceptable safety profile

Conclusions	Treatment with **elafibranor** led to significant improvement in **biochemical response**, along with **potential anti-pruritic benefits,** and was **generally well tolerated** Elafibranor may provide an effective new **treatment for patients with PBC**

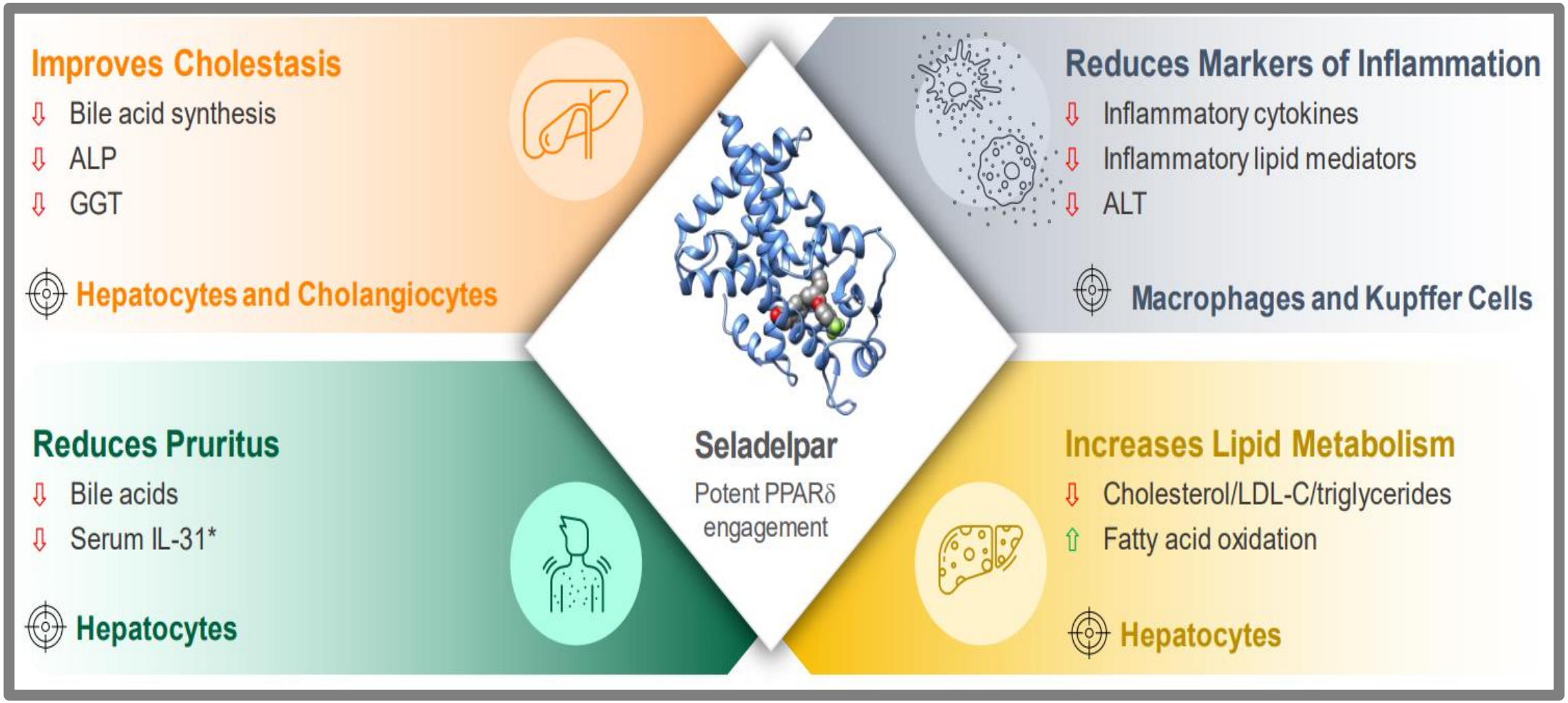
Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis in the RESPONSE Trial:

A Phase 3 International, Randomized, Placebo-Controlled Study

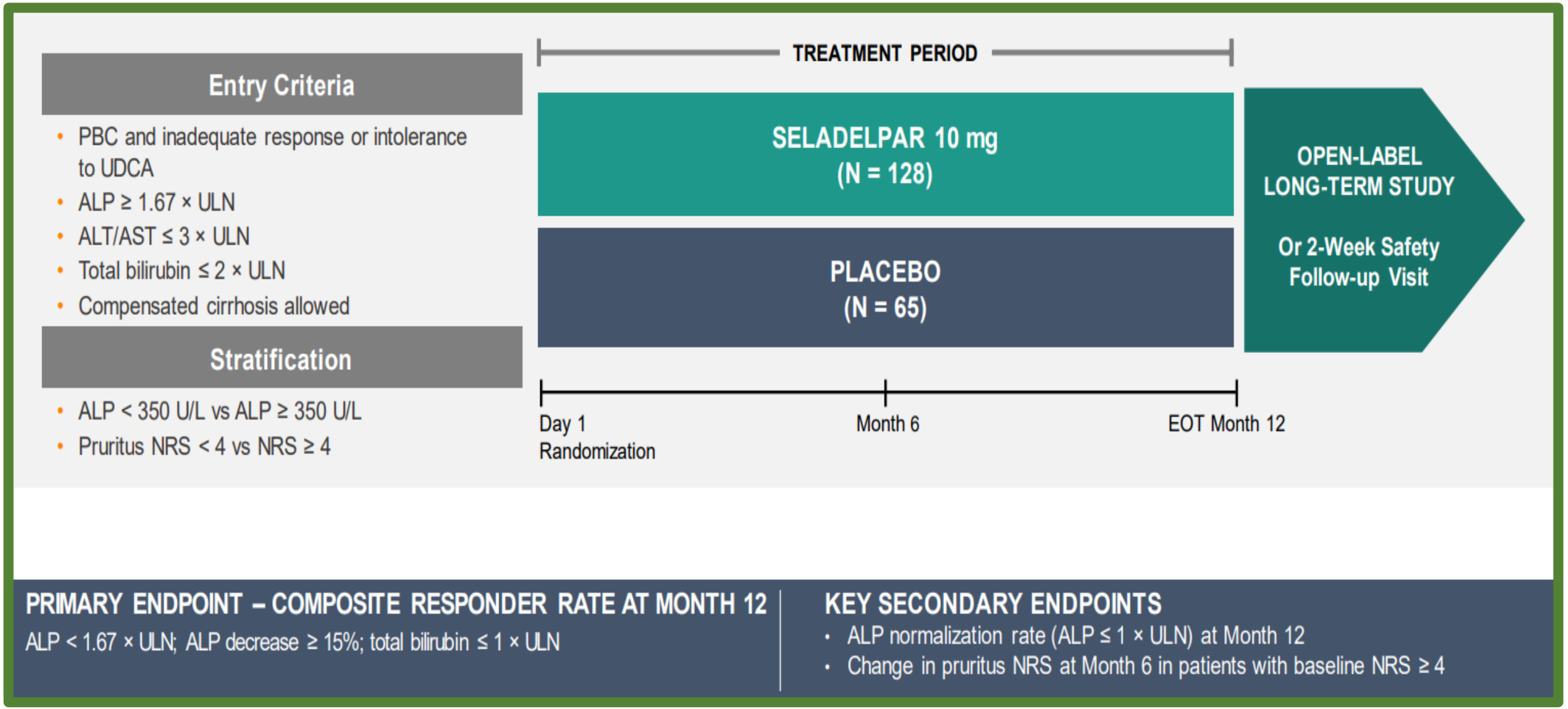
Gideon M. Hirschfield,[1] Christopher L. Bowlus,[2] Marlyn J. Mayo,[3] Andreas E. Kremer,[4] John M. Vierling,[5] Kris V. Kowdley,[6] Cynthia Levy,[7] Susheela Carroll,[8] Ke Yang,[8] Yun-Jung Choi,[8] Daria B. Crittenden,[8] Charles A. McWherter,[8] the RESPONSE Study Investigators

Seladelpar

First-in-Class, Potent, Selective Delpar (PPARδ Agonist) Targeting Multiple Cell Types and Processes in PBC

