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# Phase II INTEGRIS-PSC trial of bexotegrast, an $\alpha_v\beta_6/\alpha_v\beta_1$ integrin inhibitor, in primary sclerosing cholangitis

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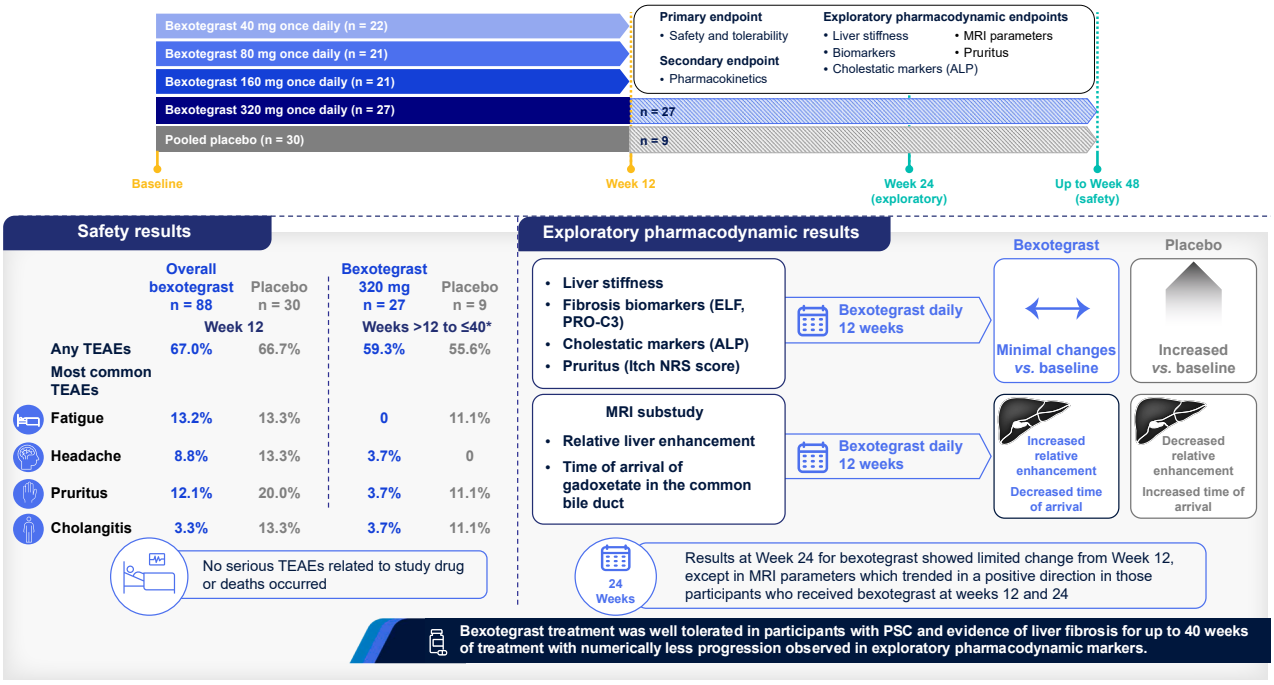
## Graphical abstract




## Highlights

- This phase II study evaluated bexotegrast, an oral $\alpha_v\beta_1$ and $\alpha_v\beta_6$ integrin inhibitor, for primary sclerosing cholangitis.
- Bexotegrast had a favorable safety and tolerability profile over 40 weeks.
- Adverse events of cholangitis and pruritus were observed less frequently with bexotegrast than with placebo.
- Less progression was observed for liver fibrosis biomarkers at Week 12 with bexotegrast *vs.* placebo.
- MRI parameters of liver fibrosis trended in a positive direction through Week 24 with bexotegrast treatment.

## Impact and implications

Primary sclerosing cholangitis (PSC) is a rare cholestatic disease of unknown etiology. Currently, there is an unmet medical need for safe and effective therapies capable of halting or reversing progression of PSC. In this phase II study in participants with PSC and suspected liver fibrosis, bexotegrast, an oral, once-daily, dual selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, had a favorable safety and tolerability profile. This study supports targeting integrin-mediated transforming growth factor-β activation as a potential therapeutic approach for PSC.

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# Phase II INTEGRIS-PSC trial of bexotegrast, an $\alpha_v\beta_6/\alpha_v\beta_1$ integrin inhibitor, in primary sclerosing cholangitis

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**Background & Aims:** Transforming growth factor-β signaling activated by $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins drives liver fibrosis in primary sclerosing cholangitis (PSC). The aim of this study was to investigate the safety and exploratory pharmacodynamics of bexotegrast (PLN-74809), an oral, once-daily inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, in participants with PSC and liver fibrosis.

**Methods:** In this phase II, double-blind, dose-ranging study, 117 participants with PSC were randomized 3:1 to receive once-daily oral bexotegrast or placebo in three cohorts: 40 mg or placebo for 12 weeks (part 1); 80 mg, 160 mg, or placebo for 12 weeks (part 2); and 320 mg or placebo for up to 40 weeks (part 3). The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs). Exploratory pharmacodynamic endpoints included changes in alkaline phosphatase values, enhanced liver fibrosis (ELF) scores, neoepitope-specific N-terminal pro-peptide of type III collagen (PRO-C3) levels, liver stiffness measurements, gadoxetate-enhanced MRI measures, and the Itch Numeric Rating Scale.

**Results:** A total of 117 participants received bexotegrast (40 mg [n = 22], 80 mg [n = 21], 160 mg [n = 21], 320 mg [n = 27]) or placebo (n = 30). Bexotegrast was well tolerated, with similar rates of TEAEs in the pooled bexotegrast and placebo groups (72.7% and 70.0%). TEAEs were mild to moderate, and no serious TEAEs related to study drug were observed. Numerically less pharmacodynamic progression was observed with bexotegrast in ELF score, PRO-C3, and MRI assessments at Week 12 compared with placebo. Pharmacodynamic results at Week 24 showed limited change from Week 12 except in MRI parameters which continued to improve.

**Conclusions:** Bexotegrast was well tolerated for up to 40 weeks in participants with PSC and liver fibrosis and was associated with numerically less progression in exploratory pharmacodynamic markers.

**Trial registration number:** NCT04480840.



## Introduction

Primary sclerosing cholangitis (PSC) is a rare cholestatic disease of unknown etiology characterized by biliary inflammation and progressive fibrosis.[1–3] PSC onset begins as heterogeneous biliary fibrosis, which then progresses to parenchymal liver fibrosis, typically with a slow and variable disease course, especially prior to symptom development.[4,5] Over time, biliary and parenchymal liver fibrosis from PSC progresses to cirrhosis with serious and often fatal liver complications, such as portal hypertension, end-stage liver disease, and increased risk of malignancy.[2,6] Up to 40% of participants with PSC require liver transplantation within 13–22 years of diagnosis, and the disease recurs in approximately 20–30% of participants within 10 years after transplant.[3,7–10] The majority of people living with PSC have associated inflammatory bowel disease (IBD), commonly ulcerative colitis. While PSC is associated with IBD, causal relationships remain to be established.[11]

Transforming growth factor (TGF)-β is involved in multiple biological functions, including tissue homeostasis, cell proliferation and migration, metabolic adaptation, and immune

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homeostasis.[12] In the liver, TGF-β is involved in homeostasis of epithelial cells and stromal compartments, as well as liver development and regeneration.[13,14] However, TGF-β signaling activated by $\alpha_v$ integrins is a key driver of fibrosis in the liver.[15] $\alpha_v\beta_6$ integrin expression is increased on injured cholangiocytes, and $\alpha_v\beta_1$ integrin is expressed on hepatic stellate cells and fibroblasts.[16,17] In preclinical models of biliary and parenchymal fibrosis, loss of or inhibition of $\alpha_v\beta_6$ or $\alpha_v\beta_1$ integrins resulted in reduced fibrosis.[16–18] As systemic inhibition of TGF-β signaling carries safety concerns, a TGF-β–based therapy providing localized inhibition of TGF-β at the site of fibrosis is preferred.[19–22]

Bexotegrast is an oral, once-daily, dual selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins currently in development for the treatment of PSC and has been evaluated in clinical trials for idiopathic pulmonary fibrosis and progressive pulmonary fibrosis. Bexotegrast inhibits the activation of TGF-β at sites of fibrosis by blocking locally upregulated $\alpha_v\beta_6$ or $\alpha_v\beta_1$ integrins.[23] The mechanism of action of bexotegrast is predicted to directly prevent new fibrosis by reducing TGF-β signaling and therefore the downstream expression of profibrotic genes, such as collagen type 1 alpha 1, the main component of fibrotic scar. Because the extracellular matrix is constantly turning over – with new matrix being deposited while existing matrix is degraded – bexotegrast is expected, over time, to reduce existing fibrosis by decreasing matrix deposition.

