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Safety and efficacy of elafibranor in primary sclerosing cholangitis: The ELMWOOD phase II randomized-controlled trial

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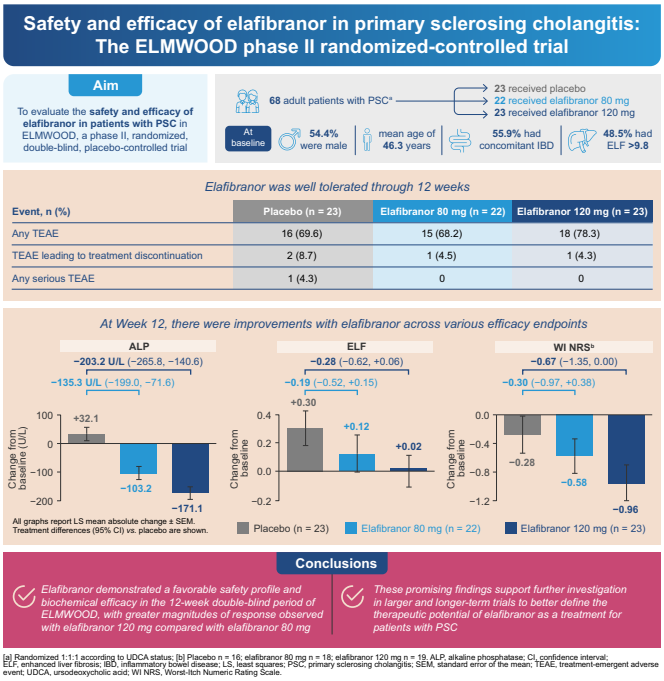
Graphical abstract



Highlights

- There remains an unmet need for a well-tolerated and effective treatment for primary sclerosing cholangitis.
- This phase II trial tested elafibranor, a dual PPAR-α/δ agonist, for the treatment of primary sclerosing cholangitis.
- Elafibranor was well tolerated and provided greater liver biochemical improvements over 12 weeks compared with placebo.
- Elafibranor 120 mg appeared to provide greater improvement in pruritus compared with placebo.

Impact and implications

For people with primary sclerosing cholangitis (PSC), there is a need for a well-tolerated and effective treatment that will enhance quality of life, prevent disease progression, and improve long-term outcomes. Here, we present results from the double-blind period of the phase II ELMWOOD trial in PSC, wherein elafibranor, a peroxisome proliferator-activated receptor-α/δ agonist, demonstrated a favorable safety profile, provided greater biochemical improvements over 12 weeks compared with placebo, and appeared to stabilize markers of fibrosis and improve pruritus. These findings support larger and longer term investigations of elafibranor to explore its therapeutic potential as a treatment for people with PSC.

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Safety and efficacy of elafibranor in primary sclerosing cholangitis: The ELMWOOD phase II randomized-controlled trial

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Background & Aims: Primary sclerosing cholangitis (PSC) is a rare, chronic liver disease. Elafibranor, a dual peroxisome proliferator-activated receptor-α/δ agonist, was investigated in the phase II ELMWOOD trial (NCT05627362).

Methods: This 12-week, double-blind trial enrolled adults with PSC and alkaline phosphatase (ALP) ≥1.5× the upper limit of normal. The primary endpoint was elafibranor safety *vs*. placebo. Additional endpoints included relative mean change from baseline in ALP and enhanced liver fibrosis (ELF) score.

Results: A total of 68 participants (male: 54.4%; mean age: 46.3 years; inflammatory bowel disease: 55.9%) were randomized to elafibranor 80 mg (n = 22), elafibranor 120 mg (n = 23), or placebo (n = 23). At baseline, 70.6% were on ursodeoxycholic acid, 48.5% had ELF scores >9.8, and the mean ALP level was 369.5 U/L. At Week 12, rates of treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation in participants on elafibranor 80 mg, 120 mg, and placebo were 68.2%, 78.3%, and 69.6%, and 4.5%, 4.3%, and 8.7%, respectively. Serious TEAEs occurred only in participants on placebo (4.3%). Participants on elafibranor 80 mg and 120 mg had reductions in ALP *vs.* placebo (least squares mean treatment difference [95% CI]: –35.3% [–49.2, –21.4] and –54.7% [–68.3, –41.0], respectively). ALP normalization occurred only in participants on elafibranor 80 mg (9.1%) and 120 mg (17.4%). The LS mean treatment differences (95% CI) in change from baseline in ELF scores in participants on elafibranor 80 mg and 120 mg *vs.* placebo were –0.19 (–0.52, +0.15) and –0.28 (–0.62, +0.06), respectively.

Conclusions: Elafibranor was well tolerated in people with PSC and associated with greater biochemical improvements over 12 weeks compared with placebo. A greater magnitude of response was observed with elafibranor 120 mg compared with 80 mg.

Introduction

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic disease of unknown etiology characterized by persistent inflammation and progressive fibrosis of the biliary tree.[1,2] PSC is a rare disease with an estimated global incidence of 0.6–0.8 per 100,000 person-years and prevalence of 10.0–13.5 per 100,000 persons, although significant geographic variation exists.[3–5] In PSC, multifocal strictures in both intrahepatic and extrahepatic bile ducts lead to impaired bile flow.[6] The resulting bile acid accumulation and toxicity is postulated to play a role in the pathogenesis and progression of the disease, leading to cholangiocyte injury and hepatocellular inflammation, with subsequent development of fibrosis.[7] The majority of people with PSC have concomitant inflammatory bowel disease (IBD), and symptoms of PSC can include abdominal pain, pruritus, and fatigue.[1]

To date, no treatment has demonstrated improvement in clinical outcomes or disease progression in PSC, and liver transplantation is the only life-extending intervention for those with advanced disease.[4,8–10] Progression to end-stage liver disease with decompensation, early-stage biliary tract malignancies, and recurring bacterial cholangitis leading to impaired

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quality of life are frequent indicators for liver transplantation.[1,8,11] Reported median transplant-free survival estimates range from 9.7 to 20.6 years in people presenting with PSC at a median age of less than 40 years.[4,12] As such, there remains a major unmet need for an effective treatment for people with PSC.[2,9]

While PSC is mechanistically complex, dysregulation of peroxisome proliferator-activated receptor (PPAR)-linked pathways has been associated with disease pathophysiology, largely due to their role in immunoregulation, cholestasis, and fibrotic processes. As a consequence, PPARs represent a potential treatment target in PSC.[13,14] Elafibranor is a PPAR-α/δ agonist that is approved for the treatment of primary biliary cholangitis (PBC).[15–17] Activation of PPAR-α reduces pro-inflammatory cytokines, improves bile acid detoxification, and mitigates oxidative stress, while activation of PPAR-δ enhances bile flow, energy metabolism, and anti-fibrotic pathways.[14,18,19] Therefore, dual activation of PPAR-α and PPAR-δ by elafibranor may function synergistically by addressing cholestasis, inflammation, and fibrosis in PSC.

Here, we report safety and tolerability results alongside early insights into efficacy from ELMWOOD, a phase II, randomized, double-blind, placebo-controlled trial of daily elafibranor in adults with PSC.

A plain language summary is provided in the supplementary materials.

Patients and methods

Trial design

This was a phase II, randomized, double-blind, placebo-controlled trial (NCT05627362). Participants were randomized 1:1:1 to receive daily oral placebo, elafibranor 80 mg, or elafibranor 120 mg for 12 weeks. Randomization was stratified according to participants' baseline ursodeoxycholic acid (UDCA) status (ongoing treatment *vs*. no ongoing treatment). Following their baseline visit, participants completed assessments at Weeks 4, 8, and 12. Following completion of the 12-week double-blind period, participants had the option to enter an open-label extension and receive elafibranor 120 mg for a period of up to 96 weeks. Here, we report findings from the 12-week double-blind period of the trial in accordance with the planned primary analysis.

Approvals of the trial protocol were obtained from Ethics Committees for all participating institutions. The trial was conducted in accordance with the protocol and with the guiding ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines.

Participants

Adults aged 18–75 years with PSC who provided informed consent were eligible to participate in this trial. Participants must have had a diagnosis of large-duct PSC as demonstrated by historical evidence of elevated alkaline phosphatase (ALP) values (above the upper limit of normal [ULN]; 129 U/L in men and 104 U/L in women) for ≥6 months prior to the first screening visit (SV1) and a cholangiogram with compatible imaging features, in the absence of apparent causes of secondary sclerosing cholangitis. Eligible individuals had ALP values ≥1.5x ULN during screening, with ≤40% variability based on two consecutive values taken ≥2–≤4 weeks apart, and total bilirubin (TB) ≤2.0x ULN at SV1. Participants with concomitant IBD could be on any necessary stable treatment but needed to have been in remission for >3 months prior to inclusion. Participants receiving medications for the management of pruritus must have been on a stable dose for ≥3 months prior to SV1.

Key exclusion criteria included presence of small-duct PSC or PSC with features of autoimmune hepatitis, history or presence of other concomitant chronic liver diseases including immunoglobulin G4-related sclerosing cholangitis, PBC, alcohol-related liver disease, and metabolic dysfunction-associated steatohepatitis; a history of bacterial cholangitis ≤60 days prior to SV1, or ongoing/planned long-term prophylactic antibiotics for recurrent cholangitis; presence of advanced cirrhosis defined as Child-Pugh B or C, and a history of clinically significant hepatic decompensation or significant renal disease. Individuals were not eligible if they had received specified treatments ≤3 months prior to SV1, including fibric acid derivatives, vancomycin, glitazones, obeticholic acid, chronic systemic corticosteroids (unless for management of IBD), or potentially hepatotoxic drugs.

Full eligibility criteria can be found in the trial protocol, provided in the supplementary material.

Trial endpoints

The primary endpoint was to assess the safety and tolerability of daily elafibranor 80 mg and 120 mg compared with placebo after 12 weeks of treatment. Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs), classified according to the Medical Dictionary for Regulatory Activities (MedDRA) v27.1 preferred terms, including serious TEAEs and adverse events of special interest (AESIs), and changes in clinical laboratory tests, physical examination findings, vital signs, and electrocardiogram (ECG); the full list of pre-specified AESIs can be found in the trial protocol.

Secondary efficacy endpoints were assessed over 12 weeks of treatment and included: relative and absolute change from baseline in ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and TB levels; the proportions of participants with a reduction in ALP of ≥40% from baseline, and those with an ALP value <1.5x ULN and <ULN (normalization); and absolute and relative change from baseline in non-invasive markers of fibrosis. These markers included enhanced liver fibrosis (ELF) scores, liver stiffness measurement (LSM) assessed by transient elastography (FibroScan®), and N-terminal type III collagen propeptide (pro-C3) levels.

Symptoms of PSC were monitored as exploratory endpoints, including pruritus, which was assessed using the Worst-Itch Numeric Rating Scale (WI NRS). Changes from baseline in WI NRS were assessed in all participants and in a subgroup with moderate to severe pruritus (WI NRS score ≥4) at baseline.

Other exploratory endpoints included changes from baseline in lipid profiles and in IBD activity, assessed by the Clinical Global Impression-Change scale (CGI-C). The impact of different baseline participant and disease characteristics on changes in ALP levels from baseline to Week 12 were also assessed in exploratory subgroup analyses. The subgroups

evaluated included UDCA status (ongoing treatment *vs.* no ongoing treatment), IBD (present *vs.* absent), sex (male *vs.* female), LSM (>9.5 kPa *vs.* ≤9.5 kPa), ELF score (>9.8 *vs.* ≤9.8), and anti-inflammatory or immunosuppressant treatment for IBD in those with concomitant IBD (use *vs.* no use). An ELF score cut-off of 10.6 was specified in the statistical analysis plan, but the more commonly used 9.8 cut-off was reported as a *post hoc* analysis.[20]

Statistical analyses

The probability of observing at least one AE with an incidence of 5% within each treatment arm was 64% for a group size of 20 participants. With an estimated 15% dropout rate and a two-sided type-1 error rate of 5%, a sample size of 60 participants was deemed to provide adequate power, considering the main secondary endpoint to detect treatment difference between elafibranor and placebo, which was relative (94%) and absolute (81%) change in ALP levels from baseline to Week 12. This calculation was based on a group separation (elafibranor minus placebo) of –25% (SD: 20%) and –70 U/L (SD: 70 U/L), respectively.

Safety analyses were performed using data from the safety analysis set, defined as all participants who received at least one dose of the trial intervention. Efficacy analyses were performed using data from the intent-to-treat (ITT) analysis set, defined as all randomized individuals regardless of whether the trial intervention was received.