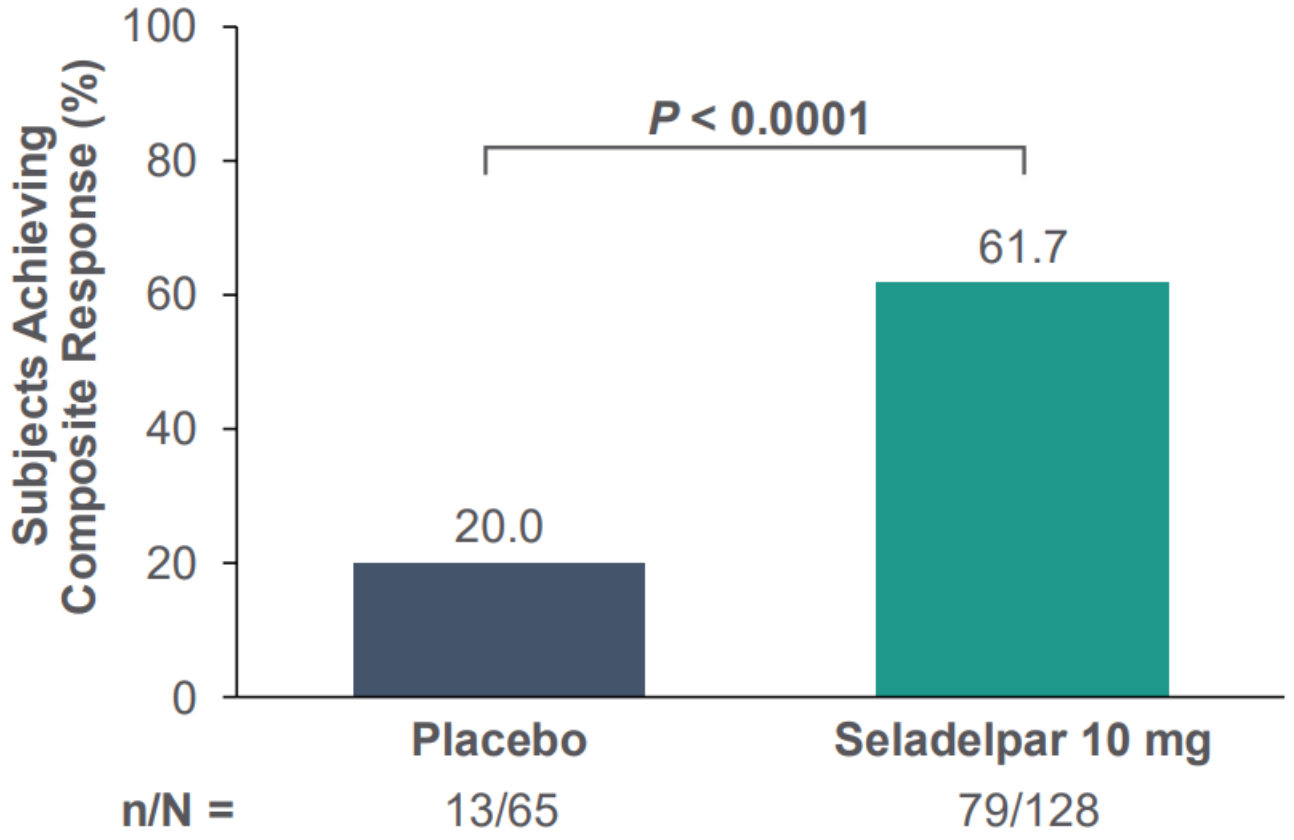


RESPONSE: Phase 3 Study Design



Primary Endpoint: Month 12 Composite Biochemical Response

ALP < 1.67 × ULN, ≥ 15% Decrease in ALP, Total Bilirubin ≤ ULN

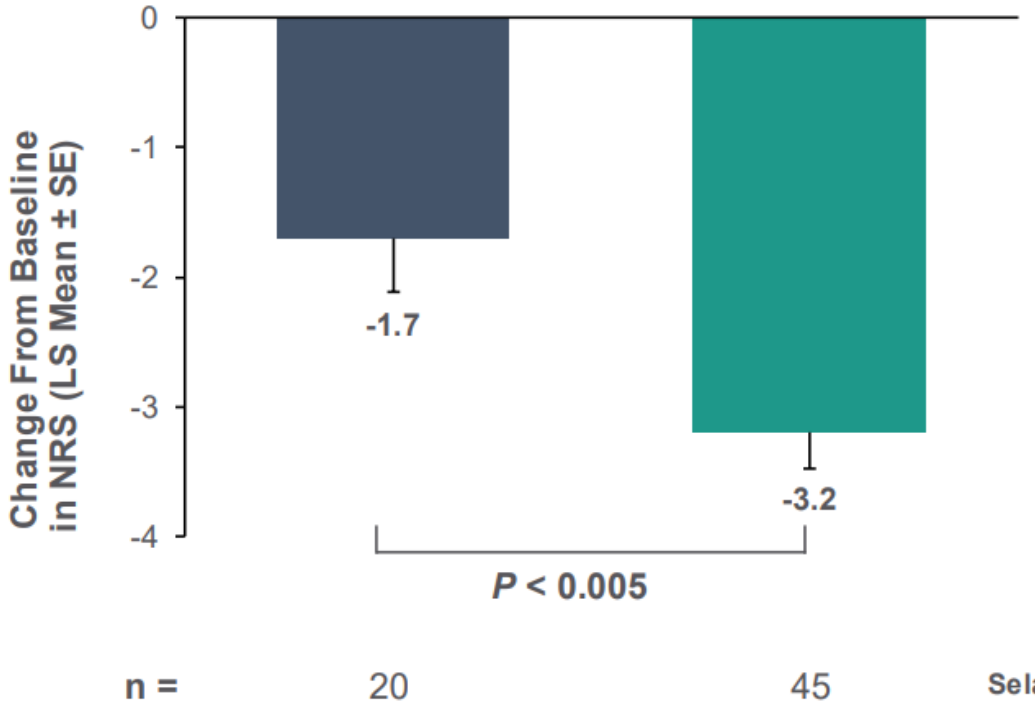


Approximately 6 in 10 patients achieved the biochemical composite response at Month 12

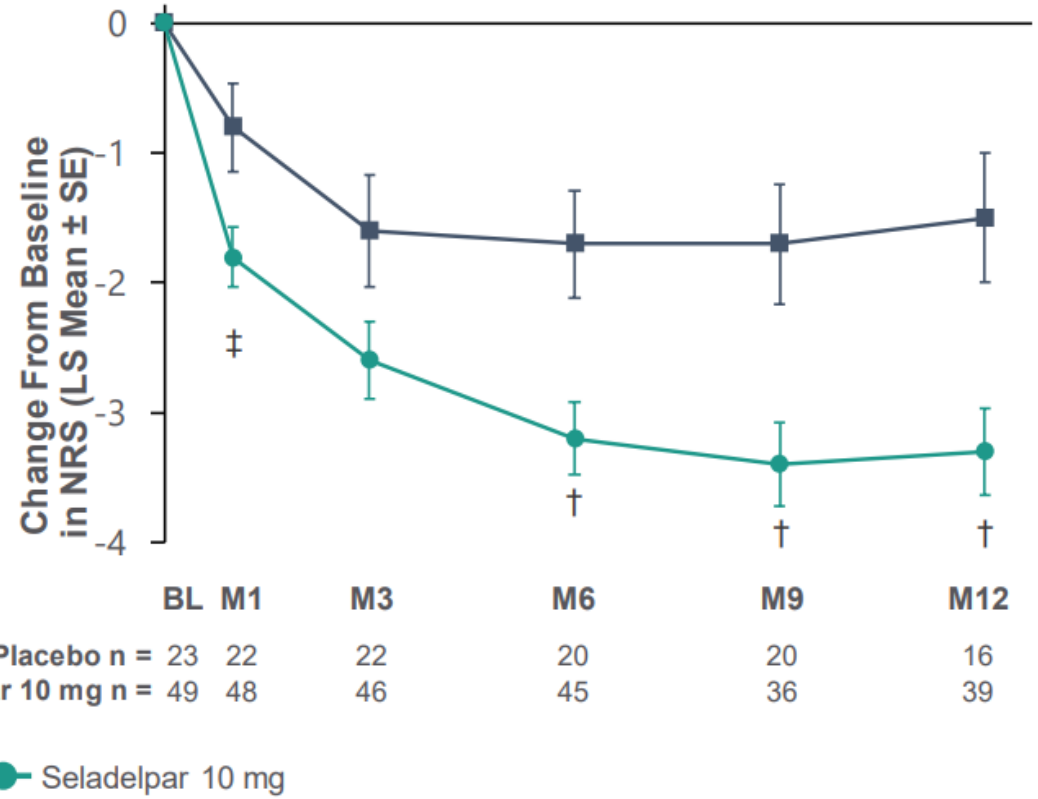
Seladelpar Significantly Improved Pruritus

Subjects With Baseline NRS ≥ 4

Key Secondary Endpoint: Change in Pruritus NRS at Month 6



Change in Pruritus NRS Over Time



The RESPONSE Phase 3 Study Met Both Primary and Key Secondary Endpoints

Seladelpar Improved Markers of Disease Activity and Pruritus in Patients With PBC

- **Significantly more patients met the composite biochemical endpoint and ALP normalization with seladelpar vs placebo at Month 12**
  - Approximately 6 in 10 patients met the primary composite endpoint
  - Approximately 1 in 4 patients met the key secondary endpoint of ALP normalization
  - Mean reduction in ALP was 42% or 133.9 U/L at Month 12
- **The improvement in pruritus at Month 6 in patients with moderate to severe itch was highly statistically significant**
- **In the overall population, seladelpar reduced pruritus as well as the pruritogenic cytokine IL-31 through Month 12**
- **Treatment with seladelpar decreased ALT, GGT, triglycerides, and LDL cholesterol**
- **Seladelpar appeared safe and well tolerated**

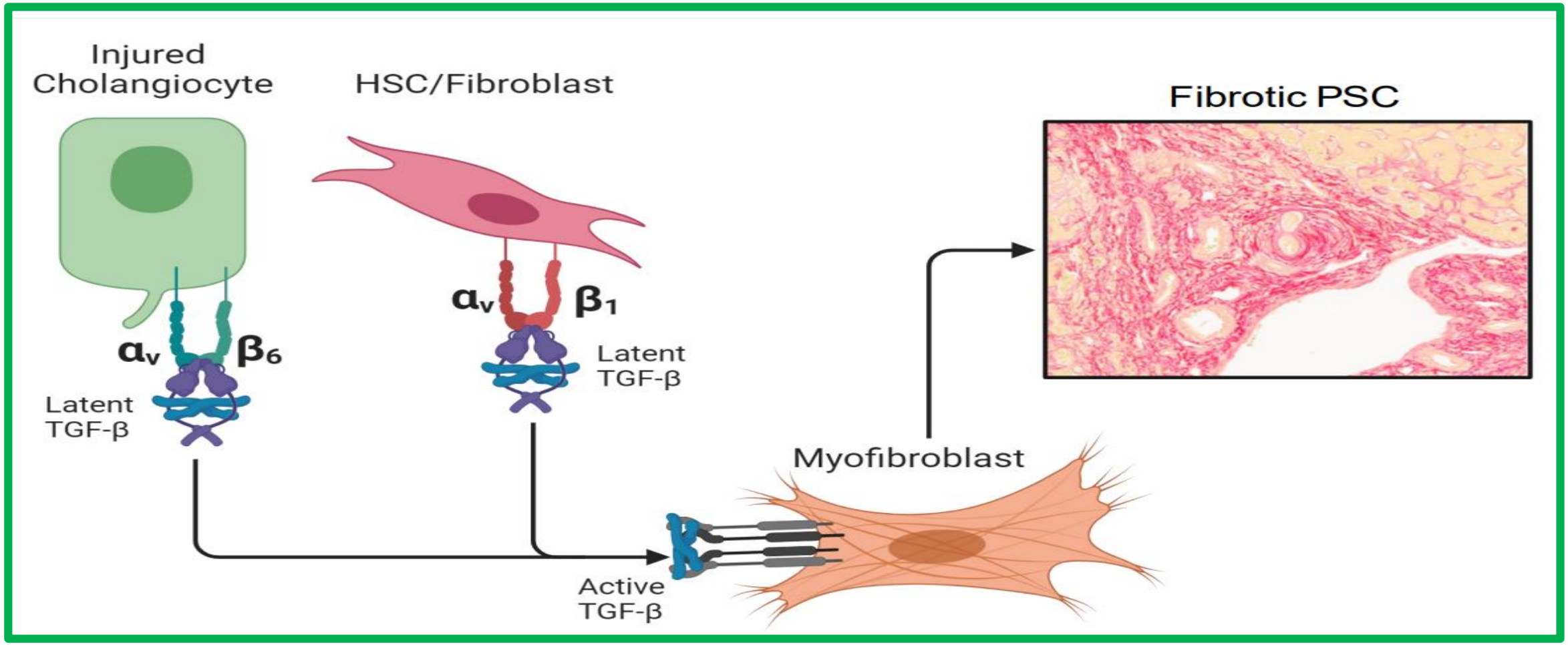
LATE BREAKING ABSTRACTS

Oral $\alpha_v\beta_6/\alpha_v\beta_1$ Integrin Inhibition in Primary Sclerosing Cholangitis: 12-week Interim Safety and Efficacy Analysis of INTEGRIS-PSC, A Phase 2a Trial of Bexotegrast

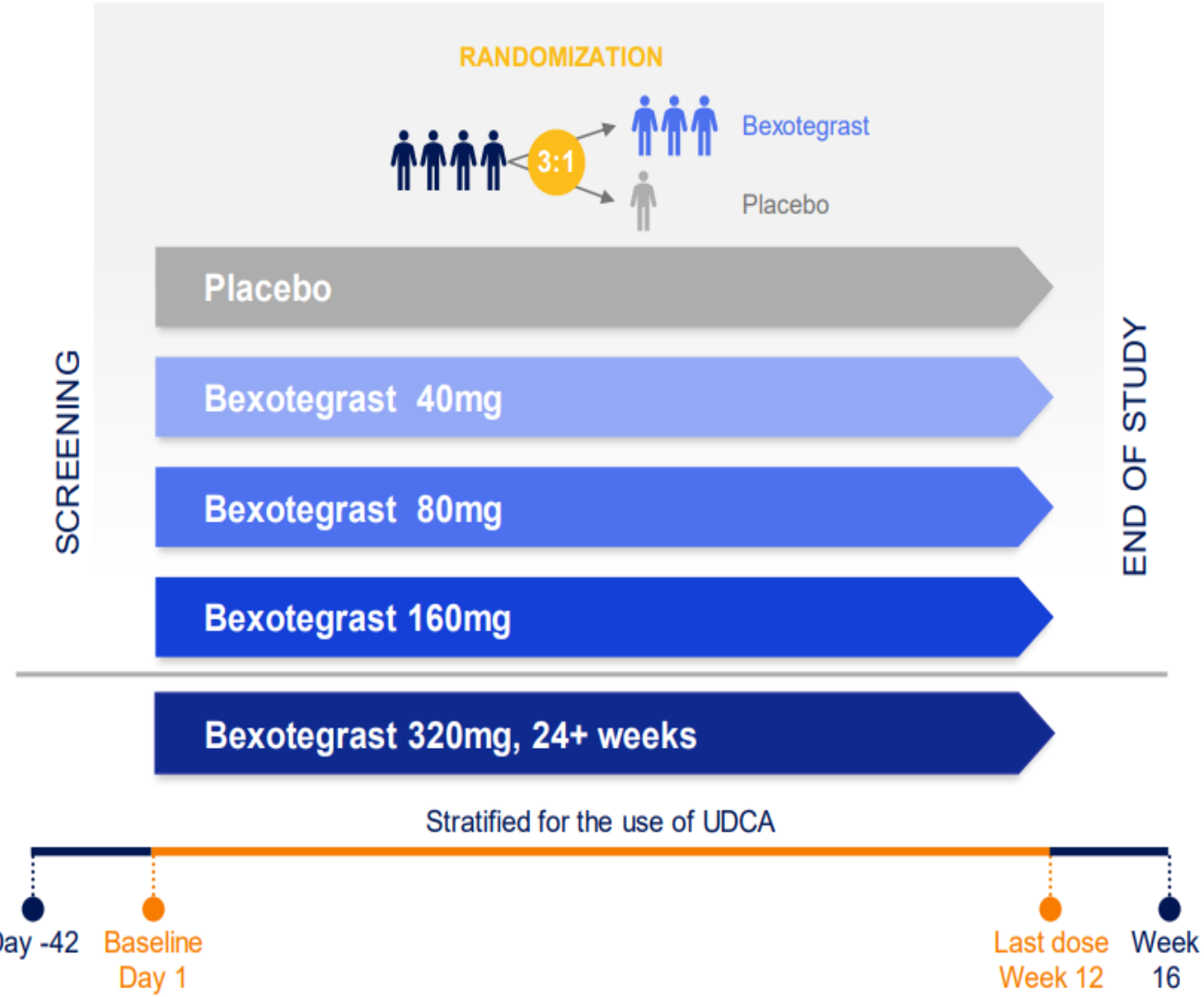
Gideon M. Hirschfield[1], Kris V. Kowdley[2,3], Michael Trauner[4], Palak J. Trivedi[5], Éric A. Lefebvre[6], Johanna Schaub[6], Martin Decaris[6], Annie Clark[6], Theresa Thuener[6], Hardean E. Achneck[6], Chris N. Barnes[6], Richard Pencek[6], Aldo J. Montano-Loza[7], Christopher L. Bowlus[8], Christoph Schramm[9] and Cynthia Levy[10]