In phase II studies in participants with the $\alpha_v\beta_6$ or $\alpha_v\beta_1$ integrin-mediated fibrotic lung disease, idiopathic pulmonary fibrosis, bexotegrast was shown to be well tolerated for up to 40 weeks of treatment. It improved lung function and demonstrated antifibrotic effects compared with placebo,[24] with decreases in collagen deposition from baseline and potentially beneficial architectural changes in the lung as determined by dual PET/MRI.[25]

The objective of the INTEGRIS-PSC study (NCT04480840) was to assess the safety and tolerability of bexotegrast in participants with PSC and liver fibrosis. Liver stiffness measurement (LSM), circulating biomarkers, cholestatic markers, MRI parameters, and pruritus severity were also assessed.

## Patients and methods

### Study population

INTEGRIS-PSC was a phase II, randomized, double-blind, dose-ranging, placebo-controlled, parallel-group evaluation of bexotegrast in participants with PSC and suspected liver fibrosis (supplementary CTAT table). Adult participants (aged 18-75 years, inclusive) with confirmed large-duct PSC based on an abnormal cholangiogram by MRI, endoscopic retrograde cholangiopancreaticography, and/or percutaneous transhepatic cholangiography were included. Additional inclusion criteria were stable IBD, if present, and serum alkaline phosphatase (ALP) concentration of ≤10× the upper limit of normal (ULN). The study was initially conducted with an ALP eligibility criterion of >1.5× ULN to ≤10× ULN, which was later amended to include participants with ALP levels from the normal range up to ≤10× ULN. The study was enriched for liver fibrosis, as evidenced by ≥1 of the following: LSM by vibration-controlled transient elastography (VCTE; FibroScan® value [Echosens; Paris, France] of 8-14.4 kPa, inclusive); enhanced liver fibrosis (ELF) score of ≥7.7; magnetic resonance elastography value between 2.4 and 4.9 kPa, inclusive; or previous biopsy confirming liver fibrosis without cirrhosis. Acute cholangitis was assessed by the study's principal investigators and reported as an adverse event.

Key exclusion criteria included other causes of liver disease, such as secondary sclerosing cholangitis or viral, metabolic dysfunction–associated, or alcohol-related liver disease (as assessed clinically); evidence of cirrhosis; known or suspected overlapping diagnosis of autoimmune hepatitis; worsening liver chemistry during screening; a medical history of or current cholangiocarcinoma, other hepatobiliary malignancy, colorectal cancer, or other abdominal malignancy; and small-duct PSC without evidence of large-duct involvement.

Concomitant treatment with ursodeoxycholic acid (UDCA) <25 mg/kg/day was permitted, provided it was stable for at least 3 months before screening with the intent to remain stable throughout the study. Concomitant medications for the treatment of IBD were also allowed, provided that therapy was stable at screening. Escalation of permitted concomitant IBD treatment was allowed during the study, if necessary.

### Study design

The study was conducted using an ascending-dose cohort approach, with participants in each cohort randomized 3:1 to receive once-daily bexotegrast or placebo (40 mg or placebo for 12 weeks [part 1]; 80 mg or 160 mg or placebo for 12 weeks [part 2]; 320 mg or placebo for >24 weeks and ≤48 weeks [part 3]); pooling of participants in the placebo group following completion of all dosing cohorts was planned *a priori* (Fig. 1). The study was conducted in three parts (40 mg; 80 mg and 160 mg; and 320 mg) with an independent data and safety monitoring board review of safety findings. In the 320-mg cohort, once the last participant reached Week 24, all participants remaining in the study proceeded to their next scheduled clinic visit and completed the study. Due to the rapid enrollment of the 320-mg cohort, the longest treatment duration was 40 weeks. Randomization was stratified according to whether participants were receiving UDCA (yes/no) at baseline. Participants, investigators, and those involved in the trial conduct were blinded to the trial treatment assignments.

This study was conducted in accordance with the study protocol, the Declaration of Helsinki, and International Council on Harmonization Good Clinical Practice regulations. The study was approved by local institutional review boards, and all participants provided written informed consent.

### Study assessments

The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs) and secondary safety endpoints were clinical laboratory tests, including hematology, serum chemistry, coagulation, and urinalysis, electrocardiograms and vital signs measurements. The secondary pharmacokinetic endpoints are plasma bexotegrast concentrations (total and unbound concentrations) at each sampling time point. Exploratory pharmacodynamic endpoints included changes from baseline to Weeks 12 and 24 in the following: liver chemistry, including ALP, gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin; the liver fibrosis biomarkers ELF, and neoepitope-specific N-terminal pro-peptide of type III collagen (PRO-C3) as measured using an ELISA (Roche Elecsys Cobas®); MRI parameters,

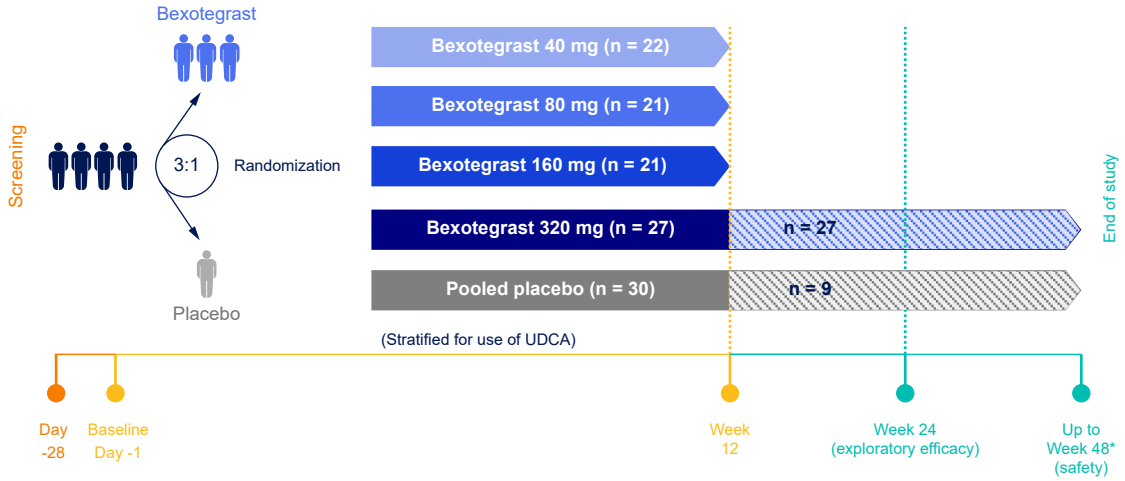


**Fig. 1. INTEGRIS-PSC study design.** * *Due to trial design and enrollment trajectory, the longest treatment duration was 40 weeks. R, randomization; UDCA, ursodeoxycholic acid.

including gadoxetate contrast relative enhancement and gadoxetate time of arrival to the common bile duct; and patient-reported outcomes, including the Itch Numeric Rating Scale (NRS, defined as severity of itch over the last 24 h on a scale of 0 [no itch] to 10 [worst imaginable itching]).[26] MRI assessments were conducted in a voluntary substudy at investigational sites able to perform these scans. Using the magnetic resonance contrast agent gadoxetate, relative enhancement of the liver was used to determine hepatocyte function, and time of arrival of gadoxetate to the common bile duct was measured to determine hepatobiliary excretory function.[27,28] Biliary stricture burden was assessed qualitatively and centrally by a single radiologist blinded to treatment assignment. An additional endpoint was LSM as measured by VCTE (FibroScan®).

### Statistical analysis

As this was a proof-of-concept (POC) study, the sample size (n = 21 per treatment group) was determined based on the historical precedent of phase IIa PSC POC trials,[29,30] and empirically to allow for an initial characterization of the safety and tolerability of bexotegrast and provide data to support potential POC studies using a range of exploratory pharmacodynamic markers. No power calculations were conducted for the exploratory pharmacodynamic markers. Descriptive statistics, including means and SD or SE and 95% CIs, were provided for the summary of observed change from baseline.