The double-blind period was completed when the last enrolled participant had completed their Week 12 visit. Analyses for the primary endpoints are descriptive as there were no formal statistical hypotheses associated with the safety evaluations. For the other endpoints, data from the elafibranor groups were compared with the placebo group separately, without adjustment for multiplicity. Continuous endpoints were analyzed using ANCOVA adjusted for baseline values. Parametric results are presented; non-parametric analyses were performed to confirm the validity of the results where data were not normally distributed.

Full details can be found in the statistical analysis plan, provided in the supplementary materials.

Results

Trial population

Of 123 people screened from 39 centers across seven countries, 68 individuals with PSC met the eligibility criteria and were randomized to receive placebo (n = 23), elafibranor 80 mg (n = 22), or elafibranor 120 mg (n = 23). A breakdown of the numbers of people who were not eligible to participate following their screening visits is provided in Table S1; ALP variability at screening in both people who were not eligible to participate and in randomized participants – stratified by UDCA status – is also provided in Table S2. All randomized participants received at least one dose of the trial intervention; therefore, the safety and ITT analysis sets comprised the same individuals. Of the 68 individuals who were randomized, 63 (93%) entered the open-label extension (placebo: n = 20; elafibranor 80 mg: n = 21; elafibranor 120 mg: n = 22).

Participant demographics and disease characteristics are presented in Table 1. Some minor differences were observed; the elafibranor 120 mg group comprised a lower proportion of male participants and a slightly higher proportion with concomitant IBD compared with the placebo and elafibranor 80 mg groups. Other demographics and characteristics were largely similar. Overall, just over half of participants were men (54.4%) and the majority were White (85.3%). Participants had a mean age of 46.3 years (SD: 12.1 years) and a mean BMI of 26.5 kg/m^2 (SD: 5.3 kg/m^2). The mean time since PSC diagnosis was 9.7 years prior to the first dose administration; 22.1% of participants had a history of complications of PSC, and most were on background UDCA treatment (70.6%; mean dose of 13.0 mg/kg/day [SD: 3.4 mg/kg/day]). Over half (55.9%) presented with concomitant IBD (38.2% with ulcerative colitis; 10.3% with Crohn's disease), and 41.2% of these individuals were receiving concomitant anti-inflammatory or immunosuppressant treatment for IBD at baseline (Table S3). Common PSC-related symptoms reported at baseline included pruritus (44.1%), fatigue (35.3%), and abdominal pain (19.1%).

Overall, 26.5% of participants had cirrhosis at baseline, all classified as Child-Pugh A. The mean ALP level was 369.5 U/L (SD: 192.3 U/L) at baseline. Baseline ALP and GGT levels were slightly higher in the placebo group compared with the elafibranor groups. There were no notable differences in baseline TB, AST, or ALT levels. In total, 48.5% of participants had an ELF score >9.8 and 55.9% had an LSM of >9.5 kPa, indicating moderate or advanced fibrosis in these individuals at baseline. The mean overall pro-C3 level at baseline (59.1 ng/ml) was substantially higher than the ULN (34.3 ng/ml). Eleven individuals (16.2%) had moderate to severe pruritus (WI NRS score ≥4) at baseline. Baseline mean WI NRS scores for the overall population and for the subgroup with moderate to severe pruritus were 1.9 (SD: 2.2) and 5.9 (SD: 1.1), respectively. Levels of total cholesterol and low-density lipoprotein (LDL) were above their respective ULN values at baseline. Very low-density lipoprotein (VLDL), triglycerides, and high-density lipoprotein (HDL) levels were within their normal ranges.

Primary endpoint

Overall, 69.6%, 68.2%, and 78.3% of participants on placebo, elafibranor 80 mg, and elafibranor 120 mg had TEAEs, respectively. A summary of the proportions with TEAEs, TEAEs occurring in >5% of participants in any group, treatment-related TEAEs, TEAEs that led to treatment discontinuation, and serious TEAEs during the double-blind period is provided in Table 2.

One serious TEAE (procedural pancreatitis) occurred in one individual in the placebo group following an endoscopic retrograde cholangiopancreaticogram (ERCP), while none occurred in the elafibranor groups. No other participants underwent an ERCP in the double-blind period. TEAEs that led to treatment discontinuation occurred in two individuals in the placebo group (8.7%; liver function test increase and procedural pancreatitis) and one individual in each of the elafibranor 80 mg (4.5%; hypertension) and 120 mg (4.3%; hepatic enzyme increase) groups. The TEAE of hepatic enzyme increase did not meet the criteria for potential Hy's law (ALT and AST were >3x ULN; TB remained within normal levels) and resolved approximately 1 week later with no interruption in treatment. Three individuals (13.6%) in the elafibranor 80 mg group had non-serious events of cholangitis (preferred terms: cholangitis [n =

ELMWOOD primary safety and efficacy results

Table 1. Baseline patient demographics and disease characteristics.

	Placebo n = 23	Elafibranor 80 mg n = 22	Elafibranor 120 mg n = 23	Overall N = 68
Demographics and characteristics				
Age, years, mean (SD)	47.1 (13.6)	42.0 (11.6)	49.6 (10.3)	46.3 (12.1)
Sex, n (%)				
Male	13 (56.5)	15 (68.2)	9 (39.1)	37 (54.4)
Female	10 (43.5)	7 (31.8)	14 (60.9)	31 (45.6)
Race, n (%)				
White	22 (95.7)	17 (77.3)	19 (82.6)	58 (85.3)
Asian	1 (4.3)	2 (9.1)	1 (4.3)	4 (5.9)
Black or African American	0	0	2 (8.7)	2 (2.9)
Multiracial	0	1 (4.5)	1 (4.3)	2 (2.9)
Not reported	0	2 (9.1)	0	2 (2.9)
Ethnicity, n (%)				
Hispanic or Latino	0	1 (4.5)	1 (4.3)	2 (2.9)
Not Hispanic or Latino	23 (100)	19 (86.4)	21 (91.3)	63 (92.6)
Not reported	0	2 (9.1)	1 (4.3)	3 (4.4)
Bodyweight, kg, mean (SD)	74.0 (15.1)	78.7 (13.9)	82.3 (19.0)	78.4 (16.3)
BMI, kg/m^2, mean (SD)	24.8 (4.1)	26.3 (4.4)	28.5 (6.5)	26.5 (5.3)
Time since PSC diagnosis, months, mean (SD)	113.8 (89.8)	109.8 (94.5)	125.9 (74.4)	116.6 (85.5)
Concomitant UDCA treatment, n (%)	17 (73.9)	16 (72.7)	15 (65.2)	48 (70.6)
Dose, mg/kg/day, mean (SD)	13.5 (2.9)	11.5 (3.6)	14.0 (3.3)	13.0 (3.4)
History of complications of PSC, n (%)	3 (13.0)	5 (22.7)	7 (30.4)	15 (22.1)
Biliary strictures requiring intervention	2 (8.7)	5 (22.7)	7 (30.4)	14 (20.6)
Bacterial cholangitis	1 (4.3)	3 (13.6)	3 (13.0)	7 (10.3)
Cirrhosis, n (%)				
No	15 (65.2)	15 (68.2)	19 (82.6)	49 (72.1)
Yes (Child-Pugh A)[a]	8 (34.8)	6 (27.3)	4 (17.4)	18 (26.5)
Not reported	0	1 (4.5)	0	1 (1.5)
Liver biochemistry				
ALP, U/L, mean (SD)	415.8 (234.6)	329.0 (142.6)	361.8 (185.0)	369.5 (192.3)
TB, µmol/L, mean (SD)	19.1 (9.0)	18.9 (13.1)	19.9 (10.2)	19.3 (10.7)
AST, U/L, mean (SD)	62.3 (31.9)	57.4 (30.7)	68.3 (47.9)	62.7 (37.5)
ALT, U/L, mean (SD)	85.9 (46.5)	80.6 (57.6)	87.4 (60.2)	84.7 (54.3)
GGT, U/L, mean (SD)	556.7 (605.4)	376.0 (336.9)	405.7 (324.3)	447.2 (443.7)
Non-invasive markers of fibrosis				
ELF, mean (SD)	9.9 (1.1)	9.7 (1.0)	10.2 (1.1)	9.9 (1.1)
>9.8, n (%)	11 (47.8)	9 (40.9)	13 (56.5)	33 (48.5)
≤9.8, n (%)	12 (52.2)	13 (59.1)	10 (43.5)	35 (51.5)
LSM[b], kPa, mean (SD)	11.8 (5.6)	11.5 (5.9)	12.3 (5.6)	11.9 (5.6)
>9.5 kPa, n (%)	15 (65.2)	11 (50.0)	12 (52.2)	38 (55.9)
≤9.5 kPa, n (%)	8 (34.8)	11 (50.0)	10 (43.5)	29 (42.6)
Not reported	0	0	1 (4.3)	1 (1.5)
Pro-C3, ng/ml, mean (SD)	56.9 (22.5)	63.1 (24.9)	57.6 (19.1)	59.1 (22.1)
Symptoms and concomitant disease				
Concomitant IBD, n (%)	12 (52.2)	11 (50.0)	15 (65.2)	38 (55.9)
Ulcerative colitis	10 (43.5)	5 (22.7)	11 (47.8)	26 (38.2)
Crohn's disease	1 (4.3)	3 (13.6)	3 (13.0)	7 (10.3)
Not specified	1 (4.3)	3 (13.6)	1 (4.3)	5 (7.4)
Concomitant anti-inflammatory or immunosuppressant treatment for IBD in those with concomitant IBD, n (%)	8 (34.8)	9 (40.9)	11 (47.8)	28 (41.2)
Symptoms related to PSC, n (%)	14 (60.9)	14 (63.6)	13 (56.5)	41 (60.3)
Pruritus	9 (39.1)	11 (50.0)	10 (43.5)	30 (44.1)
Fatigue	8 (34.8)	7 (31.8)	9 (39.1)	24 (35.3)
Abdominal pain	6 (26.1)	2 (9.1)	5 (21.7)	13 (19.1)
Other	4 (17.4)	2 (9.1)	3 (13.0)	9 (13.2)
Pruritus intensity, WI NRS score, mean (SD)	1.4 (2.0)	2.0 (2.1)	2.4 (2.5)	1.9 (2.2)
Moderate to severe pruritus, n (%)				
Yes (WI NRS score ≥4)	3 (13.0)	3 (13.6)	5 (21.7)	11 (16.2)
No (WI NRS score <4)	17 (73.9)	16 (72.7)	16 (69.6)	49 (72.1)
Not reported	3 (13.0)	3 (13.6)	2 (8.7)	8 (11.8)
Concomitant treatment for pruritus, n (%)	3 (13.0)	5 (22.7)	7 (30.4)	15 (22.1)
Lipid profiles				
Total cholesterol, mmol/L, mean (SD)	6.1 (1.5)	6.0 (1.8)	6.3 (1.8)	6.1 (1.7)
VLDL, mmol/L, mean (SD)	0.6 (0.3)	0.6 (0.5)	0.5 (0.2)	0.6 (0.3)

(*continued on next page*)

Table 1. (*continued*)

	Placebo n = 23	Elafibranor 80 mg n = 22	Elafibranor 120 mg n = 23	Overall N = 68
LDL, mmol/L, mean (SD)	3.6 (1.3)	3.7 (1.2)	3.9 (1.8)	3.7 (1.4)
Triglycerides, mmol/L, mean (SD)	1.3 (0.6)	1.2 (0.9)	1.2 (0.4)	1.2 (0.6)
HDL, mmol/L, mean (SD)	1.9 (0.4)	1.7 (0.6)	1.9 (0.4)	1.8 (0.5)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; IBD, inflammatory bowel disease; LDL, low-density lipoprotein; LSM, liver stiffness measurement; pro-C3, N-terminal type III collagen propeptide; PSC, primary sclerosing cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; VLDL, very low-density lipoprotein; WI NRS, Worst-Itch Numeric Rating Scale.
[a]Individuals with cirrhosis classified as Child-Pugh B or C were not eligible to participate.
[b]Liver stiffness was assessed by vibration-controlled transient elastography.

2]; cholangitis acute [n = 1]), reported at the discretion of the investigator; no participant in elafibranor 120 mg and placebo groups had events of cholangitis. There were no AESIs of major adverse cardiovascular events (MACE), liver injury, including drug-induced liver injury, renal TEAEs, creatine phosphokinase elevations, or muscle injuries. Vital signs (including ECG) remained stable in all treatment groups.