[1]Toronto Centre for Liver Disease, Toronto General Hospital, University of Toronto, Toronto, ON, Canada, [2]Liver Institute Northwest, Seattle, WA, [3]Elson S. Floyd College of Medicine, Washington State University, Seattle, WA, USA, [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Austria [5]National Institute of Health Research Birmingham Biomedical Research Centre, Centre for Liver and Gastrointestinal Research, University of Birmingham, Birmingham, UK, [6]Pliant Therapeutics, Inc, South San Francisco, CA, United States, [7]University of Alberta, Edmonton, AB, Canada, [8]University of California Davis, Sacramento, CA, [9]University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, [10]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA

$\alpha_v\beta_6$ / $\alpha_v\beta_1$ Integrins Promote Biliary Fibrosis by Activating TGF-β



localized TGF-β inhibition in the fibrotic liver may provide a novel approach to treat PSC, without affecting TGF-β signaling systemically



PRIMARY AND SECONDARY ENDPOINTS

- Safety and tolerability
- Pharmacokinetics[a]

EXPLORATORY ENDPOINTS

- Change in liver fibrosis markers: ELF score and PRO-C3
- Change in gadoxetate-enhanced MR parameters (voluntary sub-study)
- Change in ALP
- Change in Itch NRS

INCLUSION

- Large duct PSC
- **Suspected liver fibrosis (moderate to severe) with at least one of the following:**
  - ELF score ≥7.7
  - Transient elastography ≥8 to ≤14.4 kPa
  - MR elastography ≥2.4 to ≤4.9 kPa
  - Historical liver biopsy showing fibrosis without cirrhosis
- Stable IBD, if present
- UDCA dose allowed up to <25 mg/kg/day

In this Interim Analysis of INTEGRIS-PSC which Evaluated Oral $\alpha_v\beta_6/\alpha_v\beta_1$ Integrin Inhibition with Bexotegrast in PSC:

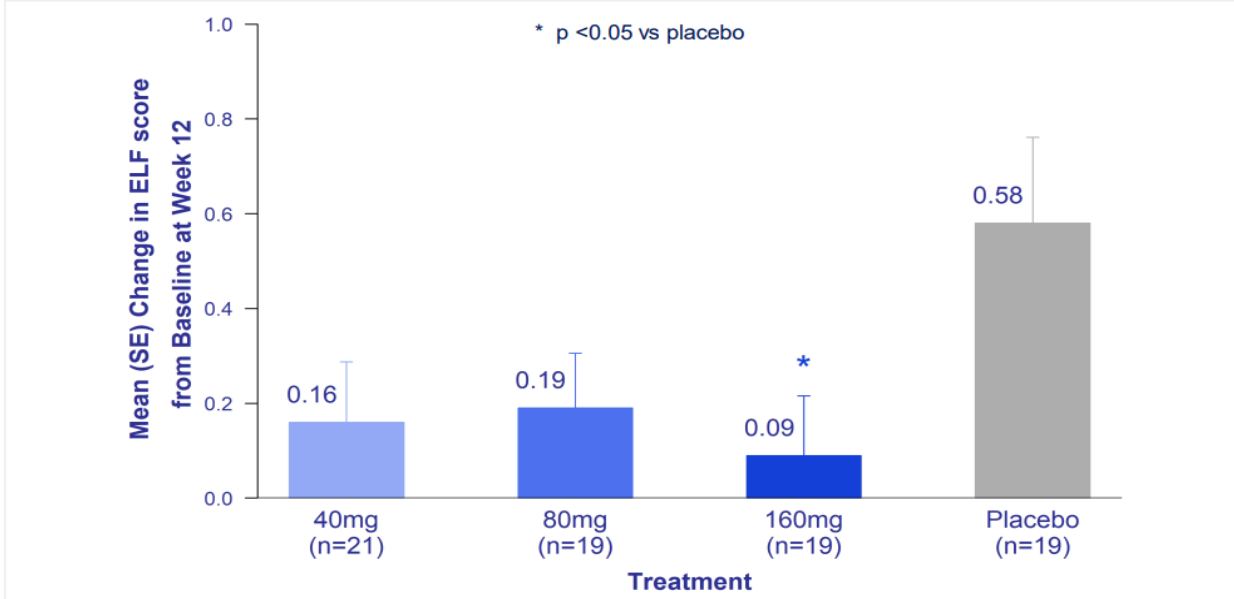
Bexotegrast was well tolerated over 12 weeks of treatment

- Adverse events rates were comparable to placebo with all drug-related events mild or moderate in severity
- Low rate of discontinuation due to adverse events and no treatment-related severe or serious AEs

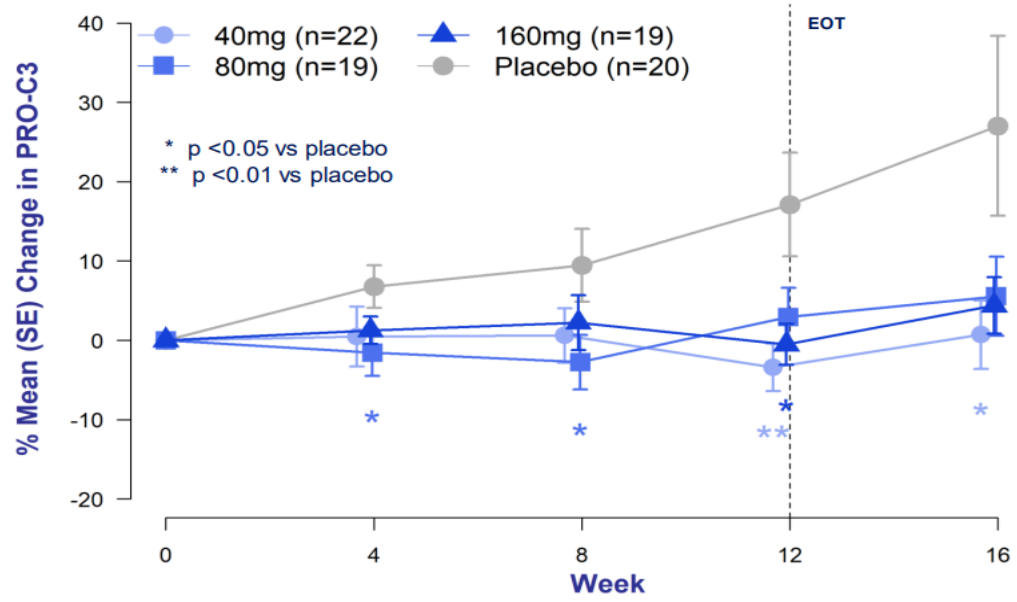
Bexotegrast reduced changes in serum biomarkers of liver fibrosis in a PSC population with suspected moderate to severe liver fibrosis

- Exploratory endpoints demonstrated all doses reduced changes in ELF scores and collagen synthesis (PRO-C3) relative to placebo with a statistically significant differences for both observed with 160mg
- Exploratory MR imaging analysis suggested improved hepatocyte function and bile flow relative to placebo at Week 12

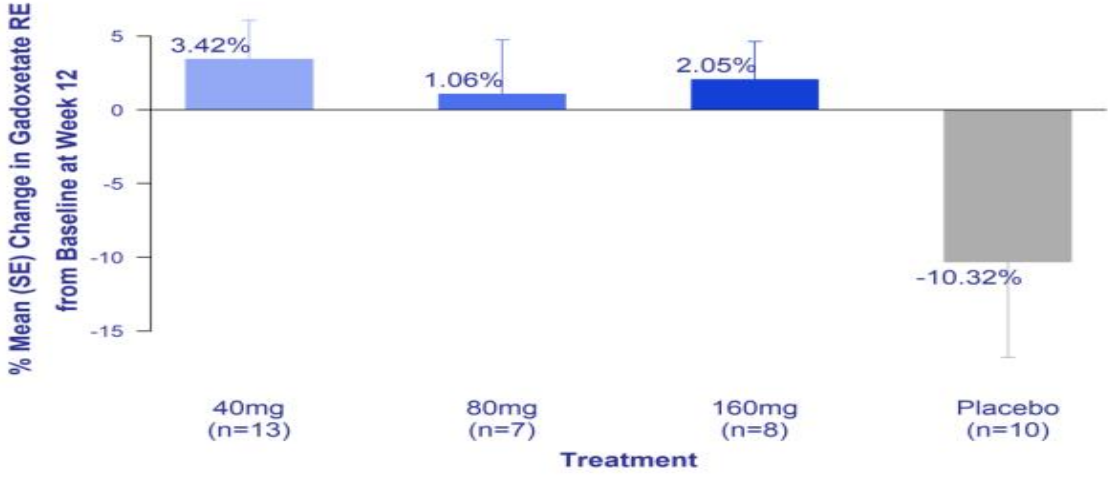
ELF Score Change from Baseline at Week 12