All participants who received ≥1 dose of bexotegrast or placebo were included in the safety population, which was the primary population for both safety and exploratory pharmacodynamic summaries. Safety data, based on TEAEs, are presented by treatment group and included events occurring during bexotegrast treatment through a 4-week follow-up period. No imputation of missing data was performed.

## Results

### Study participants

A total of 201 participants underwent screening, of whom 117 met the eligibility criteria and were randomized to receive once-daily, oral bexotegrast 40 mg (n = 22), 80 mg (n = 21), 160 mg (n = 21), or 320 mg (n = 27) or placebo (n = 30) (Fig. 2). Of the 112 participants who failed screening, most (102 [91.1%]) did not meet inclusion/exclusion criteria, primarily due to the presence of liver cirrhosis, not meeting suspected liver fibrosis criteria, worsening of liver disease, or ALP levels ≤1.5× ULN (criterion removed before enrollment in the bexotegrast 80-mg and 160-mg cohorts). Four participants were each enrolled in two separate cohorts with a minimum washout period of 6 months between completion of treatment in the first cohort and screening in the second cohort. Of these participants, three were randomized to two bexotegrast doses and one was randomized to bexotegrast and to placebo. For safety reporting, these participants are counted independently in each individual treatment group but only once in the overall bexotegrast group if they repeated bexotegrast doses. For exploratory pharmacodynamics, these repeat bexotegrast participants are counted in each individual treatment group and twice in the overall bexotegrast group given the new baseline for the second treatment group.

Participant disease characteristics at baseline were generally similar between treatment groups (Table 1). The mean age was 45 years in both groups, with a similar time since PSC diagnosis (approximately 9 years). The majority of participants in each treatment group (range, 58-75%) received concomitant UDCA. Concomitant IBD was present in 61.4% and 56.7% of participants in the overall bexotegrast and placebo groups, respectively, with those participants receiving concomitant medications including IBD treatments such as stable doses of corticosteroids and biologics (Table S1). The proportion of men was higher in the placebo group than in the overall bexotegrast group (80.0% *vs*. 65.9%, respectively). Liver chemistry parameters were similar in the overall bexotegrast and placebo groups, although heterogeneity was found for some parameters across the bexotegrast dose groups. Briefly, amending the lower limit of the ALP eligibility criterion from >1.5× ULN to normal during the conduct of the trial explains the higher baseline ALP in the 40-mg cohort, which was the first to enroll. The overall bexotegrast and placebo groups had similar baseline ELF scores (9.3 in both groups, respectively) and LSMs (9.0 and 8.6 kPa). None of the participants had high

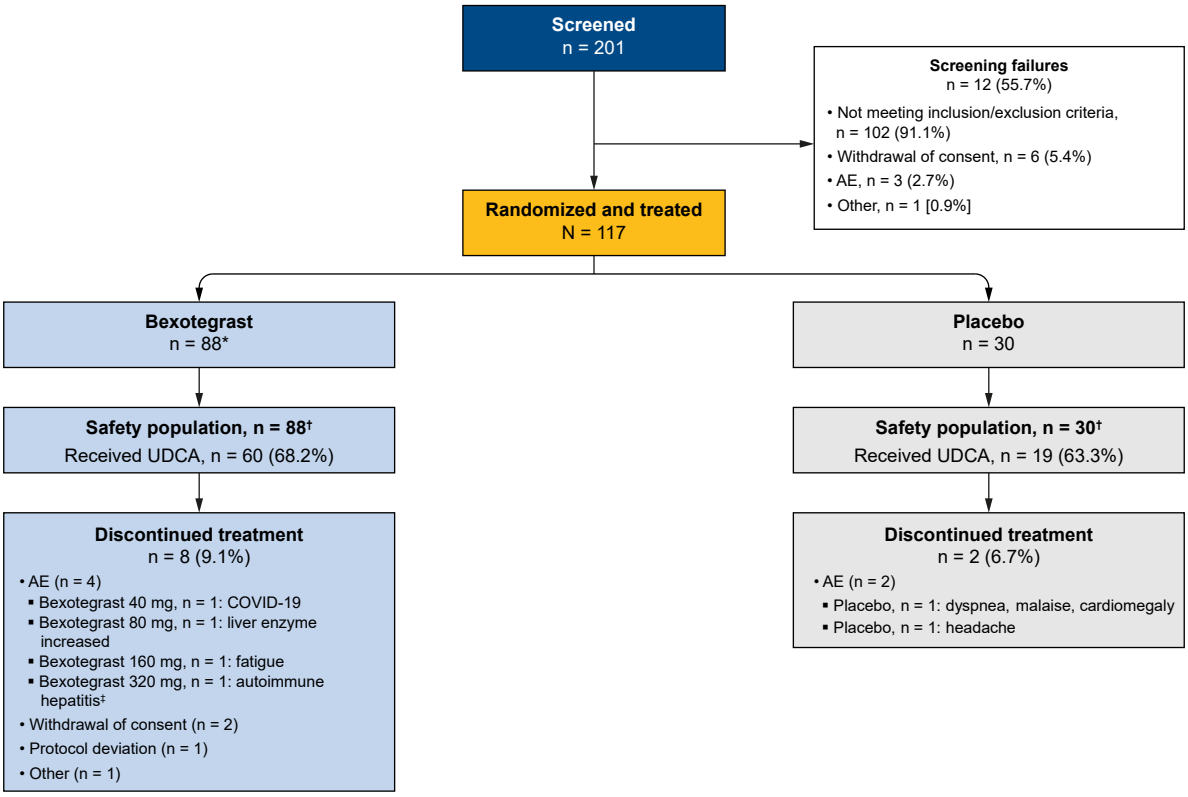


**Fig. 2. Participant disposition.** *Three participants who were randomized to receive bexotegrast were subsequently re-randomized following a minimum washout period of 6 months and successful re-screening to receive bexotegrast 320 mg for up to 48 weeks; one was re-randomized to placebo. †Safety population was used for analysis of both safety and exploratory pharmacodynamics. AE, adverse event; UDCA, ursodeoxycholic acid.

grade biliary strictures (*i.e.* dominant), as required for study eligibility (Table S2). The majority of participants in each of the groups had minimal-to-moderate strictures with one participant in the bexotegrast 80 mg, 320 mg and placebo groups having moderate-to-severe strictures. Baseline itch NRS scores were low (1.5 and 1.0 out of 10 in the overall bexotegrast and placebo groups, respectively).

## Safety

All bexotegrast doses were well tolerated, with similar rates of TEAEs in the overall bexotegrast and placebo groups up to 40 weeks (72.7% and 70.0%, respectively; Table S3). All TEAEs were mild to moderate in severity, and all TEAEs leading to early termination of treatment (four in bexotegrast and two in placebo; Fig. 2) were deemed not related to study drug by the principal investigators. The most common TEAEs in participants receiving bexotegrast were fatigue, pruritus, headache, and COVID-19, all reported at lower proportions and rates compared with the placebo group; and nasopharyngitis and nausea, reported at higher proportions and rates compared with the placebo group (Tables 2 and S3). Events of pruritus were more common in the placebo group (7/30 [23.3%]) compared with the overall bexotegrast group (12/88 [13.6%]) up to Week 40. No serious TEAEs related to the study drug were reported, and no deaths occurred up to 40 weeks of treatment (Tables 2 and S3). When stratified by UDCA use, TEAEs reported in bexotegrast-treated participants were comparable between those who did and did not receive concomitant UDCA and included pruritus, fatigue, COVID-19, and gastrointestinal events (Tables S4 and S5).

No notable changes in physical examination findings, vital signs, electrocardiograms, or laboratory test parameters occurred, except for liver biochemistry changes described below, in either placebo or bexotegrast groups up to 40 weeks of treatment.

Participants in the overall bexotegrast group had fewer TEAEs classified as hepatobiliary disorders up to Week 12 compared with those receiving placebo (5/91 [5.5%] *vs.* 5/30 [16.7%], respectively) (Table 2). The difference in hepatobiliary events was driven by differences in cholangitis events (3/91 [3.3%] and 4/30 [13.3%]) and jaundice/ocular icterus events (0 and 4/30 [13.3%]) in the overall bexotegrast and placebo treatment groups, respectively.

