Bexotegrast, an oral inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, was shown to improve markers and symptoms of cholestasis and stabilized markers of liver fibrosis in participants with primary sclerosing cholangitis: Week 24 results from the Phase 2 INTEGRIS-PSC trial

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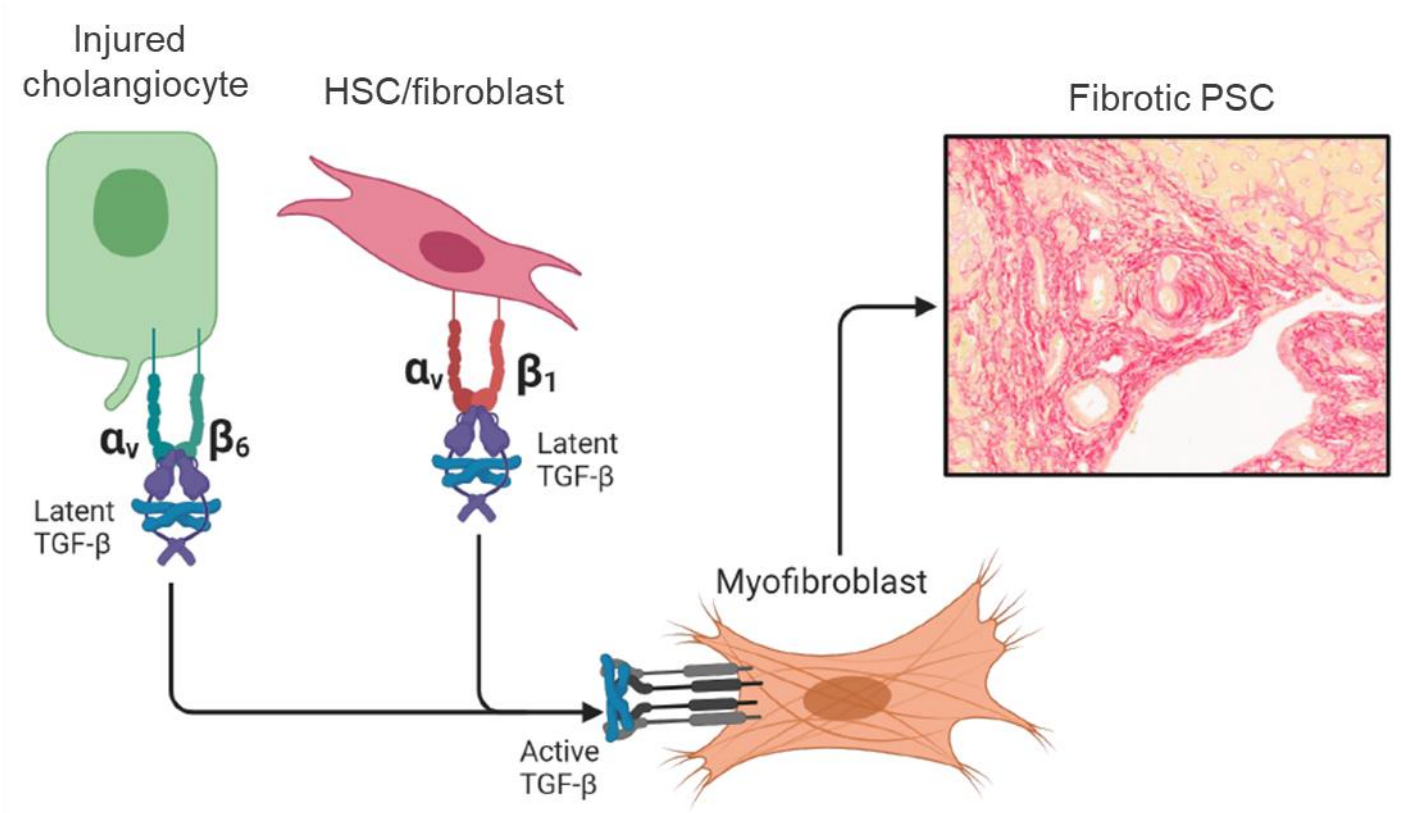
Background

- PSC is a rare, idiopathic, cholestatic liver disease characterized by biliary inflammation and progressive fibrosis[1]
  - A substantial proportion of patients also have concomitant inflammatory bowel disease
  - TGF-β signaling activated by α_v integrins is a key driver of fibrosis in the liver[2-4]
- Bexotegrast (PLN-74809) 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 idiopathic pulmonary fibrosis[5]