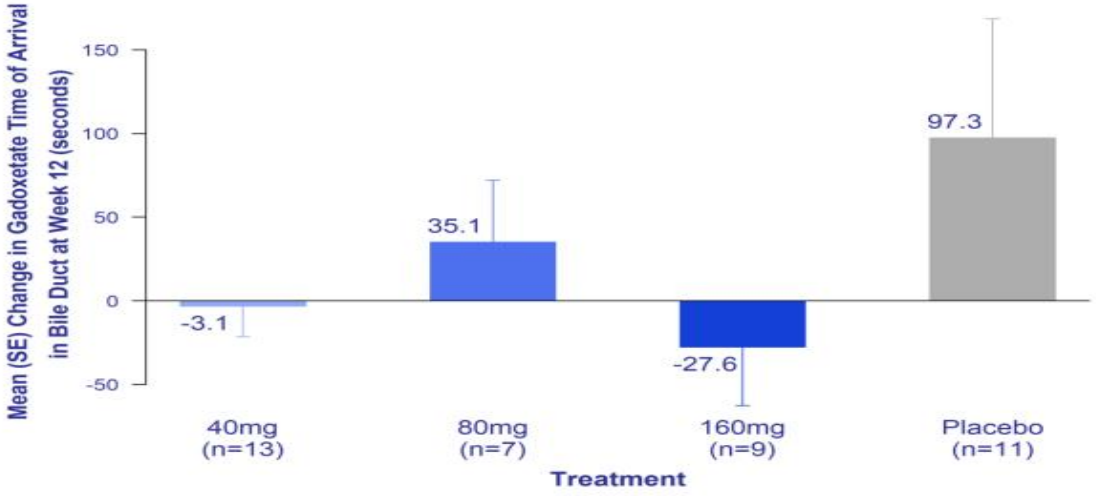
PRO-C3 Change Over Time



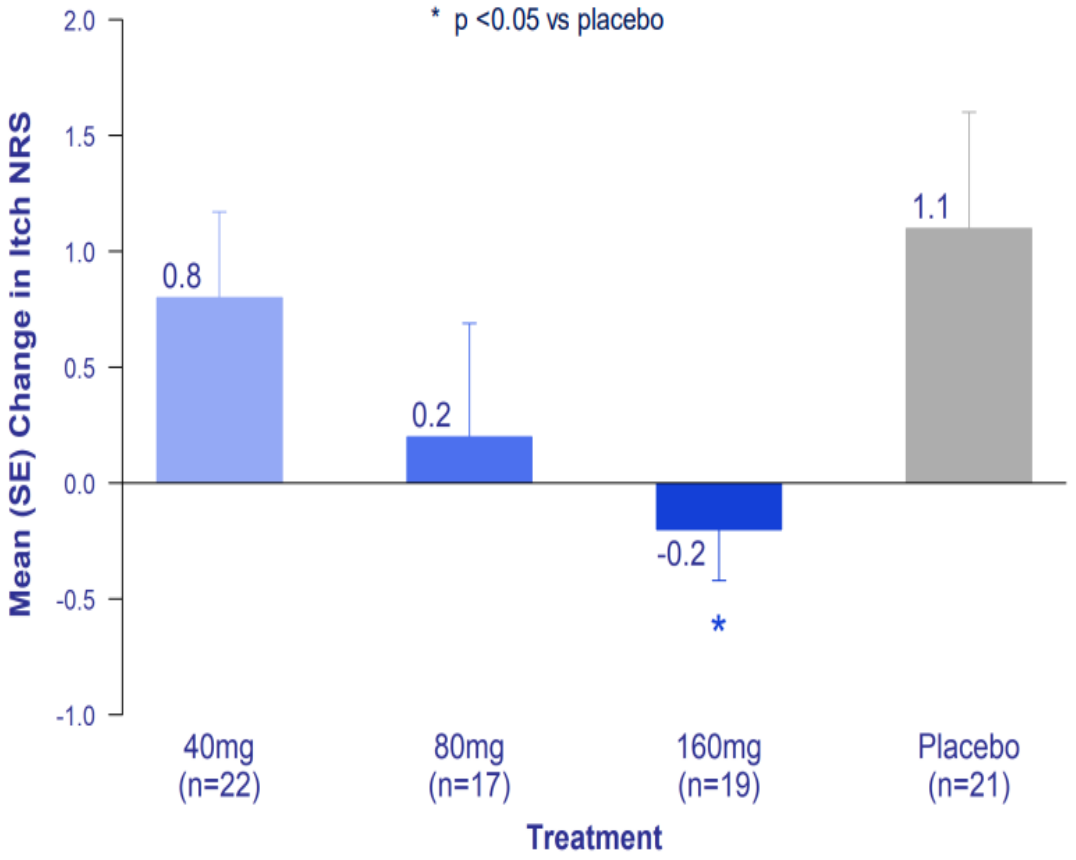
Whole Liver Relative Enhancement (%): Change from Baseline at Week 12



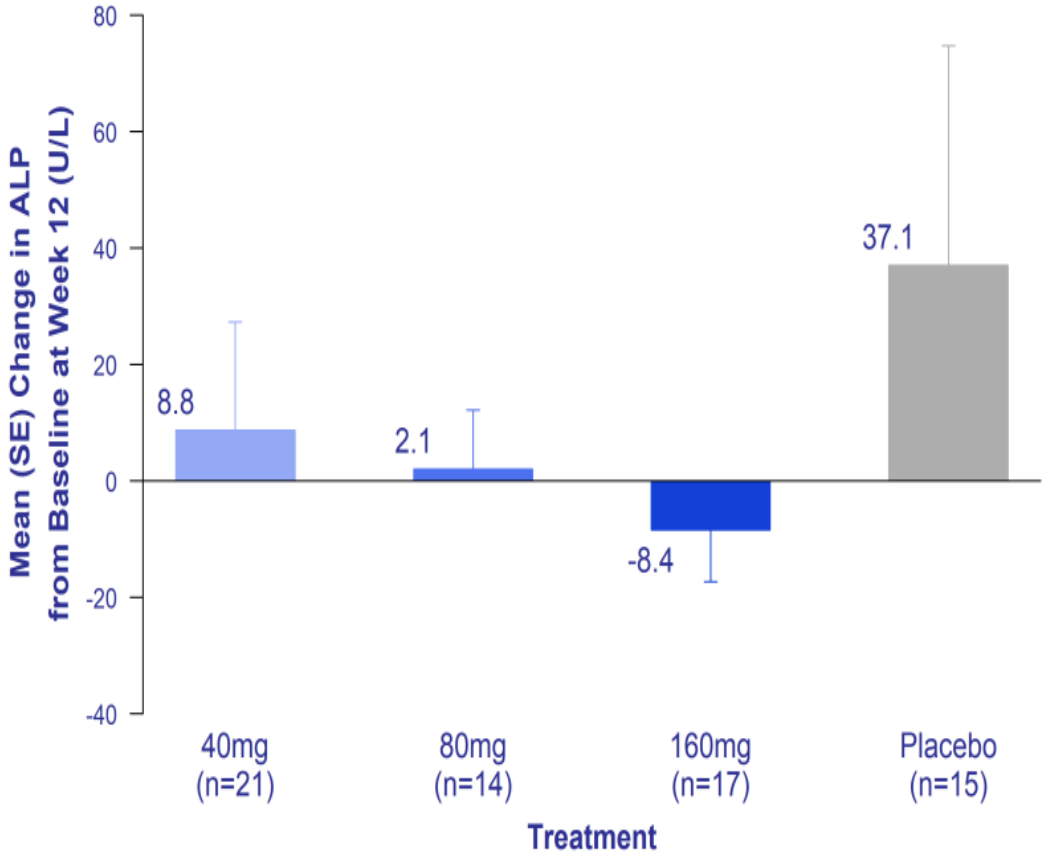
Time of Arrival in Common Bile Duct (sec): Change from Baseline at Week 12



Itch NRS Score Change from Baseline at Week 12



ALP (U/L) Change from Baseline at Week 12



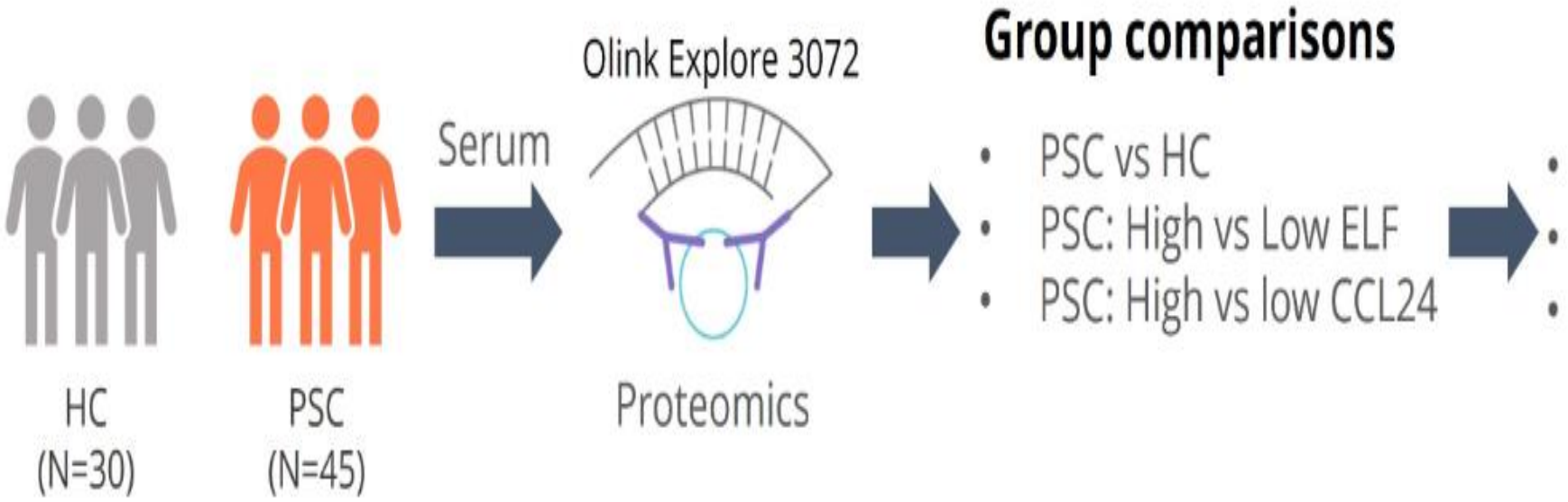
Study results support proof of concept for targeting integrin-mediated TGF-β activation as a potential antifibrotic approach in PSC

- 320mg cohort is ongoing with results expected in 2024 (NCT04480840)

111: SERUM PROTEOMICS REVEALS UNIQUE ASSOCIATION OF CCL24 WITH DISEASE-RELATED PATHWAYS AND SIGNATURES IN PSC

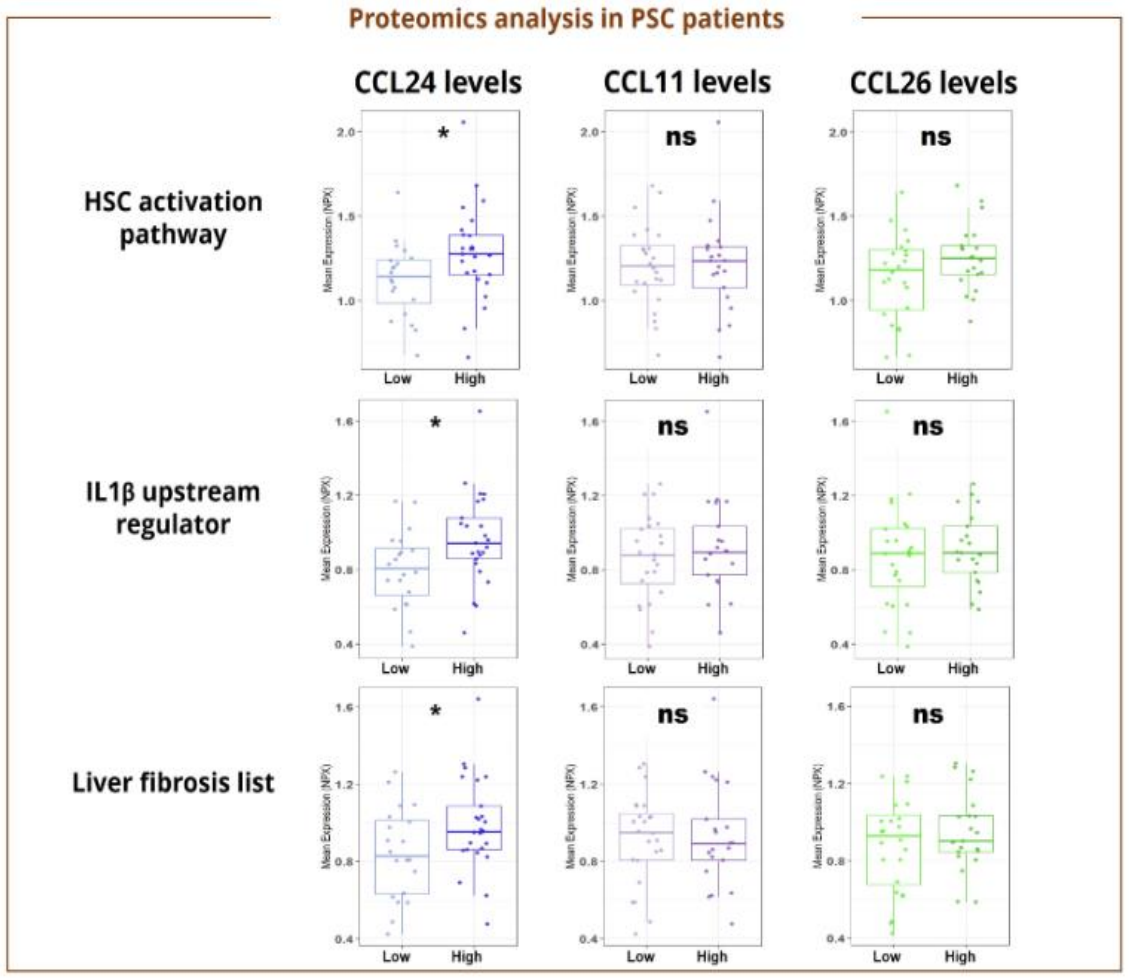
Ilan Vaknin

Background: CCL24 (Eotaxin-2) is a chemokine that promotes inflammation & fibrosis and is overexpressed in the liver of patients with PSC