TEAEs after Week 12 and up to Week 40 were similar between the bexotegrast 320 mg- and placebo-treated participants (59.3% and 55.6%, respectively; Table 2) with no notable differences. One participant (3.7%) in the bexotegrast 320-mg group experienced cholangitis compared with one participant (11.1%) who received placebo.

For those participants with active IBD, the partial Mayo scores at Weeks 12 and 24 were similar to baseline for the bexotegrast and placebo groups (Fig. S1).

## Pharmacokinetics

Total and unbound bexotegrast plasma concentrations showed dose dependency over time (Fig. S2). Mean total and

**Table 1. Baseline demographics and disease characteristics (safety population).**

| Characteristic | Bexotegrast 40 mg (n = 24)* | Bexotegrast 80 mg (n = 20)* | Bexotegrast 160 mg (n = 20)* | Bexotegrast 320 mg (n = 27) | Overall bexotegrast (n = 88) | Placebo (n = 30) |
|---|---|---|---|---|---|---|
| Male, n (%) | 17 (70.8) | 16 (80.0) | 14 (70.0) | 13 (48.1) | 58 (64.9) | 24 (80.0) |
| Age, mean (SD), years | 46.9 (15.1) | 40.5 (15.3) | 45.1 (12.7) | 47.1 (14.5) | 44.9 (14.6) | 45.2 (11.7) |
| Race, n (%) | | | | | | |
| White | 20 (83.3) | 16 (80.0) | 18 (90.0) | 26 (96.3) | 77 (87.5) | 25 (83.3) |
| Black | 2 (8.3) | 2 (10.0) | 1 (5.0) | 0 | 5 (5.7) | 2 (6.7) |
| Asian | 2 (8.3) | 1 (5.0) | 1 (5.0) | 1 (3.7) | 5 (5.7) | 1 (3.3) |
| Other/not reported/unknown | 0 | 1 (5.0) | 0 | 0 | 1 (1.1) | 2 (6.7) |
| Time since PSC diagnosis, mean (SD), years | 11.1 (8.2) | 8.3 (8.0) | 7.8 (6.8) | 9.4 (11.2) | 9.1 (8.7) | 9.0 (7.3) |
| Concomitant UDCA use, n (%) | 14 (58.3) | 15 (75.0) | 13 (65.0) | 18 (66.7) | 60 (68.2) | 19 (63.3) |
| IBD, n (%) | 18 (75.0) | 12 (60.0) | 11 (55.0) | 13 (48.1) | 54 (61.4) | 17 (56.7) |
| Ulcerative colitis | 11 (45.8) | 6 (30.0) | 7 (35.0) | 6 (22.2) | 30 (34.1) | 10 (33.3) |
| Crohn's disease | 6 (25.0) | 4 (20.0) | 2 (10.0) | 8 (29.6) | 20 (22.7) | 6 (20.0) |
| IBD other | 3 (12.5) | 2 (10.0) | 2 (10.0) | 0 | 7 (8.0) | 1 (3.3) |
| ALP, mean, (SD), U/L† | 315.1 (140.3) | 199.2 (81.0) | 273.8 (165.6) | 190.6 (91.3) | 243.6 (132.1) | 277.4 (215.9) |
| ALT, mean (SD), U/L | 91.5 (62.1) | 67.6 (63.2) | 98.4 (73.1) | 60.4 (37.8) | 78.5 (60.2) | 73.1 (59.8) |
| AST, mean (SD), U/L | 67.2 (49.3) | 46.4 (30.1) | 69.0 (39.6) | 44.6 (24.7) | 56.3 (38.1) | 51.6 (37.1) |
| Total bilirubin, mean (SD), mg/dl | 0.7 (0.3) | 0.8 (0.5) | 0.9 (0.4) | 0.5 (0.2) | 0.7 (0.4) | 0.8 (0.4) |
| Direct bilirubin, mean (SD), mg/dl | 0.3 (0.2) | 0.3 (0.2) | 0.3 (0.2) | 0.2 (0.1) | 0.2 (0.2) | 0.3 (0.2) |
| ELF score, mean (SD) | 9.6 (0.8) | 9.2 (1.0) | 9.4 (0.8) | 9.0 (0.8) | 9.3 (0.9) | 9.3 (1.0) |
| Transient elastography, mean (SD), kPa | 10.1 (2.6) | 9.1 (3.0) | 8.2 (3.2) | 8.7 (3.1) | 9.0 (3.0) | 8.6 (2.8) |
| Partial Mayo score, mean (SD) [n]‡ | 0.6 (1.0) [18] | 1.5 (2.5) [12] | 0.9 (1.2) [11] | 0.8 (1.2) [13] | 0.9 (1.5) [54] | 0.5 (1.4) [15] |
| Itch NRS score, mean (SD) | 1.8 (2.5) | 2.1 (2.6) | 1.4 (1.5) | 0.9 (1.8) | 1.5 (2.2) | 1.0 (1.4) |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; NRS, numerical rating scale; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

*Two participants (80 mg and 160 mg) received a dose of ~40 mg/day due to site errors and were grouped with the 40-mg group for all summaries.

†The study was initiated with an inclusion criterion of ALP >1.5× ULN for the 40-mg cohort; this was later removed.

‡Partial Mayo score only reported for those participants with active IBD at baseline.

Table 2. Proportion of participants reporting TEAEs through Week 12 and from Weeks >12 to ≤40 (safety population).

| | Up to Week 12 | | | | | | Weeks >12 to ≤40 | |
|---|---|---|---|---|---|---|---|---|
| TEAE, n (%) | BEXO 40 mg (n = 24) | BEXO 80 mg (n = 20) | BEXO 160 mg (n = 20) | BEXO 320 mg (n = 27) | All BEXO (n = 91) | Placebo (n = 30) | BEXO 320 mg (n = 27) | Placebo (n = 9) |
| Any TEAE | 10 (41.7) | 16 (80.0) | 15 (75.0) | 20 (74.1) | 61 (67.0) | 20 (66.7) | 16 (59.3) | 5 (55.6) |
| Serious TEAE | 1 (4.2) | 1 (5.0) | 0 | 0 | 2 (2.2) | 0 | 1 (3.7) | 1 (11.1) |
| **Most frequent TEAEs*** | | | | | | | | |
| Fatigue | 3 (12.5) | 2 (10.0) | 4 (20.0) | 3 (11.1) | 12 (13.2) | 4 (13.3) | 0 | 1 (11.1) |
| Pruritus† | 2 (8.3) | 4 (20.0) | 3 (15.0) | 2 (7.4) | 11 (12.1) | 6 (20.0) | 1 (3.7) | 1 (11.1) |
| Headache | 1 (4.2) | 2 (10.0) | 3 (15.0) | 2 (7.4) | 8 (8.8) | 4 (13.3) | 1 (3.7) | 0 |
| COVID-19 | 2 (8.3) | 1 (5.0) | 0 | 4 (14.8) | 7 (7.7) | 3 (10.0) | 1 (3.7) | 1 (11.1) |
| Nausea | 1 (4.2) | 2 (10.0) | 3 (15.0) | 1 (3.7) | 7 (7.7) | 0 | 0 | 0 |
| Diarrhea | 2 (8.3) | 0 | 0 | 2 (7.4) | 4 (4.4) | 0 | 2 (7.4) | 0 |
| Cholangitis‡ | 0 | 2 (10.0) | 1 (5.0) | 0 | 3 (3.3) | 4 (13.3) | 1 (3.7) | 1 (11.1) |
| Nasopharyngitis | 0 | 2 (10.0) | 0 | 1 (3.7) | 3 (3.3) | 1 (3.3) | 4 (14.8) | 1 (11.1) |
| Frequent bowel movements | 0 | 3 (15.0) | 0 | 0 | 3 (3.3) | 3 (10.0) | 0 | 0 |
| Pyrexia | 1 (4.2) | 0 | 0 | 0 | 1 (1.1) | 3 (10.0) | 0 | 0 |
| Dyspepsia | 0 | 0 | 0 | 0 | 0 | 3 (10.0) | 0 | 0 |
| Ocular icterus/jaundice | 0 | 0 | 0 | 0 | 0 | 4 (13.3) | 0 | 0 |
| **TEAEs by system organ class** | | | | | | | | |
| Hepato-biliary disorders | 1 (4.2) | 2 (10.0) | 2 (10.0) | 0 | 5 (5.5) | 5 (16.7) | 2 (7.4) | 2 (22.2) |

BEXO, bexotegrast; TEAE, treatment-emergent adverse event.
*n ≥3 in ≥1 arm.
†Pruritus includes preferred terms for pruritus and cholestatic pruritus.
‡Cholangitis includes preferred terms for cholangitis and cholangitis sclerosing.

unbound bexotegrast plasma concentrations increased (2 h post-dose) following dosing on Day 1, and Weeks 4, 12, and 24.