TEAEs reported in >5% of participants in any treatment group included pruritus, weight increase, headache, fatigue, constipation, nausea, and hypertension. The nature of many events was consistent with the underlying disease. The number of individuals with TEAEs of weight increase of >5% from baseline was higher in the elafibranor 120 mg group (4/23) compared with the placebo (1/23) and elafibranor 80 mg (2/22) groups. All events were non-serious, mild or moderate in severity, and only one TEAE in the elafibranor 120 mg group was assessed as possibly treatment-related by the investigator. This individual's weight increased from 50.5 kg at baseline to a peak of 53.2 kg (a change from baseline of 5.4%) after approximately 4 weeks of treatment, then gradually returned to near baseline levels with no interruption in elafibranor treatment.

Secondary endpoints

Participants in the elafibranor 80 mg and 120 mg groups had reduced ALP levels at Week 12, whereas levels increased in the placebo group (LS mean relative change from baseline: –25.3% and –44.7% *vs.* +10.0%, respectively; treatment difference [95% CI]: –35.3% [–49.2, –21.4] and –54.7% [–68.3, –41.0], respectively; Fig. 1A). Reductions in ALP stratified by UDCA status are presented in Fig. S1. In participants on elafibranor, 27.3% in the 80 mg group and 69.6% in the 120 mg group had a reduction in ALP of ≥40% from baseline, *vs.* none on placebo (Fig. 1B). Furthermore, ALP values <1.5x ULN were observed in 31.8% of participants on elafibranor 80 mg and 56.5% on elafibranor 120 mg at Week 12, *vs.* none on placebo. At Week 12, ALP normalization occurred in 9.1% and 17.4% of participants on elafibranor 80 mg and 120 mg, respectively, *vs.* none on placebo.

LS mean relative changes from baseline in ALP, AST, ALT, GGT, and TB over time are presented in Fig. 2, and LS mean absolute changes from baseline in these markers are presented in Fig. 3. Reductions in ALP, AST, ALT, and GGT were observed at Week 12 in the elafibranor 120 mg group, whereas levels increased in the placebo group. No notable differences in relative changes from baseline in TB were observed between the treatment groups at Week 12.

At Week 12, the smallest changes in ELF and LSM were observed in the elafibranor 120 mg group, while increases were observed in the placebo group (LS mean change from baseline: +0.02 and +0.4 kPa *vs.* +0.30 and +2.0 kPa, respectively; treatment difference [95% CI]: –0.28 [–0.62, +0.06] and –1.6 kPa [–5.6, +2.3], respectively; Fig. 4). Relative changes from baseline are presented in Fig. S2. The elafibranor groups also saw the smallest changes in ELF when participants were stratified by fibrosis severity based on ELF score (Fig. S3). For

Table 2. Summary of TEAEs, and TEAEs occurring in >5% of participants in any group.

Event, n (%)	Placebo n = 23	Elafibranor 80 mg n = 22	Elafibranor 120 mg n = 23
Any TEAE[a]	16 (69.6)	15 (68.2)	18 (78.3)
Pruritus	3 (13.0)	4 (18.2)	1 (4.3)
Weight increased[b]	1 (4.3)	2 (9.1)	4 (17.4)
Headache	0	3 (13.6)	2 (8.7)
Fatigue	3 (13.0)	1 (4.5)	1 (4.3)
Nausea	2 (8.7)	1 (4.5)	1 (4.3)
Hypertension	2 (8.7)	2 (9.1)	0
Constipation	2 (8.7)	0	2 (8.7)
Pyrexia	0	0	2 (8.7)
Cholangitis[c]	0	2 (9.1)	0
Back pain	0	2 (9.1)	0
Iron deficiency anemia	2 (8.7)	0	0
Any treatment-related TEAE	2 (8.7)	2 (9.1)	7 (30.4)
TEAE leading to treatment discontinuation	2 (8.7)	1 (4.5)	1 (4.3)
Any serious TEAE	1 (4.3)	0	0
Any treatment-related AESI	0	0	2 (8.7)

[a]TEAEs were defined as any adverse event that occurred on or after the date of the first administration of elafibranor or placebo up to the date of the last data collection of the double-blind period, or up to 30 days after the date of the last dose of elafibranor or placebo was received among those who discontinued treatment due to adverse events.
[b]Weight increased refers to weight gain of >5% from baseline.
[c]There was a third event of cholangitis in the elafibranor 80 mg group, reported as cholangitis acute. TEAE, treatment-emergent adverse event.

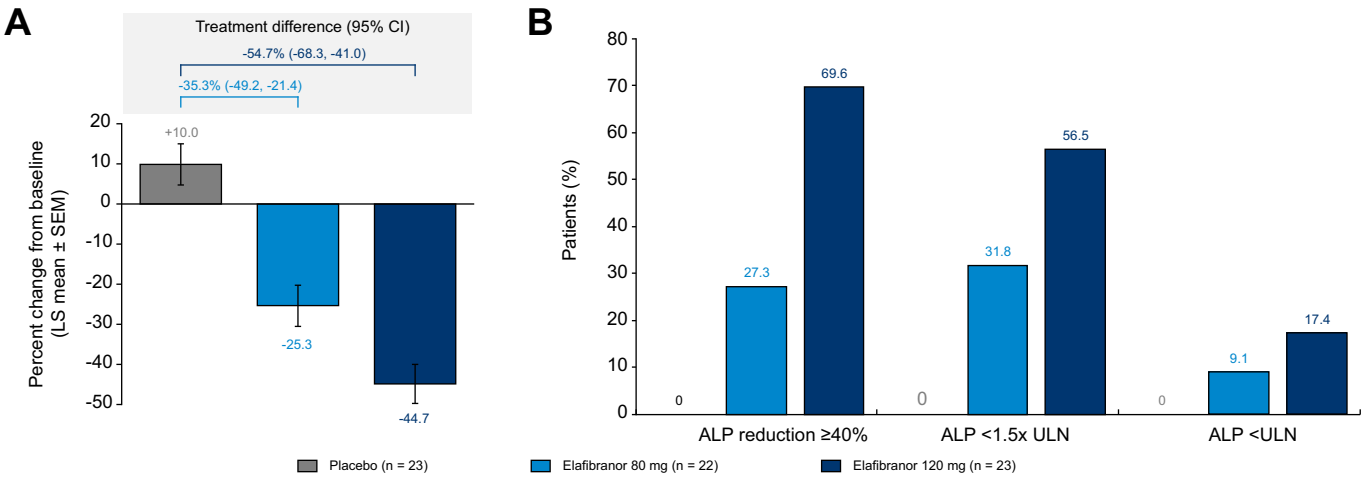

Fig. 1. ALP response at Week 12 in participants on elafibranor or placebo. (A) LS mean relative change from baseline in ALP at Week 12 (bars represent SEM). (B) ALP response according to proportions of participants with threshold reductions from baseline at Week 12. Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. ALP, alkaline phosphatase; LS, least squares; ULN, upper limit of normal.

changes from baseline in the individual components of ELF, the smallest changes were also observed in the elafibranor 120 mg group (Table S4). At Week 12, reduced pro-C3 levels were observed in the elafibranor 80 mg and 120 mg groups, while an increase was observed in the placebo group (LS mean change from baseline: –6.2 ng/ml and –2.6 ng/ml *vs.* +0.2 ng/ml; treatment difference [95% CI]: –6.4 ng/ml [–13.1, +0.2] and –2.8 ng/ml [–9.4, +3.7], respectively; Fig. 4).

Exploratory endpoints

Greater reductions in WI NRS scores were observed from baseline to Week 12 in participants on elafibranor 120 mg compared with placebo (LS mean change from baseline: –0.96 *vs.* –0.28; treatment difference [95% CI]: –0.67 [–1.35, 0.00]; Fig. 5). This improvement in WI NRS was also observed in patients with moderate to severe pruritus (WI NRS score ≥4) at baseline, where those on elafibranor 80 mg (n = 3) and elafibranor 120 mg (n = 4) had reductions of –1.52 and –2.77 at Week 12, compared with an increase of +0.10 in those on placebo (n = 2).

Most participants with IBD who had CGI-C data at baseline and Week 12 had no change in their IBD at Week 12 (29/33; 87.9%); two individuals in the placebo group had minimally improved IBD and one individual in each of the elafibranor groups had minimally worsened IBD. Reductions in total cholesterol, LDL, VLDL, and triglyceride levels were observed from baseline to Week 12 in the elafibranor groups compared with placebo (Fig. 6). HDL levels remained stable on treatment with elafibranor; no differences were observed between the treatment groups.

A consistent response in mean relative change in ALP from baseline to Week 12 was seen across each evaluable patient subgroup, with estimates of the mean difference between each treatment group in favor of elafibranor for both the 80 mg and 120 mg groups (Fig. S4).

Discussion

In this double-blind, randomized, placebo-controlled phase II trial in adults with large-duct PSC, elafibranor was well tolerated and demonstrated improvements in biochemical markers of cholestasis and inflammation, and improvements in pruritus and lipids. Elafibranor was well tolerated at 80 mg and 120 mg daily dosages, with similar safety profiles for both groups. Based on safety data available with other PPAR agonists, pre-specified AESIs included cardiovascular, muscle, liver, and renal-related adverse events, as well as weight gain. In this trial, no AESIs related to MACE, liver injury, acute kidney injury, creatine phosphokinase elevation, or muscle injury were reported. No serious TEAEs were reported in either elafibranor group, and TEAEs resulting in treatment discontinuation occurred infrequently. While more participants on elafibranor 120 mg had weight increases of >5% from baseline compared with placebo and elafibranor 80 mg, events were non-serious, mild to moderate in intensity, frequently confounded by comorbidities and concomitant medications, and elafibranor treatment continued uninterrupted in all cases. Larger trials investigating elafibranor in PBC and metabolic dysfunction-associated steatohepatitis have not demonstrated an imbalance in weight gain compared to placebo.[16,21] There were three non-serious events of cholangitis in the elafibranor 80 mg group, reported according to the investigator's assessment. Two of these events occurred in individuals with a prior history of bacterial cholangitis and biliary strictures requiring intervention; these were considered as moderate and treated with oral antibiotics, while the third event was considered mild and no antibiotics given. Overall, no new safety signals were identified.

Both dosages of elafibranor demonstrated a reduction in the mean relative change in ALP from baseline to Week 12. A reduction in the mean relative change from baseline in ALP values was observed as early as Week 4, with the greatest improvement observed in the elafibranor 120 mg group. Subgroup analyses showed a similar pattern of ALP response with elafibranor treatment at Week 12, irrespective of concomitant UDCA treatment, sex, IBD status, and degree of fibrosis. Among those on elafibranor 120 mg, the baseline ALP level was 361.8 U/L. In these participants, more than two-thirds had a decrease in ALP of ≥40%, over half had ALP levels <1.5x ULN, and 17.4% achieved ALP normalization at Week 12.