111: SERUM PROTEOMICS REVEALS UNIQUE ASSOCIATION OF CCL24 WITH DISEASE-RELATED PATHWAYS AND SIGNATURES IN PSC

Ilan Vaknin



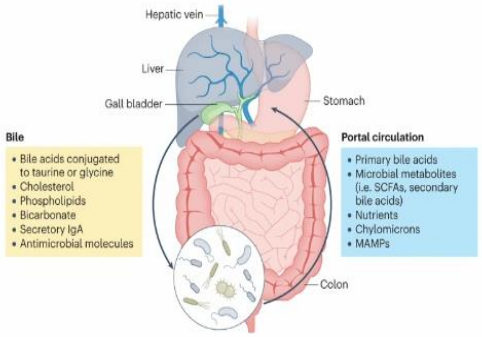
Conclusion: This study provides further evidence of the critical role of CCL24 in the pathogenesis of PSC, highlighting its unique association with disease-related pathways not shared by other eotaxins.

Targeting CCL24 could be a promising therapeutic strategy for the treatment of PSC, which supports the ongoing phase 2 study of CM-101, a CCL24 neutralizing antibody, in patients with PSC.

2

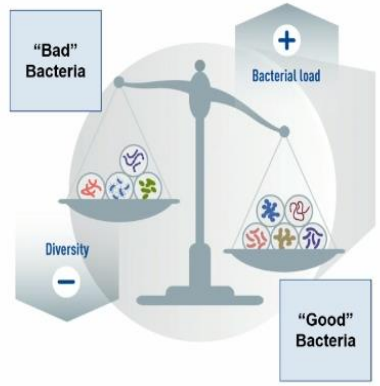
Talks

The gut-liver axis



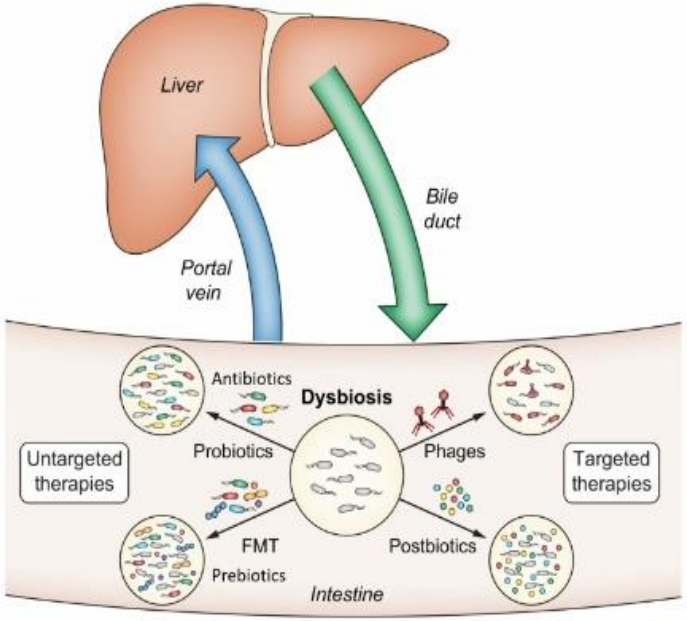
Hsu and Schnabl, *Nature Reviews Microbiology* 2023

Gut microbiota signatures in patients with chronic liver disease



Adapted from: Trebicka J et al., *J Hepatol* 2021

Translating microbiota research into clinical practice

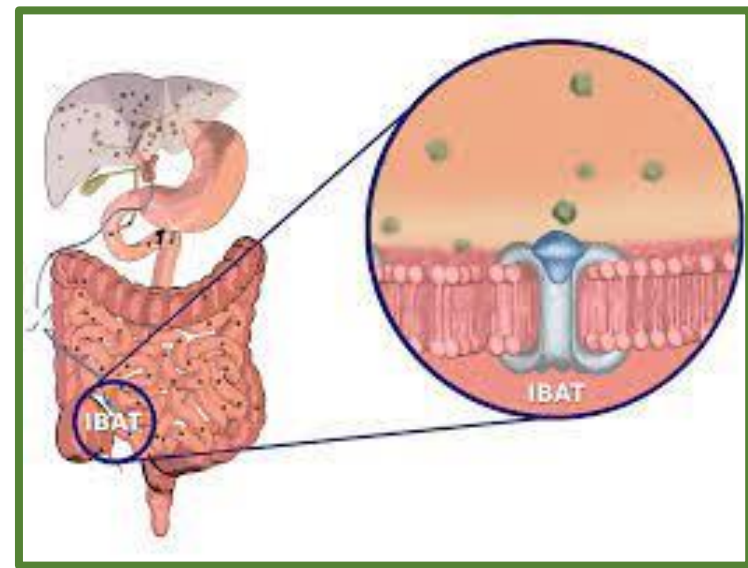


Adapted from: Bajaj JS, Ng SC, Schnabl B, *J Hepatol* 2022

Gut microbiota signatures in patients with autoimmune liver disease

Category	Primary sclerosing cholangitis	Autoimmune hepatitis	Primary biliary cholangitis
Diversity[a]	Reduced[48–55,228]	Reduced[66,71]	Reduced[68,229]
Associated bacterial taxa (sequencing)[a]	↑ *Veillonella*[48–55,228], *Streptococcus*, *Enterococcus*[50,51] ↓ *Coprococcus*[51,56]	↑ *Veillonella*[66,71,231], *Klebsiella*[66,231]	↑ *Veillonella*[232], *Streptococcus*[68,229,232], *Klebsiella*[68,232]
Altered microbial genes and/or functions	↓ Vitamin B6, BCAA[36]	No studies	No comparison with control groups[234]
Microbial metabolites	↑ TMAO[160] ↓ Vitamin B6, BCAA[36], plasma secondary to primary bile acid ratio[101], faecal secondary bile acids[55]	↓ Faecal SCFA (butyrate)[235]	↓ Faecal and serum secondary to primary bile acid ratio[236]
Gut barrier, functional tests	Normal lactulose to L-rhamnose ratio[115]	No data	Increased sucrose excretion (mixed sugar test)[238]
Gut barrier, blood biomarkers	↑ LBP, sCD14 (REF.[116]) Unchanged LPS, IFABP, zonulin	↑ LPS[241,242], zonulin[242]	↑ LPS[243], sCD14 (REF.[244]) Unchanged IFABP

Hov JR and Karlsen TH,
Nature Rev Gastro&Hep 2023


IBAT
IBAT

Maralixibat (Livmarli®) approved to treat pruritus in Alagille syndrome at an age of 2 months (EMA) and 3 months (FDA), respectively.

Gonzales E et al., Lancet 2021;398: 1581 .

Odevixibat (Bylvay®) approved to treat pruritus in PFIC at an age of 6 months (EMA) and 3 months (FDA), respectively.

Thompson RJ et al., Lancet Gastro Hepatol 2022; 7: 830

Divergent Results of IBAT inhibitors in PBC:

- Phase II RCT in PBC: maralixibat not superior to placebo (N=66, 3mo)
- Phase II RCT in PBC: linerixibat short term benefit (N-21, 2w)

Mayo. Hepatol Commun 2019, Hegade. Lancet 2017

3

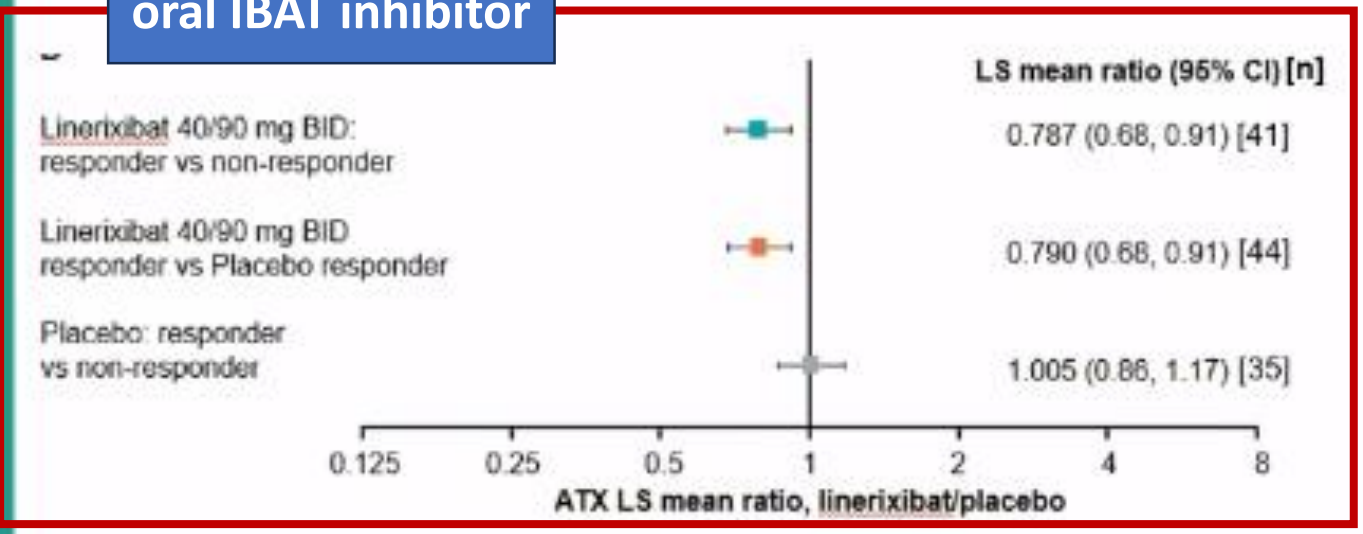
Posters

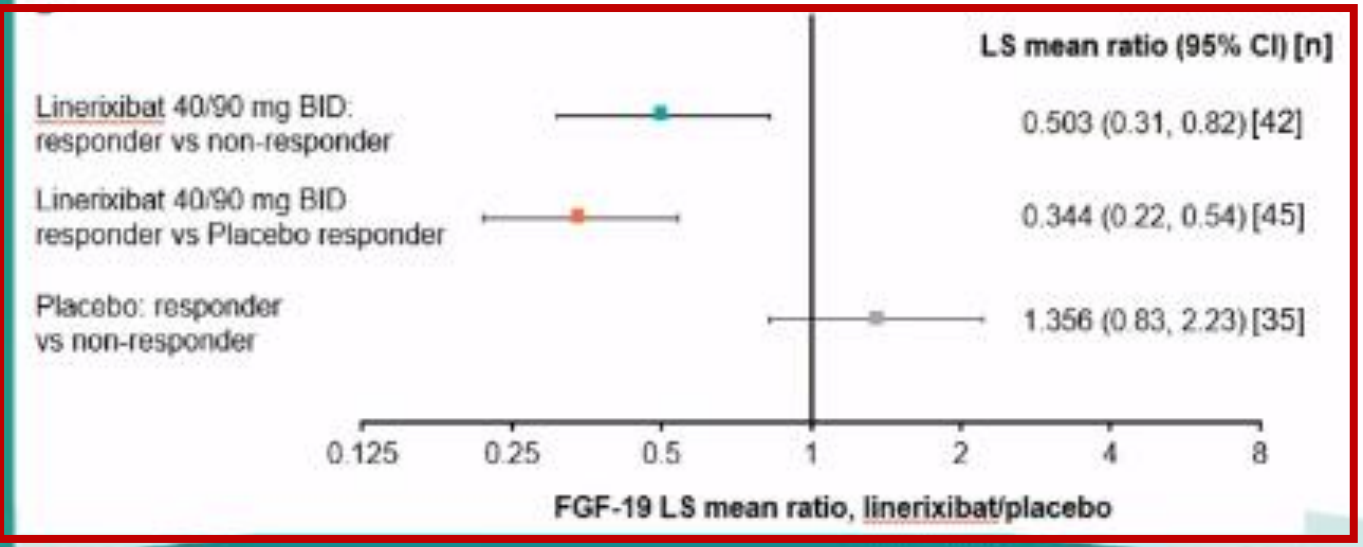
98/2000

AASLD 2023 Poster of Distinction: Serum Autotaxin and FGF-19 Are Biomarkers of Linerixibat Treatment Response in Patients with Cholestatic Pruritus in PBC