### Liver biochemistry

All doses of bexotegrast maintained ALP at near baseline levels whereas ALP increased in placebo-treated participants through Week 12 (Fig. 3). Bexotegrast 320 mg lowered ALP values from baseline to Week 24 *vs.* an increase with placebo (–26.1 U/L, [95% CI –54.2 to 2.0] *vs.* 34.4 U/L, [–9.0 to 77]) (Fig. 3). There was no consistent trend in ALP when comparing bexotegrast groups based on baseline UDCA use (Fig. S3); for placebo there was an increase in ALP at Week 12 in participants not receiving UDCA while those receiving UDCA had minimal change. Additionally, there was no difference in ALP across bexotegrast doses among participants with or without IBD.

The changes observed in ALP were mirrored in GGT and bilirubin (Fig. S4). No notable changes from baseline in ALT and AST levels were observed in either the bexotegrast or placebo treatment groups. One participant had confirmed liver biochemistry abnormalities at two consecutive study visits in each of the bexotegrast 40 mg, bexotegrast 320 mg, and placebo groups; these three participants had either baseline ALT or AST ≥1.5× ULN or baseline ALP > ULN.

### Liver fibrosis markers

At Week 4, ELF was unchanged from baseline for bexotegrast 80 mg, 160 mg and 320 mg compared with placebo which increased. All doses of bexotegrast resulted in numerically smaller increases in mean ELF scores at Week 12 compared with placebo (40 mg: 0.16 [95% CI –0.10 to 0.43]; 80 mg: 0.19 [–0.06 to 0.43]; 160 mg: 0.09 [–0.18 to 0.35]; 320 mg: 0.19 [–0.05 to 0.43]; placebo: 0.42 [0.13–0.71]) (Fig. 4A). At Week 12, the 40-mg bexotegrast group had the highest proportion of participants with a ≥0.5 reduction in ELF score (24%; Fig. 4B). At Week 24, a greater proportion of participants receiving bexotegrast 320 mg achieved this reduction compared with placebo (25% *vs.* 11%; Fig. 4C). ELF scores in the 320-mg group remained stable from Weeks 12 to 24 (Week 24: 0.19 [–0.13 to 0.51]; Fig. 4D). No consistent trends were observed across bexotegrast groups when ELF scores were analyzed by baseline UDCA use (Fig. S3); in the placebo group, ELF scores increased at Week 12 among participants not receiving UDCA, while those on UDCA showed a smaller increase. Similarly, no clear differences in ELF scores were seen across bexotegrast doses between participants with and without IBD.

Participants receiving bexotegrast also had similar percent change in PRO-C3 values, a biomarker of collagen synthesis, over time compared with those receiving placebo up to Week 8 (Fig. S5). The greatest separation in PRO-C3 levels between the bexotegrast and placebo groups was observed at Weeks 12 and 24. Mean percentage changes in the bexotegrast groups at Week 12 were 40 mg: –3.78% (95% CI –13.1 to 5.5), 80 mg: 7.1% (–3.3 to 17.6), 160 mg: 5.2% (–10.1 to 20.6), 320 mg: 2.7% (–12.2 to 17.6) compared with a 22.4% (1.7–43.0) increase in the placebo group. Lower mean percentage changes in PRO-C3 were observed with bexotegrast *vs.* placebo through Week 24; at this time point, the 320-mg

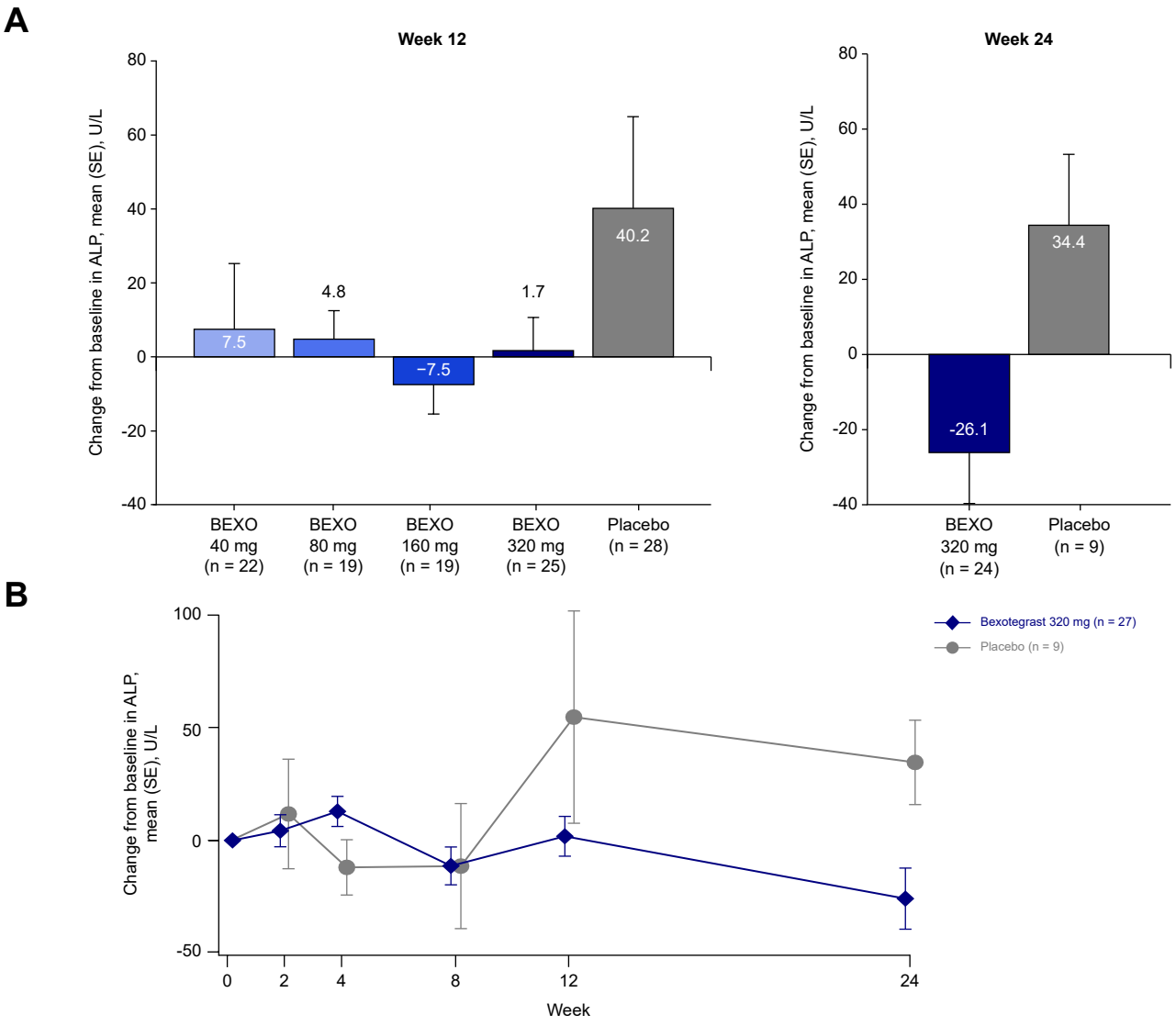


**Fig. 3. Mean change in ALP (U/L).** Change (A) from baseline to Weeks 12 and 24 and (B) by visit through Week 24 (safety population). Only the 320 mg cohort and placebo participants continued post Week 12. ALP, alkaline phosphatase; BEXO, bexotegrast.

bexotegrast group showed a –12.7% change (–24.2 to –1.3) compared with –1.4% (–29.7 to 27.0) in the placebo group.

LSM as assessed by VCTE was variable with all doses of bexotegrast through Week 12 (Fig. 5); however, median (IQR) liver stiffness remained unchanged over 24 weeks in participants receiving bexotegrast 320 mg whereas it increased with placebo (0 [–1.5 to 1.6] *vs.* 1.5 [–0.40 to 2.30]). No differences were observed in LSM between those who did or did not receive UDCA (Fig. S3), or between those with or without IBD.