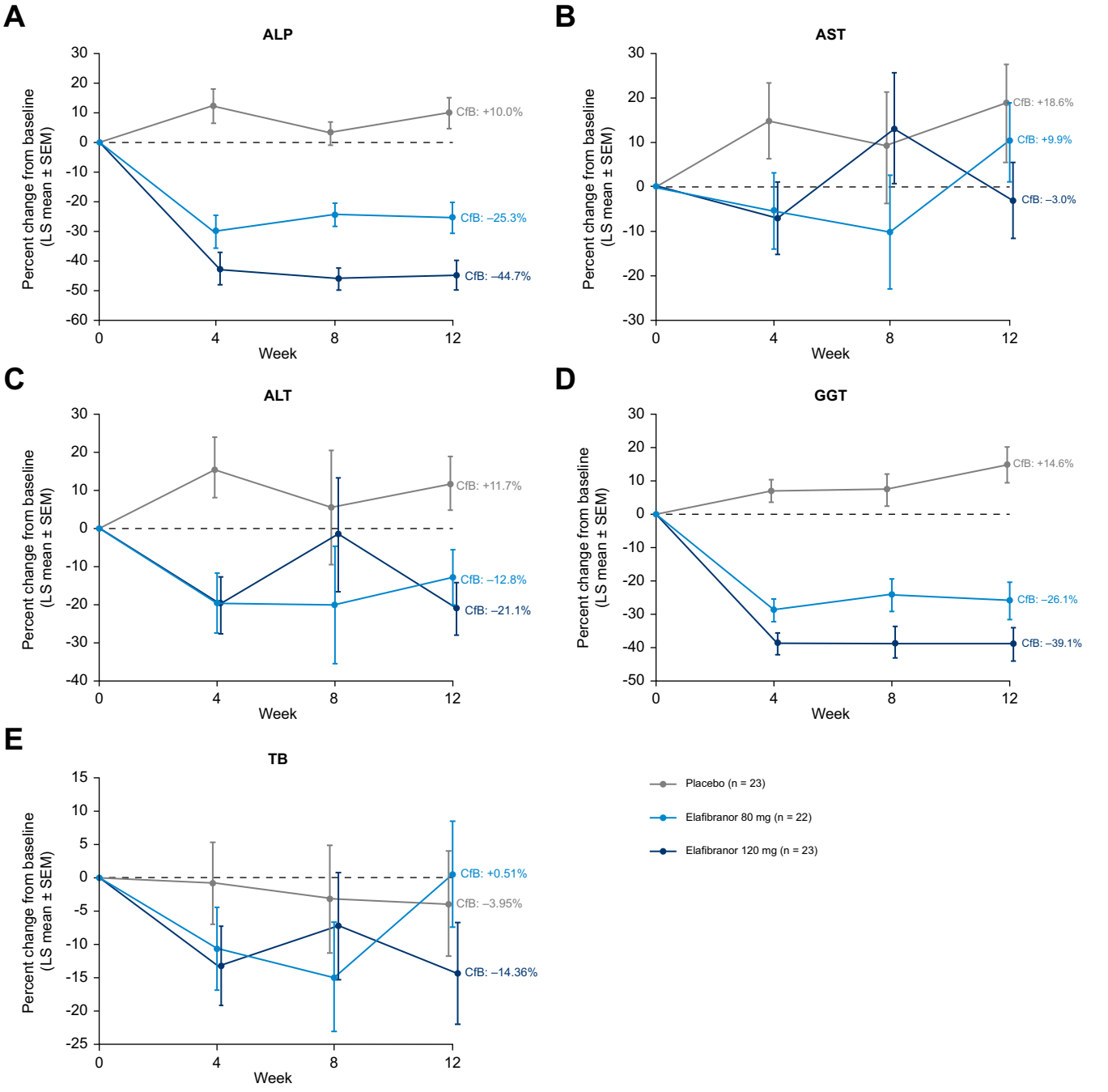

Fig. 2. Relative change from baseline in biochemical markers of cholestasis over time. (A) LS mean change in ALP levels (bars represent SEM). (B) LS mean change in AST levels (bars represent SEM). (C) LS mean change in ALT levels (bars represent SEM). (D) LS mean change in GGT levels (bars represent SEM). (E) LS mean change in TB (bars represent SEM). Relative change from baseline in ALP, AST, ALT, and GGT at Week 12 in participants with and without ongoing UDCA treatment at baseline are reported in Table S5. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CfB, change from baseline; GGT, gamma-glutamyltransferase; TB, total bilirubin.

Normalization of ALP or reduction to <1.5x ULN are associated with improved clinical outcomes for those with PSC, including extended transplant-free survival and reduced risk of hepatobiliary cancers.[22–24] The reduction in ALP was paralleled by improvements in AST, ALT, and GGT in those on elafibranor as early as Week 4. The magnitude of reductions in ALP, ALT, and GGT were consistently greater with elafibranor 120 mg compared with elafibranor 80 mg. There were no notable changes in TB, with stable levels observed from baseline to Week 12, within the normal range.

In this first phase II trial of a PPAR-α/δ agonist in PSC, the LS mean treatment differences in change from baseline in ALP levels *vs.* placebo observed after 12 weeks of elafibranor 80 mg (–35.3%) and 120 mg (–54.7%) treatment appear to be greater than the reductions observed with other treatments previously investigated in phase II trials in PSC.[25–27] For instance, after 24

ELMWOOD primary safety and efficacy results

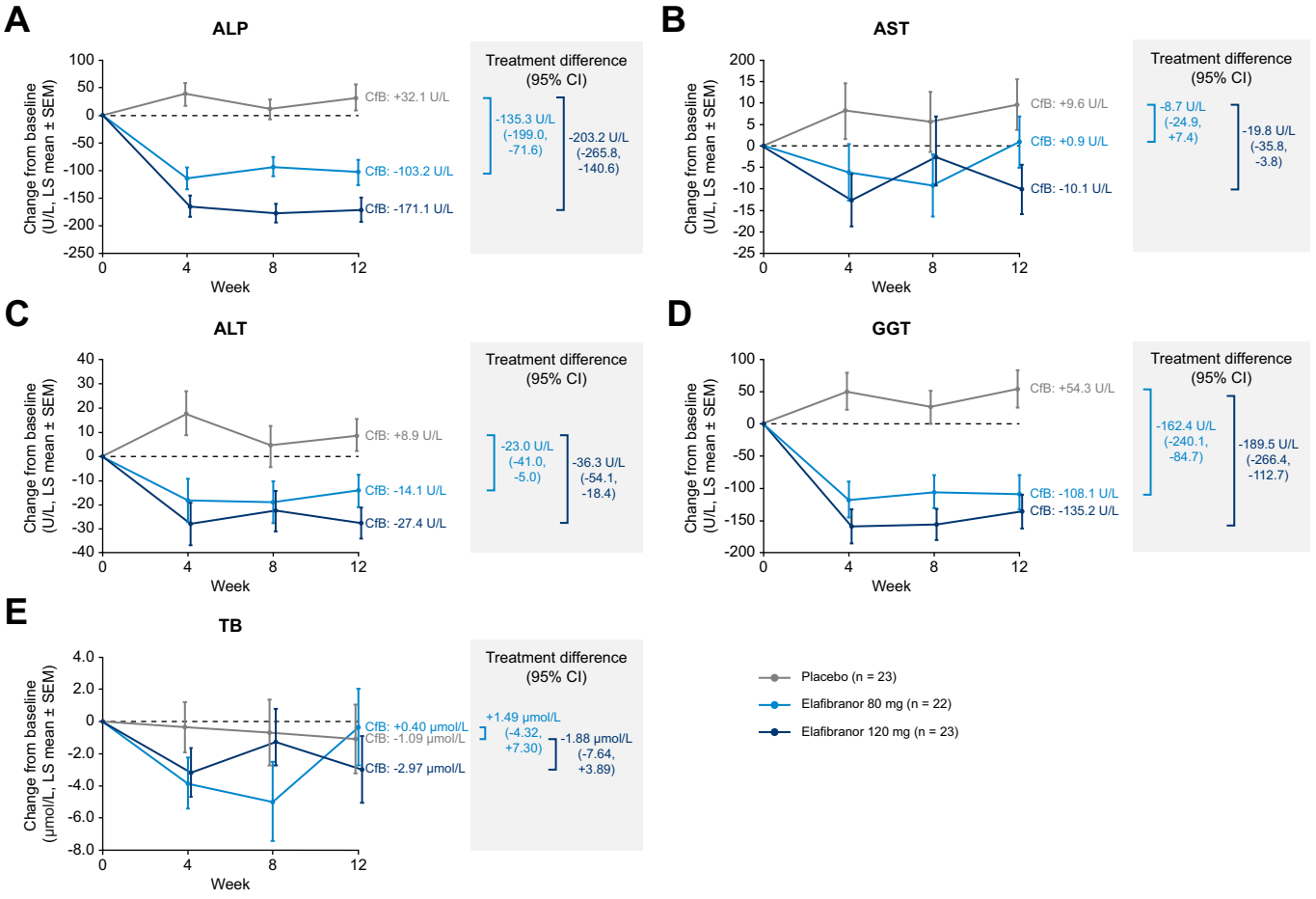

Fig. 3. Absolute change from baseline over time in biochemical markers of cholestasis. (A) LS mean ALP levels (bars represent SEM). (B) LS mean AST levels (bars represent SEM). (C) LS mean ALT levels (bars represent SEM). (D) LS mean GGT levels (bars represent SEM). (E) LS mean TB (bars represent SEM). Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CfB, change from baseline; GGT, gamma-glutamyltransferase; TB, total bilirubin.

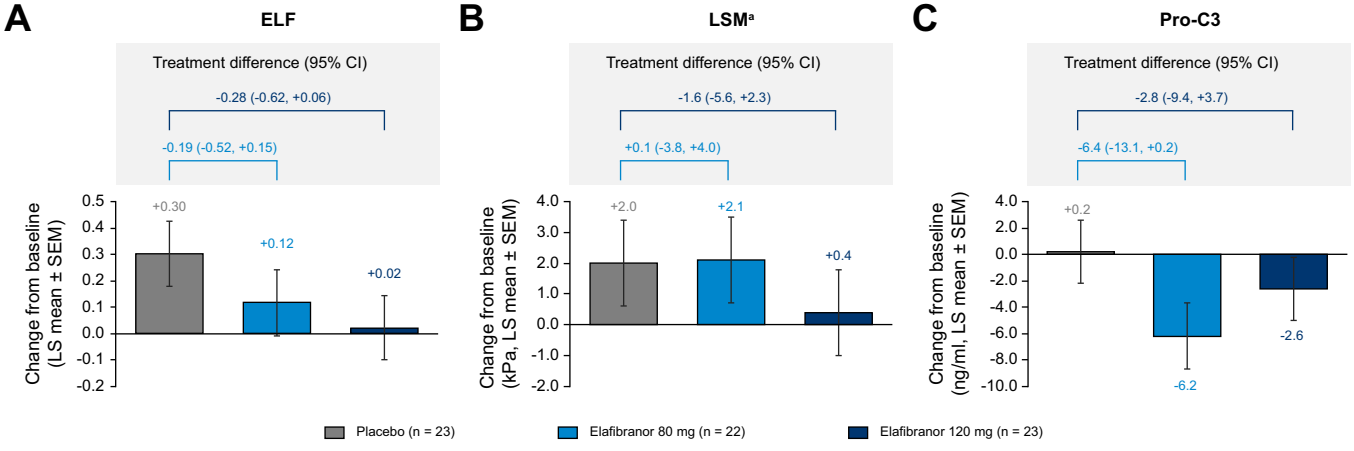

Fig. 4. Change from baseline in non-invasive markers of fibrosis at Week 12. (A) LS mean change in ELF (bars represent SEM). (B) LS mean change in LSM (bars represent SEM); [a] Placebo n = 22; elafibranor 80 mg n = 21; elafibranor 120 mg n = 21. (C) LS mean change in pro-C3 (bars represent SEM). Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. Absolute change from baseline in ELF and LSM at Week 12 in participants with and without ongoing UDCA treatment at baseline are reported in Table S5. ELF, enhanced liver fibrosis; LS, least squares; LSM, liver stiffness measurement; pro-C3, N-terminal type III collagen propeptide.

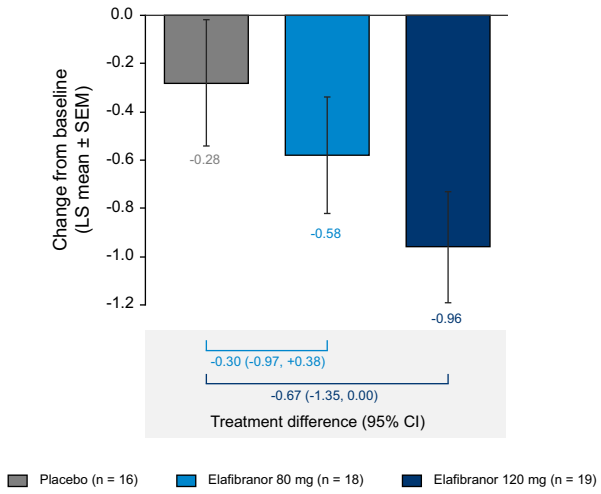

Fig. 5. Change from baseline in WI NRS at Week 12. Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. LS, least squares; WI NRS, Worst-Itch Numeric Rating Scale.

weeks of treatment, OCA 5–10 mg/day resulted in an LS mean treatment difference in change from baseline in ALP levels of approx. –25% *vs.* placebo,[26] and after 12 weeks, norUDCA 1,500 mg/day, cilofexor 100 mg/day, and bexotregrast 320 mg/day resulted in changes from baseline in ALP of –26.0%, –20.5%, and approximately –13.7% *vs.* +1.2%, +3.4%, and approximately +10.8% with placebo, respectively.[25,27,28] It should be noted that cross-trial comparisons must be interpreted with caution due to differences in trial populations and trial design. Finally, small, short-term, non-controlled studies of fibrates (synthetic PPAR ligands) in PSC have reported a median reduction in ALP levels of 40%, supporting the potential therapeutic role of PPAR activation in this disease.[29–31] Results from the ongoing two-year, phase III BEZASCLER trial will provide insights that could inform trial design and endpoints in the future.[32]

Pronounced changes in non-invasive markers of fibrosis may be challenging to detect over a short treatment period. In this trial, despite the relatively short 12-week duration of the double-blind period and roughly half of the participants having had moderate or advanced fibrosis at baseline, these markers appeared to show stabilization in those on elafibranor, compared with steady increases in these markers, suggestive of disease progression, in those on placebo. Given the short timeframe, these findings are unlikely to reflect improvement in fibrosis, but may indicate improvement in cholestasis and inflammatory processes, which can secondarily impact non-invasive markers of fibrosis. Results from the ongoing 96-week open-label extension will provide longer term data for further assessment of the potential anti-fibrotic effects of elafibranor 120 mg in PSC.