S Mukherjee, L Casillas, B Swift, J Fettiplace, S Das, M McLaughlin, AE Kremer

oral IBAT inhibitor





Change from baseline at Week 16 in serum ATX and FGF-19 in itch responders versus non-responders

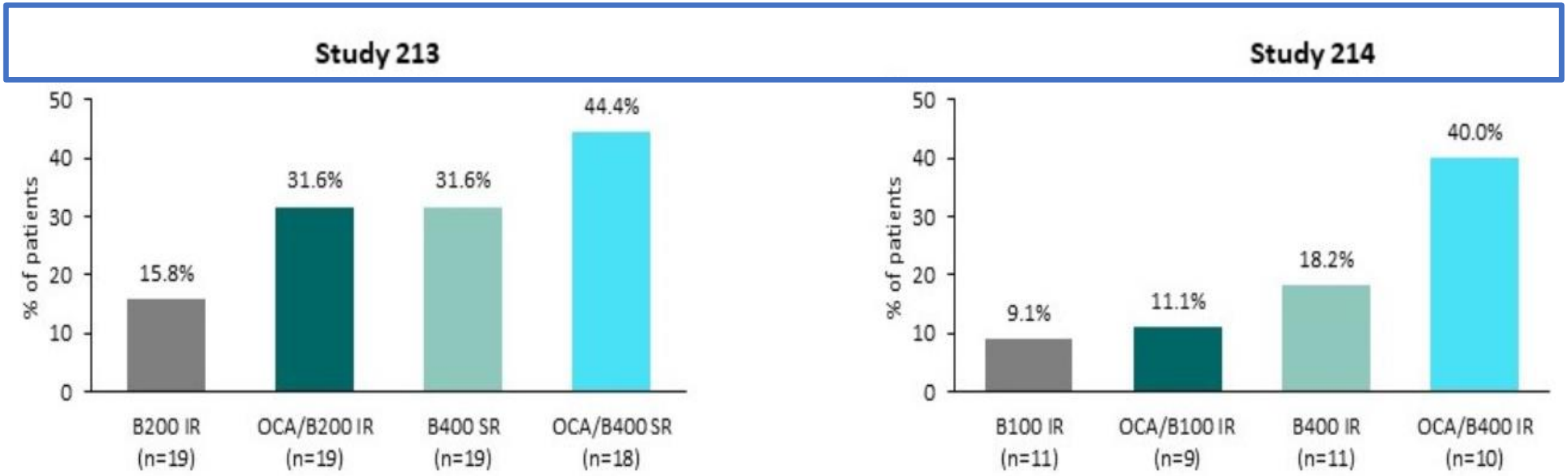
- Itch responders in the linerixibat 40/90 mg BID group, but not in the placebo group, had greater reductions, versus non-responders, in serum ATX compared with baseline
- In linerixibat-treated patients, ATX levels were reduced in itch responders compared with non-responders and with placebo
- In the individual dose groups, ATX levels, but not FGF-19 levels, were significantly reduced in itch responders versus non-responders in patients treated with linerixibat 90 mg BID, but not with linerixibat 40 mg BID (data not shown)
- Similarly, FGF-19 reduction was associated with itch response in patients receiving linerixibat 40/90mg BID compared with placebo

Study identified a significant reduction in serum levels of autotaxin (pruritogen) and FGF-19 (regulator of bile acid biosynthesis) in linerixibat itch responders (≥2 NRS point reduction)

Preliminary findings suggest that serum ATX and FGF-19 may function as biomarkers of itch response to linerixibat treatment.

5019-C: COMBINED EFFECT OF OBETICHOLIC ACID & BEZAFIBRATE IN PBC PATIENTS & INADEQUATE RESPONSE TO OR INTOLERANCE OF UDCA: RESULTS FROM TWO PHASE 2 CLINICAL TRIALS *Levy, US*

- Two randomized, double-blind, active-controlled phase 2 trials (213 (75pts) & 214 (41pts)) assessed the effects OCA/BZF vs BZF mono on safety/tolerability, serum biomarkers & biochemical remission



†Biochemical remission was defined as ALP, GGT, ALT, and AST levels ≤ULN, with TB ≤0.6xULN.

5019-C: COMBINED EFFECT OF OBETICHOLIC ACID & BEZAFIBRATE IN PBC PATIENTS & INADEQUATE RESPONSE TO OR INTOLERANCE OF UDCA: RESULTS FROM TWO PHASE 2 CLINICAL TRIALS *Levy, US*

Conclusion:

- These results suggest short-term (12w) administration of OCA/BZF was well tolerated & has therapeutic potential to normalize multiple serum biomarkers associated with improved clinical outcomes
- Low rates of pruritus were observed in the OCA/B400 SR cohort of Study 213, which were significantly lower than those in the preliminary OCA/B400 IR cohort of Study 214 & the phase 3 POISE study
- The data support progression to phase 3 development of the sustained release formulation of BZF with low doses of OCA

4569-C: REAL-WORLD EXPERIENCE WITH FIBRATES IN PATIENTS WITH PBC

Maria C. Van Hooff

Background: Evaluate the real-world use and effectiveness of fibrates (off-label use) in a nationwide cohort

Methods: Retrospective study in all Dutch hospitals >1990. Biochemical measurements before the start of fibrates and those closest to 12 mo

Results: 318 pts (female 91.5%), bezafibrate (97.8%), cirrhosis (14.2%)

- Fibrate therapy was discontinued within the first year in 67 (21.1%)
- Overall, the median ΔALP and Δbilirubin were -1.03 (IQR -0.60 to -1.77) and -0.08 (IQR -0.20 to 0.06), respectively
- **Conclusion:** Fibrate use was associated with statistically significant reductions in cholestatic surrogate markers after one year of therapy, with about a third of patients reaching the most stringent biochemical treatment goals. However, discontinuation rate was high, indicating the need to optimize fibrate treatment strategies

4563-C: PREVALENCE AND TREATMENT OF PRURITUS IN PATIENTS WITH PBC: RESULTS FROM THE GERMAN PBC REGISTRY

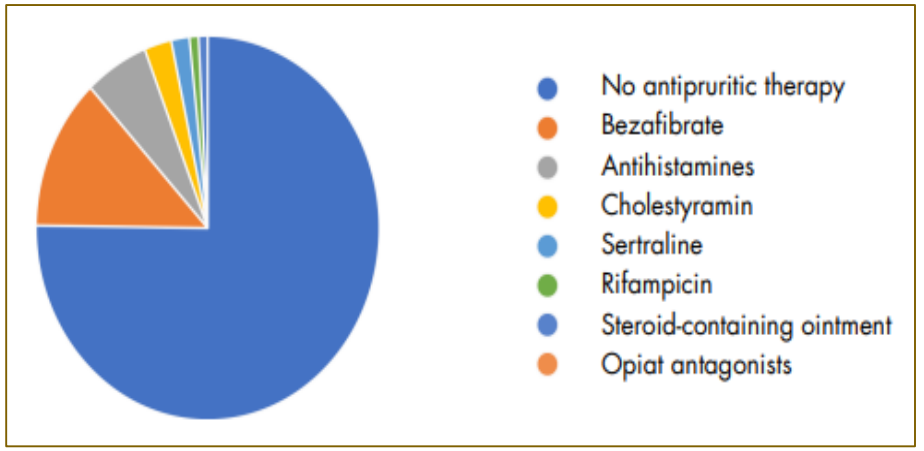
Toni Herta

Background: Limited data on prevalence & treatment of pruritus in PBC pts

Methods: 32 centers, 2019 – 2023, 4-point Lickert scale (*absent, mild, moderate, severe*)

Results: Pruritus was noted in 117/496 (24%) (mild, moderate, or severe in 57 (49%), 41 (35%), 19 (16%), younger at PBC diagnosis, more often depression)

- Prevalence of pruritus was not significantly different between both second line treatment groups (27% vs. 31%), or between UDCA responder patients and primary UDCA incomplete responders (21% vs. 27%)
- Antipruritic therapies were infrequently used:
- bezafibrate n=15, antihistamines n=7,
- cholestyramine n=3, sertraline n=2,
- rifampicin n=1, steroid-containing ointment n=1



Conclusion: Pruritus is common and inadequately treated in PBC patients. Diagnosis highly depends on the treating physician and needs harmonization. Education about antipruritic therapies should be improved.

4551-C: IMPACT OF TYPE 2 DIABETES MELLITUS ON LIVER FIBROSIS & HEPATIC STEATOSIS IN PATIENTS WITH PBC: A LONGITUDINAL STUDY

Williams, US

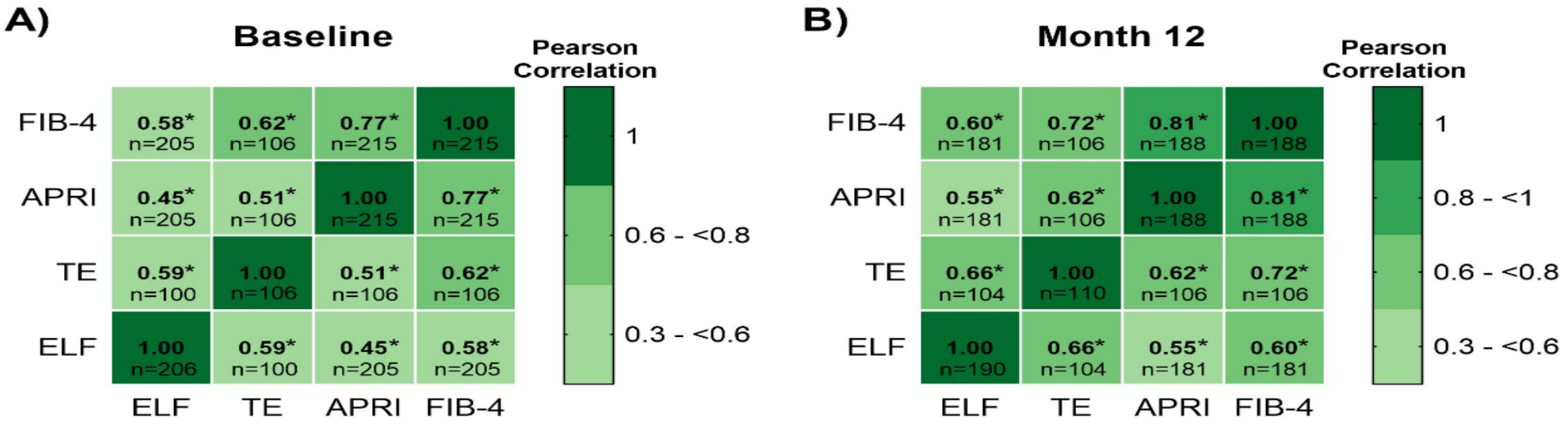
570 pts, f/u median 3.6yrs

	Initial Visit					Most Recent Visit				
	Total (n=160)	PBC with T2DM (n=26)	PBC without T2DM (n=134)	P-value	Relative Risk (95% CI)	Total (n=319)	PBC with T2DM (n=53)	PBC without T2DM (n=266)	P-value	Relative Risk (95% CI)
CAP, dB/m, mean ± SD	257.2 ± 57.6	275.6 ± 77.8	253.6 ± 52.5	0.178		274.9 ± 54.2	299.7 ± 65.8	270.0 ± 50.2	0.003	
CAP, n (%)				0.011	2.9 (1.3-6.9)				0.012	2.1 (1.2-3.9)
< 285 dB/m	108 (67.5)	12 (46.2)	96 (71.6)			188 (58.9)	23 (43.4)	165 (62.0)		
≥ 285dB/m	52 (32.5)	14 (53.8)	38 (28.4)			131 (41.1)	30 (56.6)	101 (38.0)		
LSM, kPa, mean ± SD	13.6 ± 13.0	12.5 ± 6.6	13.8 ± 13.9	0.658		13.6 ± 14.1	15.9 ± 12.9	13.1 ± 14.3	0.187	
LSM, n (%)				0.127	2.0 (0.8-4.9)				<0.001	4.1 (2.1-8.1)
• < 8.5 kPa	71 (44.4)	8 (30.8)	63 (47.0)			157 (49.2)	12 (22.6)	145 (54.5)		
• ≥ 8.5 kPa	89 (55.6)	18 (69.2)	71 (53.0)			162 (50.8)	41 (77.4)	121 (45.5)		