### MRI assessments

Whole-liver MRI read centrally was an optional substudy. MRI data were collected at baseline and at least once post baseline for a subset of participants who received bexotegrast (40 mg [n = 13], 80 mg [n = 7], 160 mg [n = 10], and 320 mg [n = 10]) or placebo (n = 13). All doses of bexotegrast resulted in improved relative liver enhancement of the gadoxetate contrast agent (reflecting hepatocellular uptake 18 min after injection) at Week 12, as indicated by increases in mean change from baseline in relative enhancement (40 mg: 3.4 [95% CI –1.8 to 8.6], 80 mg: 1.1 [–6.1 to 8.3], 160 mg: 2.1 [–3.0 to 7.2], 320 mg: 0.8 [–6.9 to 8.5]); in contrast, mean change from baseline in relative enhancement was –9.8% (–21.33 to 1.73) in the placebo group (Fig. 6A). Comparing baseline and Week 12 MRI scans, the mean time of arrival of gadoxetate in the common bile duct decreased compared with baseline (*i.e.* improved) in participants treated with bexotegrast 160 and 320 mg while it increased (*i.e.* worsened) in placebo-treated participants (Fig. 6B). Liver volume was lower in all bexotegrast groups *vs.* placebo at Week 12 as determined by MRI (Fig. 6C). MRI of the liver at Week 24 indicated continued improvement relative to Week 12, with bexotegrast 320 mg increasing relative enhancement from 0.8% (95% CI –6.9 to 8.5) at Week 12 to 4.0% (–4.2 to 12.2) at Week 24. Change from baseline in time of arrival in the common bile duct improved from –22.2 (–143.7

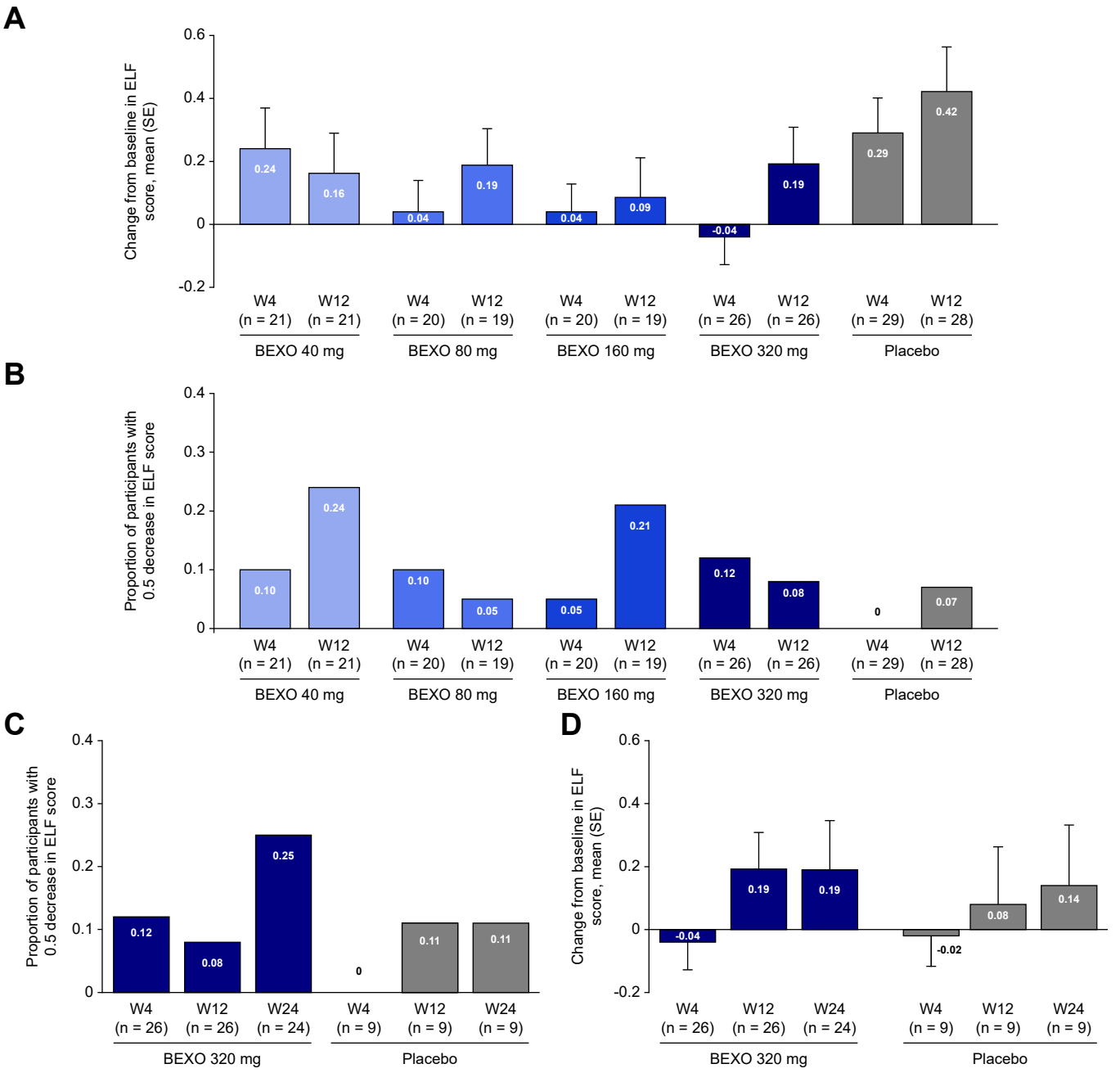


**Fig. 4. ELF scores.** Mean change from baseline (A) to Week 12 in all participants and (D) to Week 24 (part 3 only). Proportion of participants with a 0.5 decrease in ELF score from baseline (B) to Week 12 in all participants and (C) to Week 24 (part 3 only). Only the 320 mg cohort and placebo participants continued post Week 12. BEXO, bexotegrast; ELF, enhanced liver fibrosis.

to 99.3) seconds at Week 12 to −113.5 (−280.1 to 53.1) seconds at Week 24, and liver volume decreased from −5.8 (−52.8 to 41.1) ml at Week 12 to −56.5 (−148.5 to 35.4) ml at Week 24 (Fig. 6). Only two participants in the placebo group had Week 24 MRI scans (data not shown).

Comparison of MRI parameters by UDCA use is confounded by the small samples sizes which ranged from two to eight across treatment groups at Week 12 and 1 to 4 at Week 24, though no consistent trend between those who did or did not receive UDCA was observed (Fig. S3).

### Pruritus

Pruritus, as measured by the self-reported itch NRS scores, was unchanged with bexotegrast (Fig. S6). With bexotegrast doses of 80, 160, and 320 mg, itch NRS scores were unchanged from baseline to Week 12; small numerical increases were observed in the bexotegrast 40 mg and placebo groups. This response was observed through Week 24, with participants receiving bexotegrast 320 mg having unchanged scores whereas the placebo group had a small numerical increase (mean change from baseline: −0.04 *vs.* 1.0, respectively).

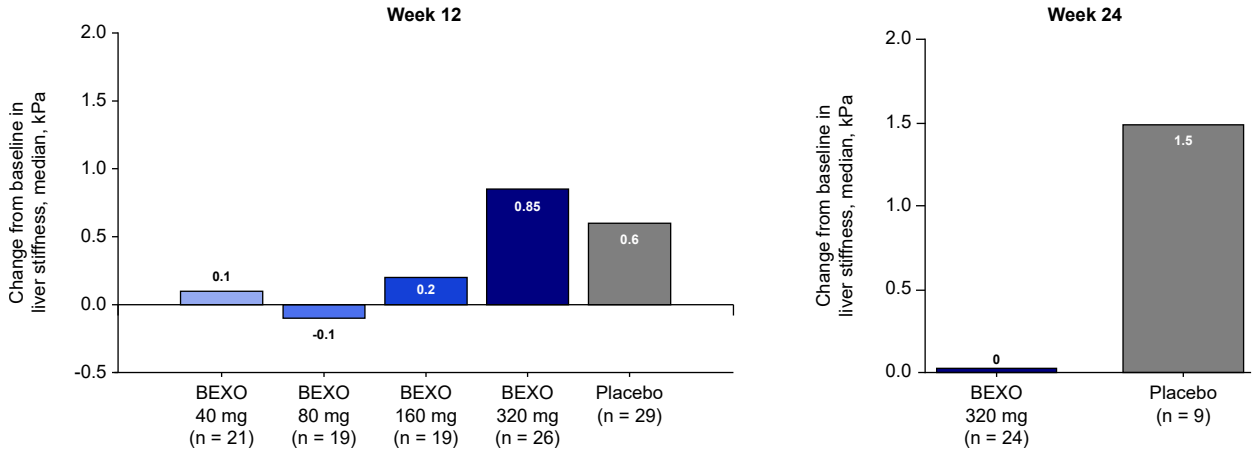


**Fig. 5. Median change in liver stiffness as measured by VCTE from baseline to Weeks 12 and 24 (safety population).** Only the 320 mg cohort and placebo participants continued post Week 12. VCTE, vibration-controlled transient elastography.