As exemplified by this trial cohort, pruritus affects up to half of people with PSC, and can be a debilitating symptom that negatively impacts health-related quality of life.[33,34] While the trial was not designed to assess the impact of elafibranor on pruritus as a key endpoint, and the baseline intensity of pruritus reported across the treatment groups was low, there appeared to be a reduction in WI NRS score with elafibranor 120 mg treatment *vs.* placebo at Week 12. Compared with the overall

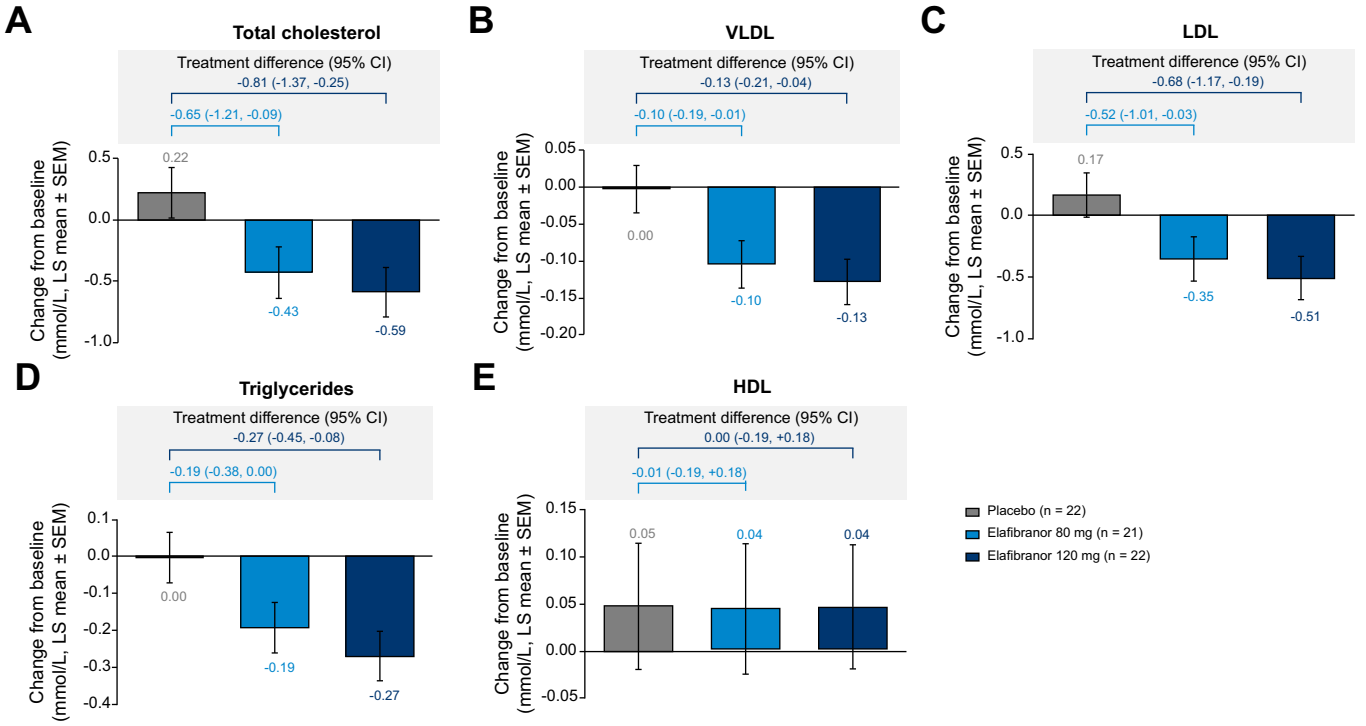

Fig. 6. Change from baseline in lipid profiles at Week 12. (A) LS mean change in total cholesterol (bars represent SEM). (B) LS mean change in VLDL (bars represent SEM). (C) LS mean change in LDL (bars represent SEM). (D) LS mean change in triglycerides (bars represent SEM). (E) LS mean change in HDL (bars represent SEM). Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; VLDL, very low-density lipoprotein.

cohort results, greater reductions in WI NRS scores were also observed with elafibranor treatment in the subgroups who had moderate to severe pruritus at baseline, and were of greater magnitude with elafibranor 120 mg. Improvements in lipid profiles were observed in participants on elafibranor, with reductions in total cholesterol, triglycerides, LDL, and VLDL compared with placebo. These lipid changes are notable, as dyslipidemia is common in PSC and may be influenced by cholestasis.[35]

One limitation of this trial is the relatively small number of participants, which may limit the extent to which its findings can be interpreted. However, a trial cohort of this size is expected for a phase II clinical trial in a rare disease, and the number enrolled was appropriate to address the primary and secondary objectives. While the use of ALP in composite efficacy endpoints is recommended for investigational trials in PSC,[23,36] its predictive value for long-term clinical benefit remains uncertain. Of note, other investigational treatments, including UDCA, that had previously shown improvement in ALP levels in phase II trials have ultimately failed to show clear long-term benefit.[37–40] As such, changes in ALP should be interpreted alongside other biochemical markers and clinically meaningful outcomes to more comprehensively assess the impact of treatment with elafibranor. The findings of this double-blind trial with respect to other biochemical markers of cholestasis and non-invasive measures of fibrosis suggest that elafibranor, a PPAR-α/δ agonist, has the potential to provide benefit in the longer term.

In ELMWOOD, the first randomized, placebo-controlled phase II trial of a PPAR-α/δ agonist in PSC, elafibranor treatment demonstrated a favorable safety profile and biochemical efficacy over 12 weeks, with elafibranor 120 mg displaying greater magnitudes of response compared with elafibranor 80 mg. These promising findings support further investigation in larger and longer term trials to better define the therapeutic potential of elafibranor as a treatment for people with PSC.

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Abbreviations

AESI, adverse event of special interest; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGI-C, Clinical Global Impression-Change scale; CI, confidence interval; ECG, electrocardiogram; ELF, enhanced liver fibrosis; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; IBD, inflammatory bowel disease; ITT, intent-to-treat; LDL, low-density lipoprotein; LS, least squares; LSM, liver stiffness measurement; MedDRA, Medical Dictionary for Regulatory Activities; PPAR, peroxisome proliferator-activated receptor; pro-C3, N-terminal type III collagen propeptide; PSC, primary sclerosing cholangitis; SV1, first screening visit; TB, total bilirubin; TEAE, treatment-emergent adverse event; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VLDL, very low-density lipoprotein; WI NRS, Worst-Itch Numeric Rating Scale.

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Conflicts of interest

CLe: Received grants from Calliditas, CymaBay, Escient, Gilead, GlaxoSmithKline, Intercept, Ipsen, Kowa, Mirum, Target RWE and Zydus. GFA: Nothing to disclose. BMB: Nothing to disclose. ABo: Received consulting fees from Alnylam, Chemobab, Cymabay, Ipsen, Intercept and GSK; Received PI grants from Chemobab, Cymabay, Gilead, Ipsen and Mirium; Medical monitor for Pfizer. CLB: Received grants from Calliditas, Chemomab, COUR, CymaBay, Gilead, GlaxoSmithKline, Hanmi, Intercept, Ipsen, Mirum, Novartis, Novo Nordisk, Pliant Therapeutics, Viking and Zydus; Received consulting fees from Chemomab, CymaBay, GlaxoSmithKline, Ipsen, Mirum, NGM Bio and Pliant Therapeutics. IC-V: Received travel grant from Chiesi; Received lecture fees from Astellas and Chiesi. NCa: Received grants or contracts from Orphalan; Received consulting fees from Albireo by Ipsen, Gilead, GlaxoSmithKline, Ipsen and Orphalan; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Advanz, Albireo by Ipsen, Gilead, Ipsen and Orphalan; Received support for attending meeting and/or travel from Albireo, Ipsen and Orphalan. NCh: Nothing to disclose. KCh: Received consulting fees from Dr Falk Pharma and Ipsen. HC-P: Received lectures and advisory board fees from Advanz, Boehringer Ingelheim, Novo Nordisk and Orphalan. MDe: Received grants from Echosens, Intercept and Merz; Received consulting fees from Boehringer Ingelheim, Gilead, GlaxoSmithKline and Ipsen; Received speaker fees from AbbVie, Advanz, AstraZeneca, Boehringer Ingelheim, Falk, Gilead, Ipsen, Merz and Sanofi; Received support for attending meetings and/or travel from AbbVie, Gilead and Ipsen. MTD: Received grants from AstraZeneca, Dr Falk Pharma, Gilead, Ipsen and Pliant Therapeutics; Received consulting fees from AstraZeneca and Eisai; Received speaker fees from AstraZeneca and Roche. BEk: Nothing to disclose. JMF: Received research support to institution from Alexion, Gilead and Ipsen; Received consulting fees from Bristol Myers Squib, Gilead and Madrigal. RGi: Nothing to disclose. HHK: Received consulting fees and honoraria from Advanz, Gilead, GlaxoSmithKline, Ipsen and Sanofi. IMJ:

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MKu: Received grants from, Akero, Altimmune, AstraZeneca, Bausch, Boehringer Ingelheim, Celgene, CymaBay, GENFIT, Genentech, Gilead, Intercept, Ionis, Inventiva, Ipsen, Madrigal, Northsea, Viking and 89bio; Received consulting fees from AbbVie, CymaBay, Gilead, Intercept, Ipsen, Madrigal, Mallinkrodt, Novo-Nordisk and Salix; Received speaker fees from Madrigal, Novo-Nordisk, Ipsen, CymaBay, Intercept, Gilead, AbbVie and Mallinkrodt. VLu: Received grants from Akero, AstraZeneca, Bristol Myers Squib, Chemomab, CymaBay, Elobix, GENFIT, Gilead, GlaxoSmithKline, Hanmi, Intercept, Inventiva, Ipsen, Madrigal, Mirum, Novo Nordisk, Pfizer, Pliant Therapeutics, Takeda, Target RWE, Zydus and 89bio. AMa: Received consulting fees from Akero, Angelini Pharma, Gilead and Madrigal; Received research support from AstraZeneca, Gilead, Madrigal and Roche. AJM-L: Participated on advisory boards for Intercept. AMu: Received grants or contracts from Ipsen; Received support for attending meetings and/or travel from Ipsen. AOl: Received consulting fees from Advanz, Gilead, GlaxoSmithKline and Ipsen; Received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Advanz, Gilead and Ipsen. BCP: Nothing to disclose. APi: Nothing to disclose. FPr: Participated on an Advisory Board for Madrigal. MSa: Received grants from Astellas and Chiesi; Received consulting from Intercept; Speaker for Chiesi and Mirum. MLS: Received grants from CymaBay, GENFIT, Intercept, Mirum and Zydus; Received consulting fees from CymaBay, Intercept and Ipsen; Received payment or honoraria from CymaBay, Intercept and Mirum; Received support for attending meetings and/or travel from CymaBay and Intercept; Speaker for Ipsen. KSp: Received consulting fees from Gilead, Ipsen and Janssen; Received lecture fees from AbbVie, Bristol Myers Squibb, Chemomab and Gilead; Received grant support from Gilead. RSw: Nothing to disclose. DTh: Received consulting fees from Chemomab, Mirum and Pliant Therapeutics; Received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Chemomab, Mirum and Pliant Therapeutics; Received support for attending meetings and/or travel from Ipsen; Participated on a Data Safety Monitoring Board or Advisory Board for GlaxoSmithKline, Mirum and Pliant Therapeutics. PJTh: Received honoraria from AbbVie, Akero, Alnylam, AstraZeneca, Gilead, Mallinckrodt and UpToDate; Received grants from Abbvie, Bayer, BioVie, Bristol Myers Squibb, Cirius Therapeutics, Corrona, CymaBay, Exact Sciences, Gilead, Hanmi, HighTide Biopharma, Intercept, Inventiva, Ipsen, Madrigal, NGM Bio, Novo Nordisk, Roche, Salix, Synthis Bio, Target, Viking and 89bio. 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Authors' contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: all authors; drafting of the publication, or reviewing it critically for important intellectual content: all authors; final approval of the publication: all authors.