Conclusion: T2DM at the initial visit is associated with an increased likelihood of hepatic steatosis, but not clinically significant liver fibrosis. Over time, patients with PBC and T2DM have a significantly higher risk of developing both hepatic steatosis and clinically significant fibrosis compared to those without T2DM.

4540-C: CORRELATIONS BETWEEN FIBROSIS SCORING SYSTEMS & TE IN THE PHASE 3 POISE STUDY OF OCA IN PBC Gish, US

Figure. Correlation across fibrosis markers at baseline (A) and Month 12 (B).



*Indicates *P*<.0001 for a given correlation.
Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; ELF, enhanced liver fibrosis; FIB-4, Fibrosis 4; TE, transient elastography.

Conclusion: This post hoc sub-analysis of the phase 3 POISE trial demonstrated significant associations across all 4 fibrosis markers. **At both time points, the correlation between FIB-4 and TE was stronger** than the others. Although FIB-4 is not validated in PBC, the moderately strong observed correlation with TE **suggests that FIB-4 may be a possible surrogate for evaluating fibrosis in patients with PBC**.

4591-C: WIDESPREAD DYSREGULATION OF METABOLIC STRESS PATHWAYS IS A CHARACTERISTIC OF PBC: COMPARISON OF THE SERUM METABOLOMES OF PBC PATIENTS TO MATCHED HEALTHY VOLUNTEERS

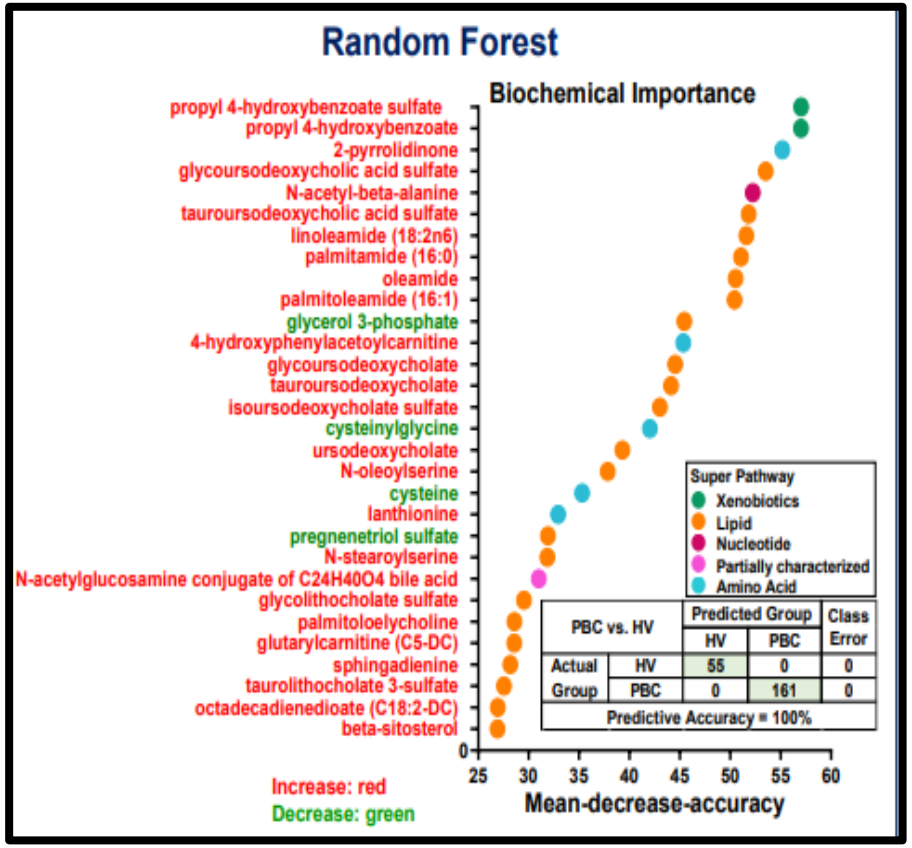
Yung-Jung Choi

Background: Current analytical methods measure > 1000 metabolites to define a serum metabolome

Methods: 161 PBC pts (phase 3 ENHANCE) & 55 healthy

Results: 1031 metabolites were identified

- 468 (45%) were significantly increased
- 189 (18%) were significantly decreased ($p \leq 0.05$)
- Bile acids were broadly elevated



Conclusion:

PBC patients displayed broad changes in serum metabolites reflective of metabolic stress indicating mitochondrial defects and liver dysfunction associated with their cholestasis.

4547-C: EFFICACY, SAFETY & TOLERABILITY OF VOLIXIBAT IN PATIENTS WITH IC PREGNANCY: A CASE SERIES OF 4 PATIENTS

Caroline Ovadia, UK

Background: Volixibat (VLX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor

4 ICP patients treated with VLX under the OHANA trial (NCT04718961)

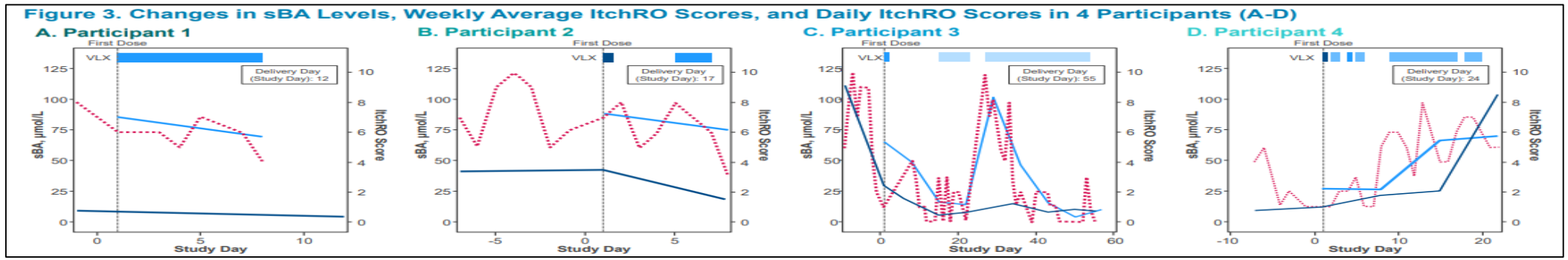
Methods: Open-label VLX 20mg or 80mg BID until delivery

- Adult ItchRO, sBA, liver enzymes, perinatal outcomes & adverse events (TEAEs) were assessed

Results: 1,000 participate, 26 screened, 4 enrolled

- All patients experienced reductions in pruritus from Baseline
- All patients had healthy live births (at weeks 34, 35 and two to term)
- The most frequent TEAEs were gastrointestinal (GI) in nature and mild to moderate in severity
- One patient tolerated treatment until delivery with no dose modifications due to AEs

Conclusion: VLX demonstrated improvements in pruritus and sBA, signaling proof of concept



4530-C: A PILOT STUDY EXAMINING A LOW-SULFUR/LOW-PROTEIN DIET VERSUS THE SPECIFIC CARBOHYDRATE DIET IN PATIENTS WITH PSC

Gila Feinman Sasson, US

Background: Little is known about the role of diet in PSC

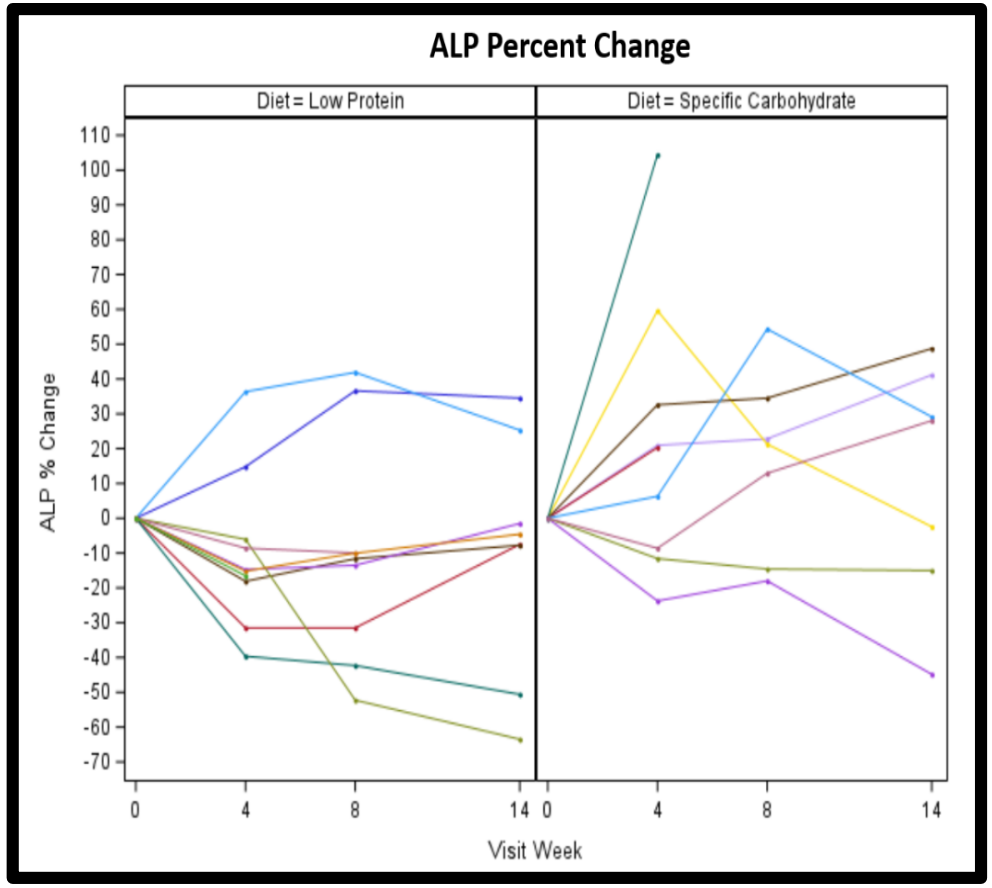
- This study compares the effects of a low-protein diet (LPD) and Specific Carbohydrate Diet (SCD) on clinical, microbial and metabolomic parameters in PSC
- SCD, with higher protein content, increases disease activity and LPD reduces activity, as assessed by (ALP), through modulatory effects on the gut microbiome

Methods: large-duct PSC, ALP >1.5 x ULN

1:1 to LPD or SCD for 8w

Results: 20pts

4w: 60% in LPD >10% reduction in ALP (14.72- 39.65%) vs 22% in SCD (11.59-23.76%) (P=0.05)



Conclusion:

LPD is associated with a meaningful ALP reduction that appears to be driven by protein consumption. In contrast, a high protein diet is associated with worsening ALP.