## Discussion

There is an unmet medical need for a well-tolerated treatment capable of halting and reversing liver fibrosis in people with PSC. No therapies are approved for PSC, and the most frequently used, UDCA, has not been demonstrated to halt disease progression and is associated with potential safety concerns at high doses.[31–33] Additionally, the recent phase III PRIMIS trial investigating a non-steroidal farnesoid X receptor agonist in participants with PSC was terminated after an interim analysis due to lack of efficacy based on liver histology (NCT03890120).[34]

Bexotegrast exhibited a favorable safety and tolerability profile compared with placebo up to 40 weeks in participants with PSC and suspected liver fibrosis (a plain language infographic is provided in the supplementary information). The most common TEAEs observed with bexotegrast and with a higher incidence than placebo were nausea and nasopharyngitis. In addition to showing no notable safety concerns, bexotegrast treatment was associated with fewer TEAEs of cholangitis compared with placebo. TEAEs of pruritus were lower overall in the bexotegrast group *vs.* placebo. Itch NRS, which has a 24-hour recall period, was unchanged from baseline at Weeks 12 and 24 for bexotegrast-treated groups.

The need for non-invasive assessments of liver fibrosis and response to therapy is heightened in a heterogeneous disease such as PSC, where variability in liver biopsy results and fluctuations in liver chemistry complicate the assessment of risk and therapeutic response,[35,36] especially in the context of a phase II study with relatively short-term exploratory pharmacodynamic outcomes at Weeks 12 and 24. Given these considerations, validated non-invasive surrogates for fibrosis-related clinical events are needed as intermediary endpoints in PSC clinical trials. ELF has emerged as an important biomarker of liver fibrosis with prognostic value in PSC[37,38] and consists of a set of serum biomarkers of the extracellular matrix (ECM), including tissue inhibitor of metalloproteinases 1, amino-terminal pro-peptide of type III procollagen, and hyaluronic acid.[39] In a study of ELF serum levels in 534 participants with PSC, ELF levels could predict clinical outcomes, including transplant-free survival; ELF levels were higher in participants who reached a combined clinical outcome of liver transplant or death.[38] Consistent with these results, a recent interventional study evaluating predictors of fibrotic progression in response to treatment with the LOXL2-binding immunomodulator simtuzumab found that both higher baseline ELF values and increasing ELF score were predictive of fibrotic progression and onset of cirrhosis.[40] In a study of the engineered FGF19 analog NGM282 in participants with PSC, ELF and PRO-C3 were reduced at Week 12, although no changes in ALP were observed.[29] In the current study at Week 12, participants receiving bexotegrast had ELF scores with smaller numerical increases compared with the placebo group. This may be due to bexotegrast affecting the TGF-β–dependent formation of ECM proteins in the fibrotic liver.[41] Similar to the ELF results, PRO-C3 – an N-terminal pro-peptide of type III collagen that is cleaved and subsequently released into the ECM and blood during fibrillar assembly[42] and is under investigation as a pharmacodynamic biomarker for PSC – showed a numerically lower percentage change at Week 12 compared with placebo.[29,36,43]

The pattern of ELF test results in the current study is supported by results for change in liver stiffness. Liver stiffness is a marker of liver fibrosis that increases over time in people with PSC, and measurement of liver stiffness by VCTE can be used to predict the severity and progression of liver fibrosis.[44] In participants receiving bexotegrast, LSM was variable across doses at Week 12, likely due to the short evaluation time, but bexotegrast 320 mg LSM remained unchanged over 6 months compared with placebo which increased. These results are consistent with the inhibition of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, with bexotegrast attenuating TGF-β–dependent differentiation of myofibroblasts and the subsequent secretion and accumulation of ECM proteins characteristic of fibrosis.[41]

In the current study, improved hepatobiliary excretion of gadoxetate with bexotegrast was observed with MRI, most notably from baseline to Week 24 at the 320-mg dose. Improved cholestasis as measured by MRI could corroborate the lack of changes in liver stiffness by bexotegrast as assessed by VCTE. Improved hepatobiliary excretion could also contribute to reduced liver stiffness as measured by VCTE

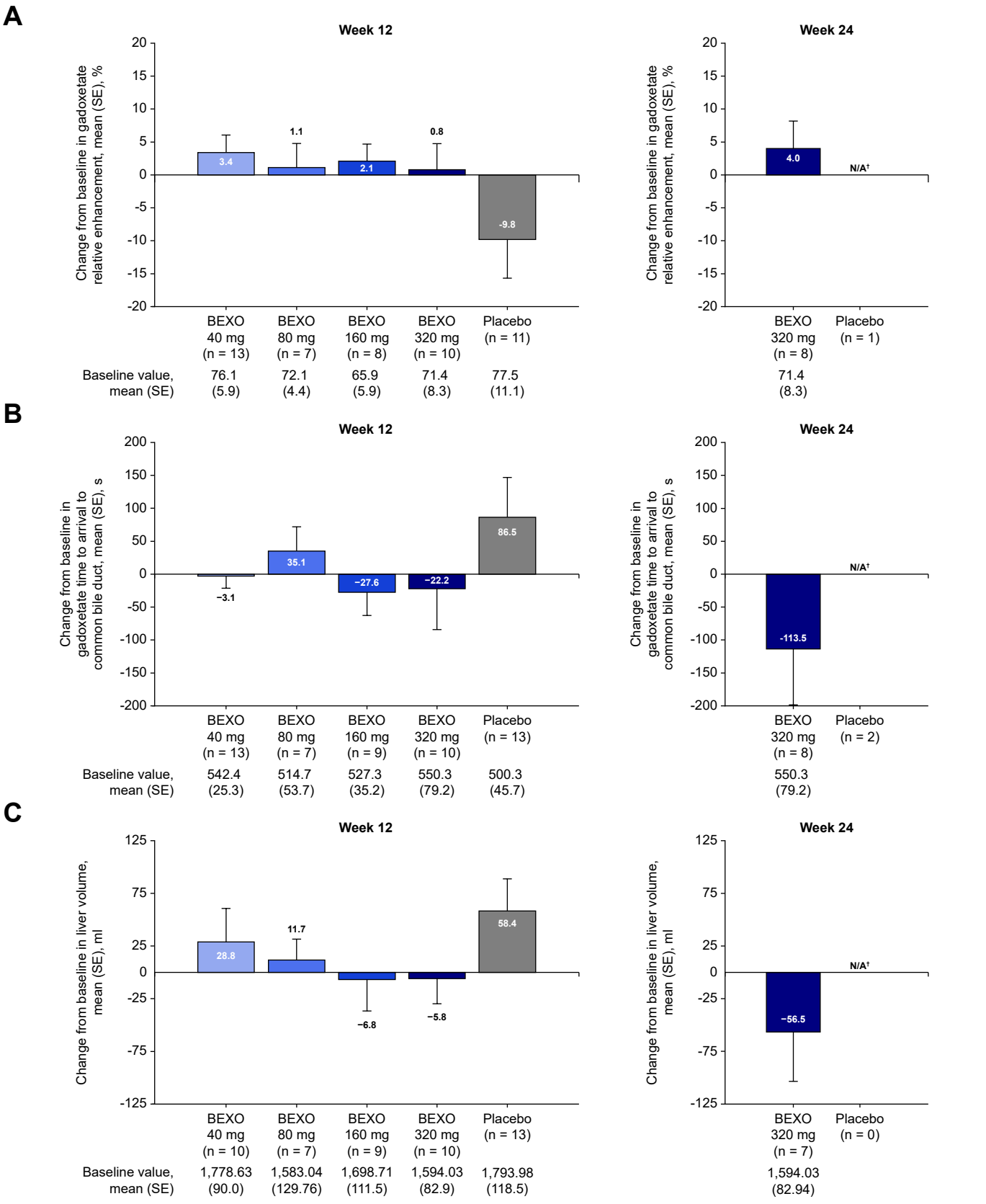


**Fig. 6. Mean change in MRI liver parameters.** Mean change in (A) gadoxetate relative enhancement, (B) time to arrival of gadoxetate in the common bile duct, and (C) liver volume from baseline to Weeks 12 and 24 (safety population). Only the 320 mg cohort and placebo participants continued post Week 12. Relative enhancement using the contrast agent gadoxetate is a measure of hepatocyte function. Time of arrival of gadoxetate to bile duct is a measure of excretory function. MRI was an optional substudy. †Placebo at Week 24 not shown due to small n value. BEXO, bexotegrast.