Data availability statement

Qualified researchers may request access to patient-level study data that underlie the results reported in this publication. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of study participants. Where applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the US and EU or after the primary manuscript describing the results has been accepted for publication, whichever is later. Further details on Ipsen's sharing criteria, eligible studies and process for sharing are available here (https://vivli.org/members/ourmembers/). Any requests should be submitted to www.vivli.org for assessment by an independent scientific review board.

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Supplementary data

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Author names in bold designate shared co-first authorship

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Supplemental information

Safety and efficacy of elafibranor in primary sclerosing cholangitis: The ELMWOOD phase II randomized-controlled trial

Cynthia Levy, George F. Abouda, Bahri M. Bilir, Alan Bonder, Christopher L. Bowlus, Isabel Campos-Varela, Nora Cazzagon, Natasha Chandok, Kuldeep Cheent, Helena Cortez-Pinto, Münevver Demir, Michael T. Dill, Bertus Eksteen, Jonathan M. Fenkel, Richard Gilroy, Hin Hin Ko, Ira M. Jacobson, Yiannis Kallis, Marcelo Kugelmas, Velimir Luketic, Alessandra Mangia, Aldo J. Montano-Loza, Ashis Mukhopadhya, Antonio Olveira, Bhaktasharan C. Patel, Antonello Pietrangelo, Faruq Pradhan, Magdalena Salcedo, Mitchell L. Shiffman, Kathrin Sprinzl, Rachael Swann, Douglas Thorburn, Paul J. Thuluvath, Palak J. Trivedi, Juan Turnes, Claudia O. Zein, Hugo Gomes da Silva, Seema Jaitly, Benjamin Miller, Claire Milligan, Aude Tavenard, and Kris V. Kowdley

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Plain Language Summary

Primary sclerosing cholangitis, or “PSC,” is a long-term illness that damages the liver. People with PSC can experience abdominal pain, itching, and tiredness. Currently, there is no medication for PSC that can improve long-term wellbeing, slow progression of the disease, or prevent serious liver issues. As a result, many people with PSC may need a liver transplant at some point in their life. People with PSC also have a higher risk of developing bowel, liver, or bile duct cancer.

Doctors and researchers understand how bad a person’s liver disease is by looking at substances in the blood. These substances include markers such as alkaline phosphatase, or “ALP,” and others. The levels of these substances can be used to see if a person’s disease is getting better over time with treatment. Questionnaires can also be filled in by people with PSC to record how severe their itchiness is, and whether it is changing over time.

Elafibranor is a drug that is already approved to treat people with another liver disease called primary biliary cholangitis, and is one of a group of drugs that work in a similar way in the body. However, elafibranor and other similar medications have not yet been looked into as potential treatments for PSC. In this study, called “ELMWOOD,” 68 people with PSC were split into three groups. One group took elafibranor at a daily dose of 80 mg, one group took elafibranor at a daily dose of 120 mg, and the other group took a tablet that looked the same as elafibranor but contained no medicine, called a “placebo,” for 12 weeks. None of the people taking part, the doctors, nor the researchers knew who was taking elafibranor and who was taking the placebo.

The people taking part in the study had an average age of 46 years, roughly half were men, and roughly half had inflammatory bowel disease. A similar number of people in each of the elafibranor groups and the placebo group had side effects. No one taking elafibranor had any serious side effects. Therefore, no safety concerns arose with elafibranor treatment. After 12 weeks, large improvements in ALP and other blood markers were seen in people taking elafibranor, whereas these markers did not change or got worse in people taking the placebo. People taking elafibranor also reported an improvement in their itch compared with people taking the placebo.

In summary, the results from this study suggest that elafibranor is well tolerated by people with PSC and could provide an effective treatment. The longer-term effects of elafibranor will be looked into in an extension of this trial, which is currently ongoing.

Supp. Table S1. Numbers of individuals who did not meet the eligibility criteria during screening

Criterion code	Eligibility criteria per protocol	Individuals who were not eligible N=55
Inclusion criteria		
INCL03[a]	ALP ≥1.5x ULN during screening (with variability ≤30% based on two consecutive values). The interval between the two measurements should be ≥2–≤4 weeks. The baseline value will be the average of all values obtained during screening and the baseline visit measurement (obtained prior to treatment initiation).	13 (23.6%)
INCL03A[a]	ALP ≥1.5x ULN during screening (with variability ≤40% based on two consecutive values). The interval between the two measurements should be ≥2–≤4 weeks. The baseline value will be the average of all values obtained during screening and the baseline visit measurement (obtained prior to treatment initiation).	5 (9.1%)
INCL04	TB ≤2.0x ULN at SV1.	5 (9.1%)
INCL06	For participants with IBD: i) Participants with Crohn's disease must be in remission based on the investigator's clinical assessment and should be on stable treatment prior to randomization and during screening; ii) Participants with ulcerative colitis must be in remission or have low activity disease as per the judgement of the investigator and should be on stable treatment prior to randomization and during screening; iii) Current treatment for IBD is permitted, if the participant has been well controlled for ≥3 months prior to the screening period and is anticipated to remain on a stable dose of drugs for IBD treatment, including biologics, immunosuppressants, immunomodulators, or systemic corticosteroids. This provision regarding stability of IBD treatment applies to the following, among others: • 5-aminosalicylic acid drugs • Azathioprine; 6-mercaptopurine; methotrexate • Budesonide (within recommended doses for management of IBD). In addition to oral formulation, topical application of budesonide (rectal foam or enema) is allowed • Other systemic corticosteroids • Biologics (e.g. anti-tumor necrosis factor or anti-integrin therapies) • Other immunosuppressants or immunomodulators used for IBD treatment.	2 (3.6%)

	iv) Participants with IBD should have a colonoscopy performed within two years prior to the screening period showing no evidence of dysplasia or cancer.	
INCL02	Participants with a diagnosis of PSC as demonstrated by the presence of the following, and in the absence of apparent causes of secondary sclerosing cholangitis: i) Historical evidence of an elevated ALP >ULN since at least 6 months prior to SV1; ii) Cholangiogram (e.g., MRCP, ERCP, PTC) with features compatible with large duct PSC.	1 (1.8%)
INCL05	Participants taking UDCA who have: i) Total daily dose ≤23 mg/kg/day; ii) ≥6 months of stable treatment prior to screening period and expected to remain on stable dose through the 12-week double-blind period.	1 (1.8%)
INCL09	Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in the trial protocol.	1 (1.8%)
Exclusion criteria		
EXCL18	ALT and/or AST >5x ULN at SV1, or variability >40% based on two consecutive values. The interval between the two measurements should be of at least 2 weeks (and up to 4 weeks). For both ALT and AST, the baseline value for the purposes of monitoring for DILI will be the average of all values obtained during screening and the baseline visit measurement (obtained prior to treatment initiation).	9 (16.4%)
EXCL04	History or any current suspicion of cholangiocarcinoma or elevated value of CA19-9 >129 U/mL at SV1.	6 (10.9%)
EXCL18A	ALT and/or AST >5x ULN, or variability >50% based on two consecutive values during screening and as described in the protocol. The interval between the two measurements should be of at least 2 weeks (and up to 4 weeks). For both ALT and AST, the baseline value for the purposes of monitoring for DILI will be the average of all values obtained during screening and the baseline visit measurement (obtained prior to treatment initiation).	4 (7.3%)
EXCL23	eGFR <60 mL/min/1.73m^2 per MDRD-6 formula at SV1. Note: In cases of decreased eGFR where the investigator believes the value may not be representative of the actual eGFR of the potential participant, re-test after adequate hydration is allowed.	3 (5.5%)
EXCL20	Platelet count <100,000/µL at SV1.	2 (3.6%)
EXCL22	CPK >2x ULN during screening period.	2 (3.6%)
EXCL31	Any other condition that, in the opinion of the investigator, would interfere with study participation or completion, or would put the individual at risk, including a potential participant assessed as being at high risk of non-compliance.	2 (3.6%)

EXCL07	History of clinically significant hepatic decompensation, including: i) History of liver transplantation, current placement on a liver transplant list, current MELD-Na score ≥12 due to hepatic impairment (MELD-Na will be calculated only when MELD >11); ii) Evidence of complications of cirrhosis, including hepatic decompensation or evidence of significant portal hypertension complications including presence of ascites requiring treatment; history or presence of spontaneous bacterial peritonitis; presence of hepatic encephalopathy grade 2 or higher per West-Haven criteria; history of esophageal variceal bleeding or related interventions (e.g. esophageal variceal banding, or transjugular intrahepatic portosystemic shunt placement). Note: Individuals with grade 1 varices may be eligible to enroll; iii) Hepatorenal syndrome (type I or II).	2 (3.6%)
EXCL13	Known malignancy or history of malignancy within the last 5 years, with the exception of local, successfully treated basal cell carcinoma or in-situ carcinoma of the uterine cervix.	2 (3.6%)
EXCL01A	History or presence of other concomitant chronic liver disease including: i) IgG4 related sclerosing cholangitis, or IgG4 ≥4x ULN at SV1; ii) Small duct PSC; iii) Documented history of secondary sclerosing cholangitis; iv) Presence of HBsAg at screening; v) HCV infection defined by positive anti-HCV antibody and positive HCV RNA (Note: Individuals with positive anti-HCV antibody due to previously treated HCV infection, may be enrolled if a confirmatory HCV RNA is undetectable and sustained viral response has been documented); vi) PBC or history of positive anti-mitochondrial antibody; vii) Alcoholic liver disease; viii) AIH: Simplified Diagnostic Criteria of the IAIHG ≥6; ix) Presence of history of PSC-PBC or PSC-AIH overlap syndrome; x) MASH; xi) Known history of alpha-1 antitrypsin deficiency.	1 (1.8%)
EXCL03	History of bacterial cholangitis within 60 days prior to the screening period, or use of antibiotics for prophylaxis of recurrent cholangitis.	1 (1.8%)
EXCL06	Individuals with cirrhosis who are also classified as Child-Pugh B or C based on the Child-Pugh score. Individuals with cirrhosis with Child-Pugh A score are allowed to participate.	1 (1.8%)
EXCL12	Evidence of any other unstable or untreated clinically significant immunological, endocrine, neurological, gastrointestinal, hematologic, psychiatric diseases as evaluated by the investigator; other clinically significant conditions that are not well controlled.	1 (1.8%)

EXCL17	ECG with QTcF >450 msec in males or QTcF >470 msec in females for individuals without bundle branch block. For individuals with bundle branch block or other intraventricular conduction delay, a longer QTcF >480 msec would be exclusionary.	1 (1.8%)
EXCL21	INR >1.3 due to altered hepatic function at SV1.	1 (1.8%)
EXCL24	Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as evidence of impaired kidney function or underlying kidney injury).	1 (1.8%)
EXCL28	A positive drug screen at screening would be exclusionary unless it can be explained by a prescribed medication.	1 (1.8%)

[a] For this exclusion criterion, most individuals (17/18; 94%) were not eligible due to an ALP value <1.5x ULN. AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CA19-9, carbohydrate antigen 19-9; CPK, creatine phosphokinase; DILI, drug-induced liver injury; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ERCP, endoscopic retrograde cholangiopancreaticogram; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IAIHG, International Autoimmune Hepatitis Group; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4; INR, international normalised ratio; MASH, metabolic dysfunction-associated steatohepatitis; MDRD, modification of diet in renal disease study; MELD, model for end-stage liver disease; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PTC, percutaneous transhepatic cholangiography; QTcF, QT interval corrected by Fridericia's formula; RNA, ribonucleic acid; SV1, first screening visit; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Supp. Table S2. ALP variability between SV1 and SV2 in individuals who were not eligible and randomized participants, stratified by UDCA status

Screening visit		Individuals who were not eligible to participate			Randomized Participants		
		No UDCA	**Concomitant UDCA**	**All**	**No UDCA**	**Concomitant UDCA**	**All**
SV1	n **ALP**, U/L, mean (SD)	23 313.0 (223.6)	32 279.9 (135.9)	55 293.8 (176.8)	20 458.0 (226.3)	48 329.6 (157.9)	68 367.4 (188.4)
SV2	n **ALP**, U/L, mean (SD)	14 359.2 (237.1)	20 253.1 (174.5)	34 296.8 (206.1)	19 428.3 (224.3)	47 315.8 (139.1)	66 348.2 (173.9)
n **Relative difference**, %, mean (SD)		14 3.8 (12.2)	20 −2.9 (14.0)	34 −0.1 (13.5)	19 -3.7 (12.2)	47 -2.2 (12.6)	66 -2.7 (12.4)

Variability between visits calculated using: [(SV2 ALP value – SV1 ALP value) / SV1 ALP value] x 100. ALP, alkaline phosphatase; SD, standard deviation; SV, screening visit; UDCA, ursodeoxycholic acid.