4534-C: ASSOCIATIONS BETWEEN LIVER BIOMARKERS & CLINICAL OUTCOMES IN PATIENTS WITH PSC: A RETROSPECTIVE REAL-WORLD STUDY

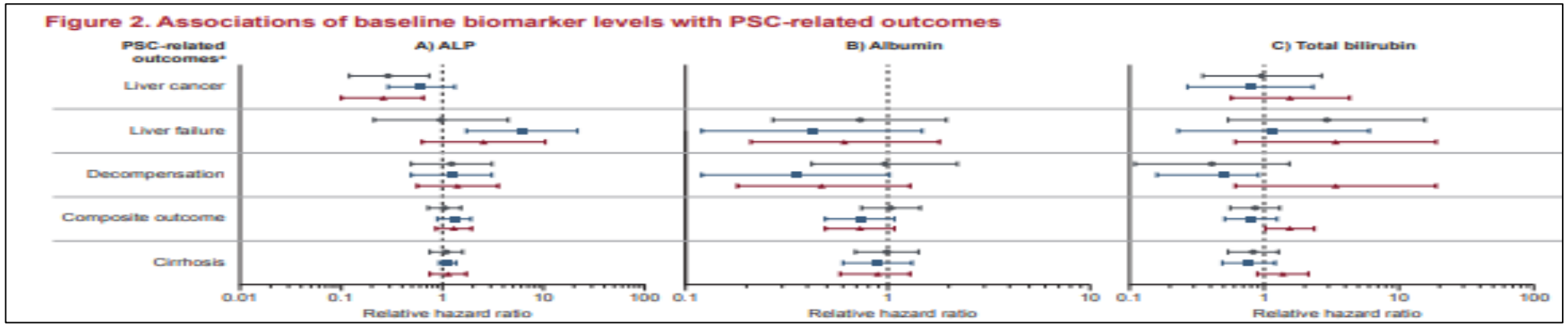
Jun Xu, US

Background: We explored the associations between liver biomarker levels and clinical outcomes in a large cohort of patients with PSC

Methods: Adult pts PSC, Liver biomarkers (alb, total bil, ALP, ALT, AST, APRI) at baseline, 6 & 12 mo

Outcomes: cirrhosis, decompensation, liver failure, liver cancer & a composite outcome

Results: (N=2373) mean follow-up 4.2 years. Percent changes in biomarkers from baseline to outcomes were associated ($p<0.05$) with most events



- **Conclusion**: Liver biomarkers at baseline and changes during follow-up were associated with PSC outcomes. Further research is needed to identify the exact clinical correlates and confirm prognostic thresholds for these biomarkers

4501-C: AZATHIOPRINE ON RISK OF EXTRAHEPATIC MALIGNANCY IN PATIENTS WITH AUTOIMMUNE HEPATITIS: A NATIONWIDE CLAIMS STUDY IN SOUTH KOREA

Sung Hwan Yoo

Background: We aimed to evaluate the impact of azathioprine (AZT) treatment on extrahepatic malignancy risks

Methods: All persons diagnosed with AIH (2008 - 2020)

8,280 pts with AIH (3,059 with AZA + 5,221 without AZA)

f/U: 49.8±43.1mo

Results: The incidence of extrahepatic malignancy was 1.36 and 1.23 per 100 person-years in the patients treated with AZT and without AZT, respectively (P=0.685)

- After confounding by age, sex, DM, cirrhosis, the HR was 1.09 (P=0.600)

Conclusion: The national claims data of HIRA did not show that AZT significantly increases the risk of extrahepatic malignancy among AIH patients

4509-C: INVESTIGATING MIF AS A BIOMARKER OF DISEASE SEVERITY IN AUTOIMMUNE HEPATITIS

Swathi Krishnan

Background: Novel biomarkers could help identify patients with more aggressive phenotypes requiring second-line immunosuppression (IS).

Macrophage migration inhibitory factor (**MIF**), a pro-inflammatory mediator, and **sCD74**, the circulating MIF receptor, are implicated in *AIH (Assis et al, Hepatology 2014)*

Methods: 106 adult AIH

- Serum MIF and sCD74 expression were measured by sandwich ELISA
- The high-risk *MIF* -173 C/G polymorphism was tested

Results:

- Significantly higher median levels of MIF (4 vs. 1.3 ng/mL, p=0.004) and sCD74 (86 vs. 7.1 ng/mL, p=0.003) were found in patients requiring second- and third-line IS (cyclo, mercapto, MMF, rituximab, tacrolimus) compared to patients on first-line therapy with AZA
- A trend toward longer time to biochemical response in patients with one or more C alleles vs. GG (36 vs. 13.9 months, p=NS)

Conclusion: Our study shows that circulating MIF and sCD74 levels are significantly higher in AIH patients requiring second- and third-line IS. This suggests that these candidate immune-based biomarkers may be able to identify patients with severe disease requiring more aggressive IS regimens

4502-C: BIOMARKER DISCOVERY IN PATIENTS WITH AIH

Claire Harringhton

Background: investigate candidate blood biomarkers of AIH activity vs. quiescence to eventually guide & personalize IST management

Methods: 38 patients

- active AIH at liver biopsy (**AD**) (n=11), AIH with complete biochemical response on IST for >1 year (**RT**) (n=16), and AIH with complete biochemical response off IST for >1 year (**NRT**) (n=11) and **healthy controls** (n=5)
- panel of 92 plasma inflammatory markers (OLINK) as well as targeted candidate biomarkers (Sandwich ELISA) identified from prior studies (*Harrington et al, Hepatology 2022*)

Results:

- AD group had significantly higher levels of BAFF, CDCP1, and CXCL11 vs. all other groups
- AD also had a higher ferritin, sCD74 and sCD74/MIF ratio vs. the RT group
- **NRT group had higher ferritin levels and sCD74/MIF ratio vs. the RT group despite both having normal liver enzymes and IgG levels**

4502-C: BIOMARKER DISCOVERY IN PATIENTS WITH AIH

Claire Harringhton

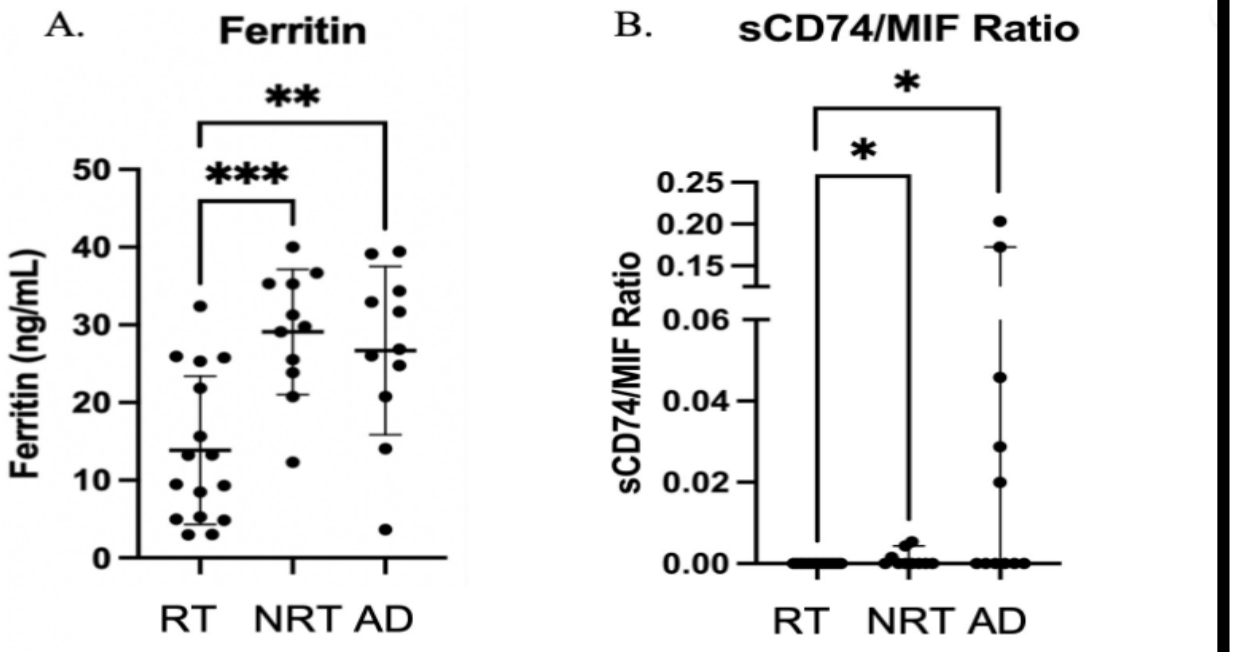


Figure 1: Using ELISA, analysis resulted in a significant finding of higher ferritin (A) and sCD74/MIF ratio (B) in the NRT group compared to the RT group.
RT (stable on IS >1 yr), NRT (stable off IS >1 yr), AD (active AIH)
***p<0.001, **p<0.01, *p<0.05

Conclusion:

Several inflammatory biomarkers associated with active vs. biochemically quiescent AIH, supporting their potential use for detecting immunoactivity.

The biomarker differences between inactive AIH vs. healthy controls and, importantly, inactive AIH on vs. off IST suggest a potential role to detect immunoactivity despite normal liver tests, which may be useful when considering IST withdrawal

4516-C: ROLE OF NITS IN ASSESSING THE DEGREE OF FIBROSIS IN AIH, PBC, & OVERLAP SYNDROME A CANADIAN MULTI-CENTER REVIEW

M. Alsager

Background: Ability of (APRI) & (FIB4) to discriminate for liver fibrosis stage based on liver biopsy

Methods: Data from Canadian Network for Autoimmune Liver Disease

- Liver biopsy vs APRI/FIB4 within one year from liver biopsy date
- F0 vs. F1-4 & F0-2 vs. F3-4

Results: 815 pts

- 28% (AIH), 57 % (PBC), 15% (OS)
- F0 (16.2%), FI-F2 (44.6%), F3-F4 (39.1%)

4516-C: ROLE OF NITS IN ASSESSING THE DEGREE OF FIBROSIS IN AIH, PBC, & OVERLAP SYNDROME A CANADIAN MULTI-CENTER REVIEW

APRI	Cut-off	AUC, (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
F1-4						
Overall	1.12	0.58 (0.53, 0.63)	45.67 (41.85, 49.49)	67.42 (59.09, 75.00)	87.85	19.39
AIH	5.58	0.53 (0.43, 0.62)	28.73 (22.10, 35.37)	80.43 (69.57, 91.30)	85.25	22.29
PBC	0.30	0.62 (0.56, 0.69)	47.95 (42.82, 53.08)	70.27 (59.46, 79.73)	89.47	20.39
Overlap	1.04	0.64 (0.47, 0.81)	69.09 (60.0, 77.27)	66.67 (41.67, 91.67)	95.00	19.05
FIB-4	Cut-off	AUC, (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
F1-4						
Overall	1.55	0.48 (0.43, 0.54)	46.11 (42.29, 50.07)	60.61 (52.27, 68.18)	85.83	17.94
AIH	0.76	0.52 (0.43, 0.61)	18.78 (13.26, 24.31)	91.3 (82.61, 97.83)	89.47	22.22
PBC	1.46	0.53 (0.46, 0.60)	42.56 (37.44, 47.69)	70.27 (59.46, 81.08)	88.30	18.84
Overlap	1.05	0.55 (0.41, 0.70)	52.73 (42.73, 62.73)	75.00 (50, 100)	95.08	14.75

Conclusion:

APRI score and FIB-4 score had reasonable PPV however, poor NPV, and therefore, both APRI and FIB-4 cannot be used to stratify patients with or without fibrosis. In patients with PBC and OS, higher APRI score was associated with advanced fibrosis.


ΣΥΝΟΨΗ
AASLD 2023
ΣΑΒΒΑΤΟ 2 ΔΕΚΕΜΒΡΙΟΥ 2023