since cholestasis may have a major impact on liver stiffness in PSC.[44] ALP was reduced in participants receiving bexotegrast but increased in those receiving placebo. This difference, albeit mild, was corroborated by changes in GGT and suggests that bexotegrast may impact liver biochemistry. Participants receiving bexotegrast also had fewer TEAEs of cholangitis compared with participants receiving placebo.

The scope of this POC study reflects the effort required and challenges faced in therapeutic development for PSC, including the need for early dose-ranging across multiple potential pharmacodynamic endpoints, given the lack of clarity on an acceptable endpoint that would meet regulatory standards for approval. Nevertheless, this study has several limitations. As all pharmacodynamic endpoints were deemed exploratory with no formal power calculations, the results of this study are limited to POC and hypothesis generation, with longer and larger studies required for confirmation. Although trends in bexotegrast treatment effect were observed across multiple exploratory pharmacodynamic endpoints, no clear dose response was observed at Week 12. This could be due to the short treatment duration and relatively small sample size in the individual treatment groups but suggests that additional dose-finding will be required in late-stage studies to determine the optimal dose. Only the 320-mg cohort was treated beyond 12 weeks, which provides a meaningful evaluation of long-term safety at the highest planned dose in the bexotegrast program but does not assist in dose selection. Although bexotegrast was shown here to stabilize ALP and symptoms associated with cholestasis compared with placebo, whether these data show clinically significant improvement *vs*. baseline or a slowing of disease progression remains unanswered. Several participants in the placebo group had events of cholangitis proximal to the Week 12 visit, which may have worsened the Week 12 results. Only participants randomized to 320 mg or placebo in the final dosing cohort were observed beyond 12 weeks, limiting comparative interpretation of these results. Late-stage evaluation is needed to confirm that targeting integrin-mediated TGF-β activation is a potential therapeutic approach for PSC.

Bexotegrast demonstrated a favorable safety and tolerability profile in a population with PSC and suspected liver fibrosis, with no drug-related serious TEAEs observed throughout the study and few treatment discontinuations. TEAEs of cholangitis and pruritus were observed less frequently with bexotegrast than with placebo. ALP and symptoms associated with cholestasis remained unchanged with bexotegrast compared with placebo where increases were observed. This study supports targeting integrin-mediated TGF-β activation as a potential therapeutic approach for PSC.


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## Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECM, extracellular matrix; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MRI, magnetic resonance imaging; NRS, Numeric Rating Scale; PRO-C3, neoepitope-specific N-terminal pro-peptide of type III collagen; PSC, primary sclerosing cholangitis; TEAE, treatment-emergent adverse event; TGF, transforming growth factor; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography.


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## Conflict of interest

GM Hirschfield was a consultant for Advanz, CymaBay, Ipsen, Gilead, Intercept, Mirum, Kowa, GSK, Pliant Therapeutics, and Escient. KV Kowdley received grants from Boston Scientific, Corcept, CymaBay, Genfit, Gilead, GSK, Hanmi, Intercept, Ipsen, Janssen, Madrigal, Mirum, Novo Nordisk, NGM, Pfizer, Pliant Therapeutics, Terns, Viking, Zydus, and 89bio Inc.; received royalties or licenses from UpToDate; received consulting fees from CymaBay, Enanta, Genfit, Gilead, HighTide, Inipharm, Intercept, Ipsen, Madrigal, Mirum, NGM, Pliant Therapeutics, Pfizer, Protagonist, Zydus, and 89bio Inc.; received payment or honoraria from AbbVie, Gilead, and Intercept; received payment for expert testimony from the US Department of Justice; participated on a data safety monitoring board or advisory board for CTI, Medpace, Labcorp, and Worldwide Clinical Trials; holds stock in Inipharm; and received equipment, materials, drugs, medical writing, gifts, or other services from Velacur. PJ Trivedi received institutional salary support from the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre (BRC); received grant support from the Wellcome Trust, the Medical Research Foundation, the NIHR, LifeArc, Regeneron, Albireo/Ipsen, Mirum, GSK, Guts UK, PSC Support, Intercept, Dr Falk Pharma, Gilead Sciences, and BMS; received speaker fees from Advanz/Intercept, Albireo/Ipsen, and Dr Falk Pharma; and received advisory board/consultancy fees from Advanz/Intercept, GSK, CymaBay, Pliant Therapeutics, and Dr Falk Pharma. B Eksteen has served on a scientific board for Pliant Therapeutics and has consulted for Jansen, Pfizer, and AbbVie. B Hameed has received grant support from Gilead, Intercept, Pliant Therapeutics, Novo Nordisk, Madrigal, and Salix; has served on an advisory board for Mallinckrodt, Pleiogenix, CLDF, and Madrigal; has served as a consultant for Gilead, Pioneering Medicine VII, Inc., and Surrozen; holds stock options in Pleiogenix; and has served as a speaker for Scholars in Medicine. C Vincent has nothing to disclose. T Chen received advisory board/consultancy fees from Advanz/Intercept and Pliant Therapeutics. A Goel has nothing to disclose. KG Reddy has received grant support from Pliant Therapeutics, COUR, Gilead, and CymaBay; has served as a consultant for CymaBay; and has served in a speaking/teaching role for Mallinckrodt and Gilead. E Orman received consulting fees from BioVie and Sitero. D Joshi received advisory board/consultancy fees from Advanz/Intercept, Boston Scientific, Cook Medical, Gilead, Ipsen Pharmaceuticals, Mirum Pharmaceuticals, Q3 Medical, and Dr Falk Pharma. ÉA Lefebvre, JR Schaub, and CN Barnes are employees and shareholders of Pliant Therapeutics, Inc. M An, A Clark, and R Pencek are former employees and shareholders of Pliant Therapeutics, Inc. D Thorburn served as an advisor to Pliant Therapeutics. AJ Montano-Loza served on advisory boards for Intercept and Pliant Therapeutics. C Schramm served as an advisor to Pliant Therapeutics, Chemomab, and Agomab; and has received travel grants from Dr. Falk Pharma. CL Bowlus advised for Chemomab, Ipsen,

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## Authors' contributions

All authors contributed to, reviewed, and approved the final draft of the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Concept and design: GMH, KVK, PJT, BE, ÉAL, JRS, DT, AM-L, CS, CLB, MT, CL. Acquisition, analysis, or interpretation of data: GMH, KVK, ÉAL, MA, AC, CNB. Statistical analysis: CNB. Drafting of manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors.

## Data availability

Clinical study data access for research use: Pliant Therapeutics, Inc. ("Pliant") understands and acknowledges the need to share clinical study data with the research community in an open and transparent manner. In furtherance of its research efforts, a member of the scientific community may request aggregated deidentified clinical data collected during a clinical study after its public disclosure by Pliant and filing of any related intellectual property protection. To the extent that Pliant has any additional supporting documentation or summary data, it may, at its discretion, also make such information available. Pliant will take into consideration any reasonable request that it receives pertaining to clinical data that has been accepted and published by a journal. Prior to receipt of clinical study data, Pliant and the requesting institution shall enter into an agreement which takes into consideration applicable data privacy laws and the use of the clinical study data for research purposes only. All requests for access to clinical study data must be submitted in writing to info@pliantrx.com.

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## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.09.016.

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*Author names in bold designate shared co-first authorship*

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