Supp. Table S3. Change from baseline in ELF components

ELF component	Placebo N=23	Elafibranor 80 mg N=22	Elafibranor 120 mg N=23
Hyaluronic acid			
Baseline, ng/mL, mean (SD)	94.3 (100.9)	66.9 (60.2)	134.1 (139.9)
Change from baseline to Week 12, ng/mL, mean (SD)	+30.1 (95.8)	+25.9 (89.2)	+18.3 (140.5)
Procollagen 3 N-Terminal Pro-peptide			
Baseline, ng/mL, mean (SD)	11.9 (5.4)	12.8 (5.4)	12.8 (6.5)
Change from baseline to Week 12, ng/mL, mean (SD)	+1.3 (4.3)	+0.4 (3.0)	+0.4 (4.6)
Tissue Inhibitor of Metalloproteinases 1			
Baseline, ng/mL, mean (SD)	344.5 (110.7)	346.1 (122.9)	362.7 (89.2)
Change from baseline to Week 12, ng/mL, mean (SD)	+21.9 (64.9)	+4.6 (56.2)	−2.1 (52.5)

ELF, enhanced liver fibrosis; SD, standard deviation.

Supp. Table S4. Participants with IBD on anti-inflammatory or immunosuppressant treatment for IBD at baseline

IBD	Year of IBD diagnosis	Anti-inflammatory or immunosuppressant treatment
Crohn's Disease	1982	Adalimumab
Crohn's Disease	1992	Ustekinumab
Crohn's Disease	2003	Mesalazine
Crohn's Disease	2005	Mesalazine
Crohn's Disease	2011	Mesalazine
Crohn's Disease	2019	Mesalazine
Ulcerative colitis	1979	Mesalazine
Ulcerative colitis	1998	Azathioprine
Ulcerative colitis	1999	Sulfasalazine
Ulcerative colitis	2000	Mesalazine
Ulcerative colitis	2001	Mesalazine
Ulcerative colitis	2001	Mesalazine, prednisone
Ulcerative colitis	2005	Mesalazine
Ulcerative colitis	2007	Mesalazine
Ulcerative colitis	2007	Mesalazine
Ulcerative colitis	2009	Adalimumab, mesalazine, prednisone
Ulcerative colitis	2011	Azathioprine, infliximab
Ulcerative colitis	2011	Mesalazine, sulfasalazine, vedolizumab
Ulcerative colitis	2012	Mesalazine
Ulcerative colitis	2013	Mesalazine
Ulcerative colitis	2015	Mesalazine
Ulcerative colitis	2016	Mesalazine
Ulcerative colitis	2020	Mesalazine
Ulcerative colitis	2020	Mirikizumab
Ulcerative colitis	2022	Mesalazine
Not specified	2001	Mesalazine
Not specified	2010	Mesalazine
Not specified	2011	Mesalazine

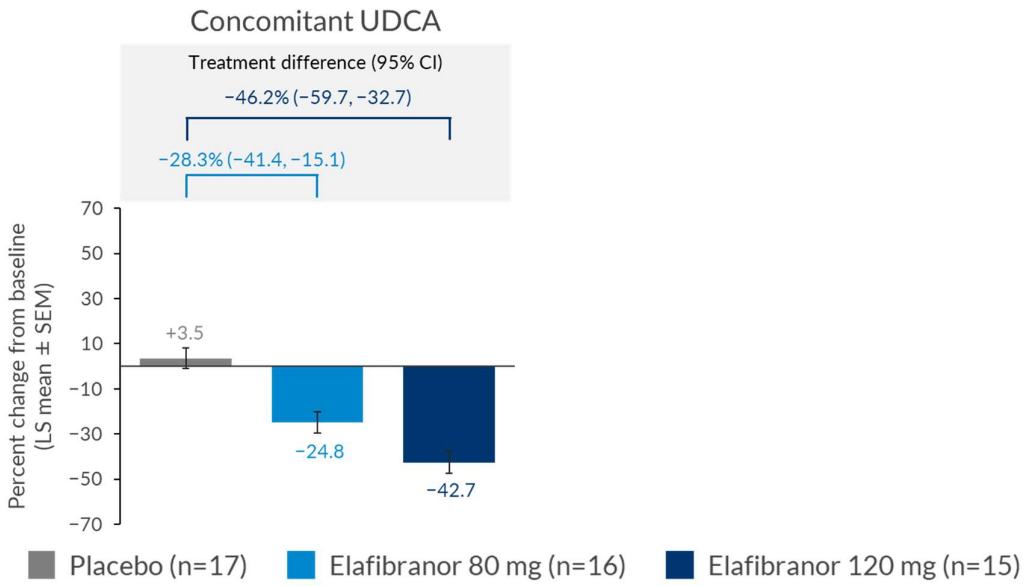
IBD, inflammatory bowel disease. Each row represents one participant.

Supp. Table S5. Change from baseline in biochemical markers of cholestasis and non-invasive markers of fibrosis at Week 12 in participants with and without ongoing UDCA at baseline

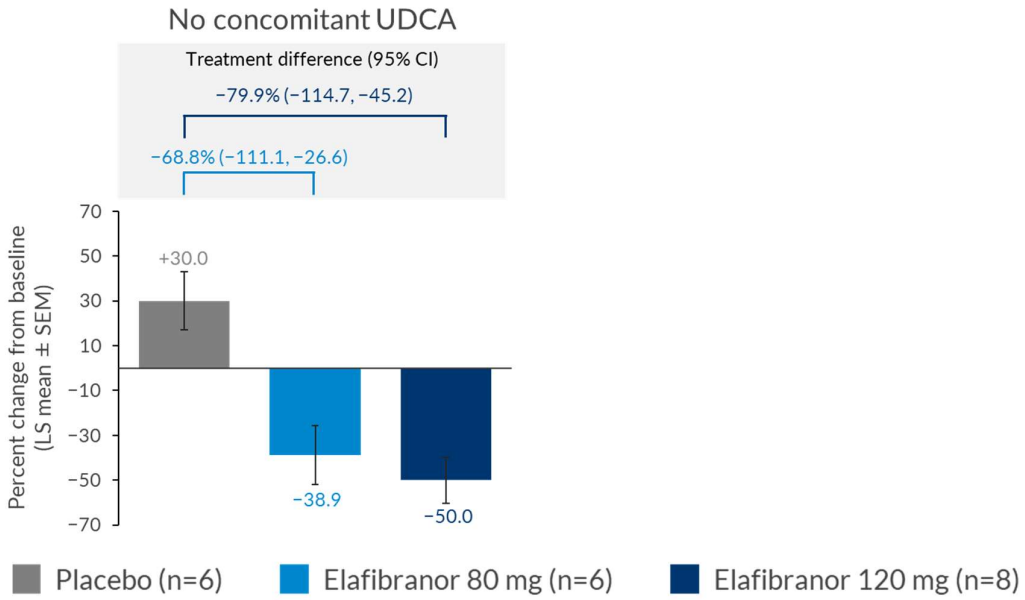
	No UDCA			Ongoing UDCA		
	Placebo (n=6)	**Elafibranor 80 mg (n=6)**	**Elafibranor 120 mg (n=8)**	**Placebo (n=17)**	**Elafibranor 80 mg (n=16)**	**Elafibranor 120 mg (n=15)**
LS mean relative change in biochemical markers of cholestasis						
ALP, % (SEM)	+30.0 (12.9)	−38.9 (13.1)	−50.0 (10.3)	+3.5 (4.6)	−24.8 (4.7)	−42.7 (4.9)
AST, % (SEM)	+30.0 (23.0)	+32.6 (24.0)	−8.1 (20.4)	+8.0 (7.7)	−5.9 (8.0)	−4.9 (8.2)
ALT, % (SEM)	+22.9 (16.2)	−6.9 (16.8)	−36.1 (13.9)	+6.2 (7.2)	−15.2 (7.5)	−14.7 (7.7)
GGT, % (SEM)	+15.5 (10.1)	−27.7 (9.3)	−40.7 (7.3)	+13.5 (6.5)	−24.5 (6.7)	−38.0 (6.9)
LS mean absolute change in non-invasive markers of fibrosis						
ELF, score (SEM)	+0.71 (0.29)	+0.02 (0.30)	+0.10 (0.24)	+0.10 (0.13)	+0.04 (0.13)	−0.07 (0.14)
LSM,[a] kPa (SEM)	+3.00 (1.66)	+1.88 (1.73)	+1.09 (1.40)	+0.97 (1.85)	+1.90 (1.91)	−0.51 (2.04)

[a] LSM in participants with ongoing UDCA treatment: placebo n=16; elafibranor 80 mg n=15; elafibranor 120 mg n=13. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, ehanced liver fibrosis; GGT, gamma-glutamyltransferase; LS, least squares; LSM, liver stiffness measurement; SEM, standard error of the mean; UDCA, ursodeoxycholic acid.

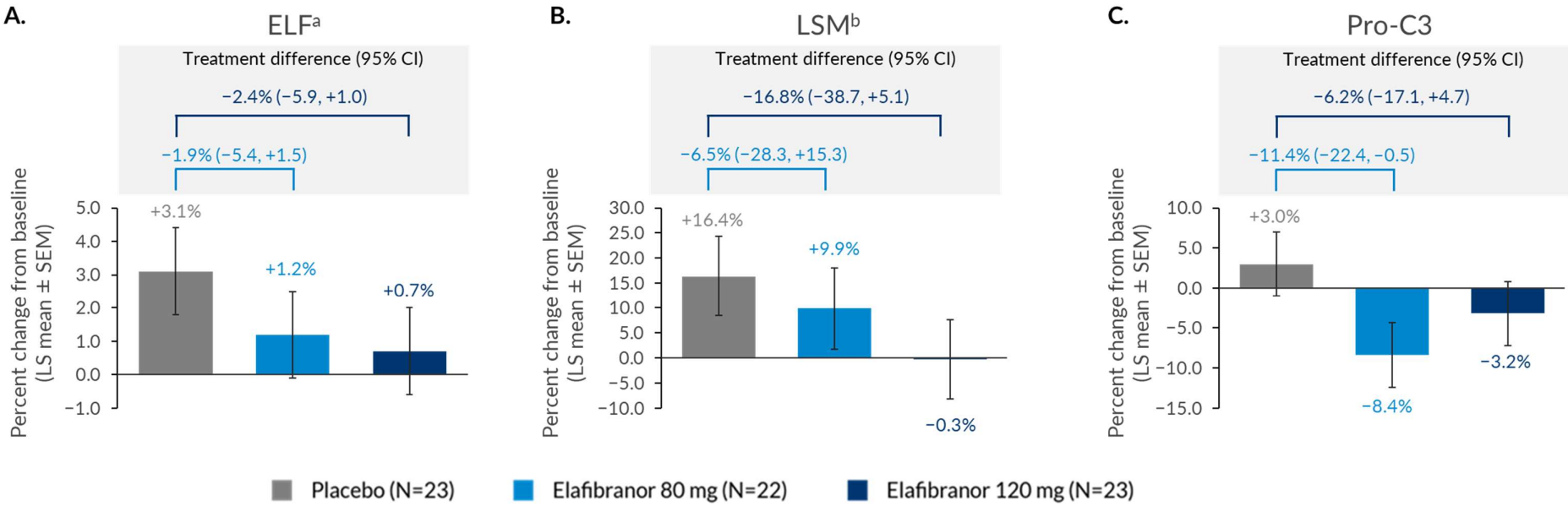
A.



B.

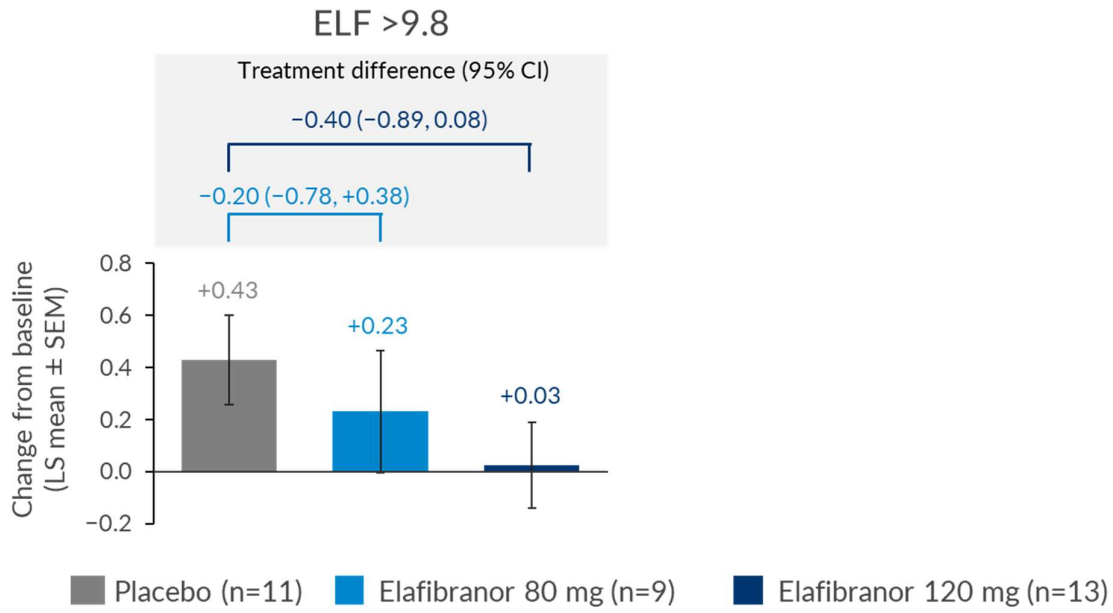


Supp. Fig. S1. Relative change from baseline in ALP at Week 12, stratified by UDCA status. (A) LS mean relative change from baseline in ALP at Week 12 in participants on concomitant UDCA (bars represent SEM). (B) LS mean relative change from baseline in ALP at Week 12 in participants not on concomitant UDCA (bars represent SEM). Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. ALP, alkaline phosphatase; CI, confidence interval; LS, least squares; SEM, standard error of the mean; UDCA, ursodeoxycholic acid.



Supp. Fig. S2. Relative change from baseline in non-invasive markers of fibrosis at Week 12. (A) LS mean change in ELF (bars represent SEM); [a] Placebo n=22; elafibranor 120 mg n=22. (B) LS mean change in LSM (bars represent SEM); [b] Placebo n=22; elafibranor 80 mg n=21; elafibranor 120 mg n=21. (C) LS mean change in pro-C3 (bars represent SEM). Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. CI, confidence interval; ELF, enhanced liver fibrosis; LS, least squares; LSM, liver stiffness measurement; pro-C3, N-terminal type III collagen propeptide; SEM, standard error of the mean.

A.



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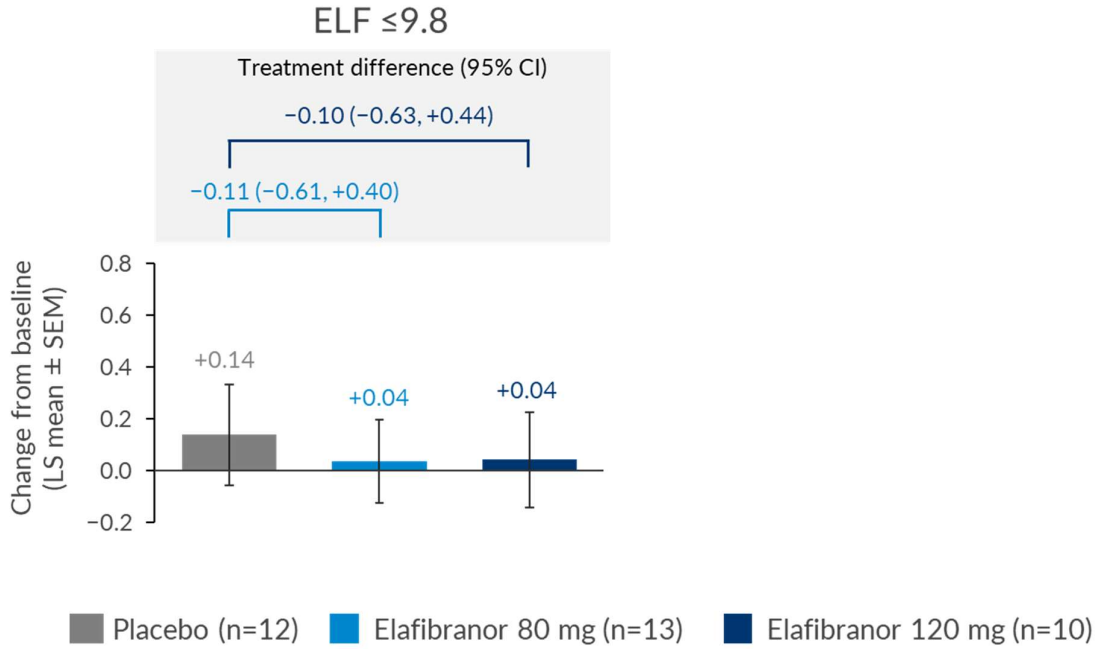
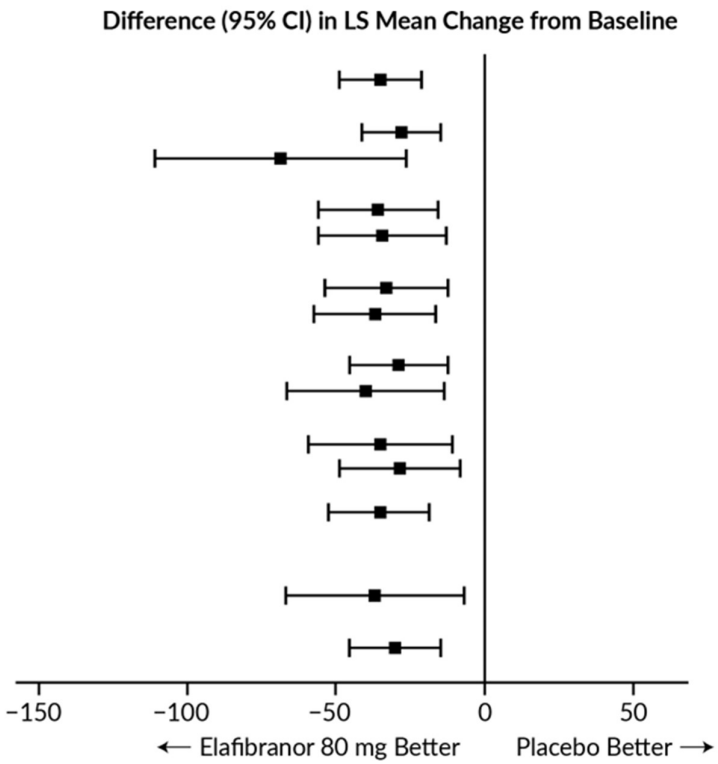


Supp. Fig. S3. Absolute mean change from baseline in ELF at Week 12, stratified by ELF severity at baseline. (A) LS mean change in ELF in participants with an ELF score >9.8 at baseline (bars represent SEM). (B) LS mean change in ELF in participants with an ELF score ≤9.8 at baseline (bars represent SEM). Treatment differences and 95% CIs analyzed by ANCOVA adjusted for baseline values. CI, confidence interval; ELF, enhanced liver fibrosis; LS, least squares; SEM, standard error of the mean.

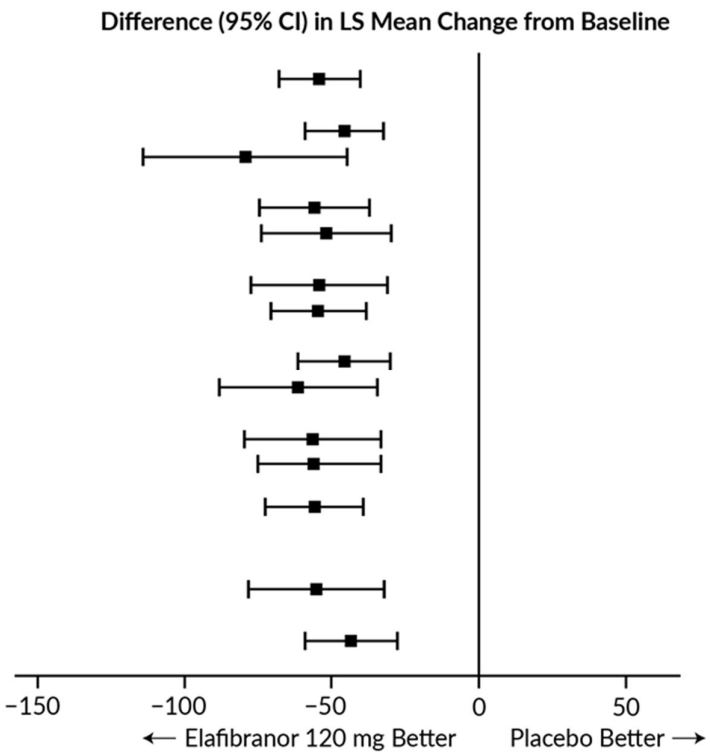
A.

Subgroup	Elafibranor 80 mg, n (%)	Placebo, n (%)	LS Means Change from Baseline Difference (%)
Overall	22 (100.0)	23 (100.0)	−35.298
UDCA			
Ongoing Treatment	16 (72.7)	17 (73.9)	−28.281
No Ongoing Treatment	6 (27.3)	6 (26.1)	−68.844
IBD			
Concomitant IBD	11 (50.0)	12 (52.2)	−36.129
No Concomitant IBD	11 (50.0)	11 (47.8)	−34.415
Sex			
Male	15 (68.2)	13 (56.5)	−33.307
Female	7 (31.8)	10 (43.5)	−37.236
LSM			
>9.5kPa	11 (50.0)	15 (65.2)	−29.143
≤9.5kPa	11 (50.0)	8 (34.8)	−40.267
ELF			
>9.8	9 (40.9)	11 (47.8)	−35.418
≤9.8	13 (59.1)	12 (52.2)	−28.578
>10.6	5 (22.7)	4 (17.4)	NE
≤10.6	17 (77.3)	19 (82.6)	−35.654
Among those with IBD			
Crohns Disease	3 (13.6)	1 (4.3)	NE
Ulcerative Colitis	5 (22.7)	10 (43.5)	−37.126
Among those with IBD			
Concomitant IBD: Anti-inflammatory Treatment Use	9 (40.9)	8 (34.8)	−30.332
Concomitant IBD: No Anti-inflammatory Treatment Use	2 (9.1)	4 (17.4)	NE



B.

Subgroup	Elafibranor 120 mg, n (%)	Placebo, n (%)	LS Means Change from Baseline Difference (%)
Overall	23 (100.0)	23 (100.0)	−54.657
UDCA			
Ongoing Treatment	15 (65.2)	17 (73.9)	−46.213
No Ongoing Treatment	8 (34.8)	6 (26.1)	−79.947
IBD			
Concomitant IBD	15 (65.2)	12 (52.2)	−56.363
No Concomitant IBD	8 (34.8)	11 (47.8)	−52.540
Sex			
Male	9 (39.1)	13 (56.5)	−54.718
Female	14 (60.9)	10 (43.5)	−55.114
LSM			
>9.5kPa	12 (52.2)	15 (65.2)	−46.287
≤9.5kPa	10 (43.5)	8 (34.8)	−61.963
ELF			
>9.8	13 (56.5)	11 (47.8)	−56.688
≤9.8	10 (43.5)	12 (52.2)	−54.246
>10.6	7 (30.4)	4 (17.4)	NE
≤10.6	16 (69.6)	19 (82.6)	−56.643
Among those with IBD			
Crohns Disease	3 (13.0)	1 (4.3)	NE
Ulcerative Colitis	11 (47.8)	10 (43.5)	−55.831
Among those with IBD			
Concomitant IBD: Anti-inflammatory Treatment Use	11 (47.8)	8 (34.8)	−44.052
Concomitant IBD: Anti-inflammatory Treatment Use	4 (17.4)	4 (17.4)	NE



Supp. Fig. S4. Subgroup analysis of mean relative difference in change from baseline in ALP in participants on elafibranor compared with placebo. (A) Relative difference between subgroups on elafibranor 80 mg versus placebo (ANCOVA). (B) Relative difference between subgroups on elafibranor 120 mg versus placebo (ANCOVA). LS means were NE when the subgroup included fewer than five individuals. ANCOVA-based comparison with placebo as reference treatment, adjusted for UDCA status (except for the UDCA subgroup analysis), and baseline values. Treatment for IBD among participants with IBD could include anti-inflammatory or immunosuppressant treatments. ALP, alkaline phosphatase; CI, confidence interval; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; LS, least squares; LSM, liver stiffness measurement; NE, non-evaluable; UDCA, ursodeoxycholic acid.