$\alpha_v\beta_6$ and $\alpha_v\beta_1$ Integrins Promote Liver Fibrosis Through Activation of TGF-β[2-4]



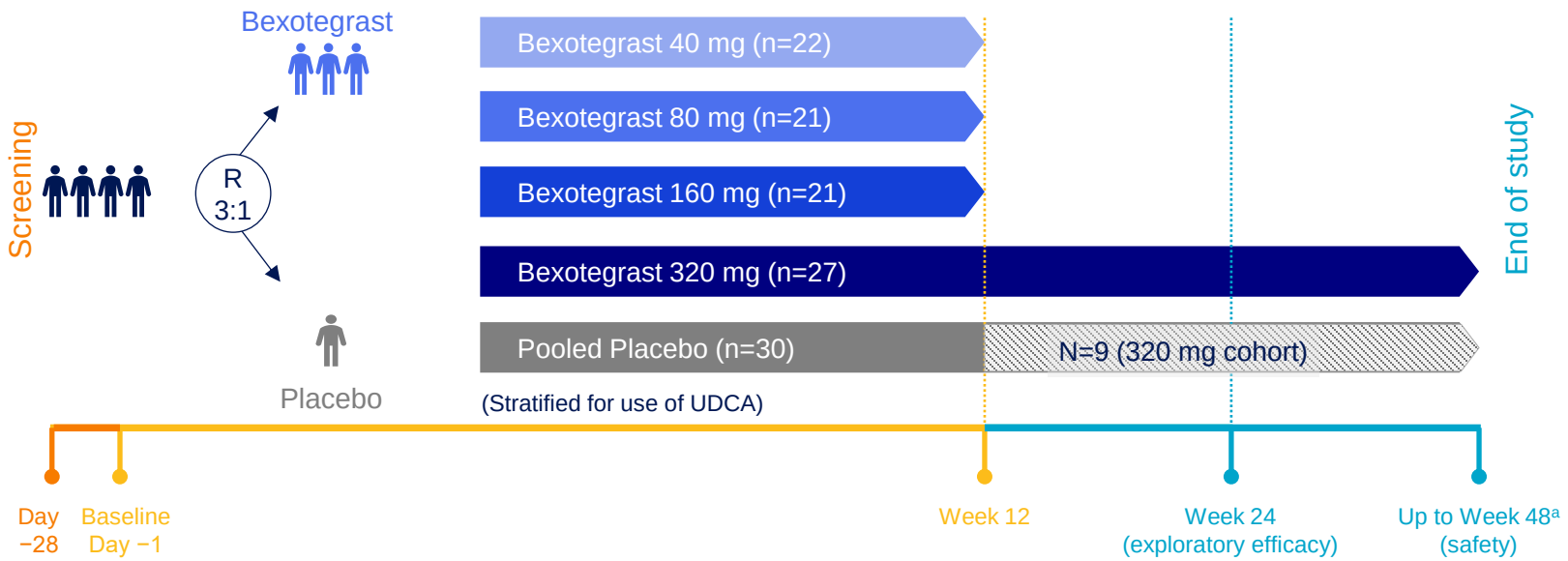
HSC, hepatic stellate cell; PSC, primary sclerosing cholangitis; TGF-β, transforming growth factor β.

1. Hirschfield GM, et al. *Lancet*. 2013;382(9904):1587-1599; 2. Peng ZW, et al. *Hepatology*. 2016;63(1):217-232; 3. Reed NI, et al. *Sci Transl Med*. 2015;7(288):288ra79; 4. Popov Y, et al. *J Hepatol*. 2008;48(3):453-464; 5. Decaris ML, et al. *Respir Res.* 2021;22(1):265.

INTEGRIS-PSC Study Design

Inclusion Criteria

- Age 18 to 75 years
- Confirmed large-duct PSC
- At-risk for liver fibrosis (≥1 criterion)
  - ELF score ≥7.7
  - TE ≥8 but ≤14.4 kPa
  - MRE ≥2.4 but ≤4.9 kPa
  - Historical biopsy
- Stable IBD, if present
- Serum ALP concentration ≤10 × ULN



Participants enrolled in 3 cohorts (40 mg/placebo, 80 mg/160 mg/placebo, 320 mg/placebo)

Primary Endpoint

- Treatment-emergent adverse events

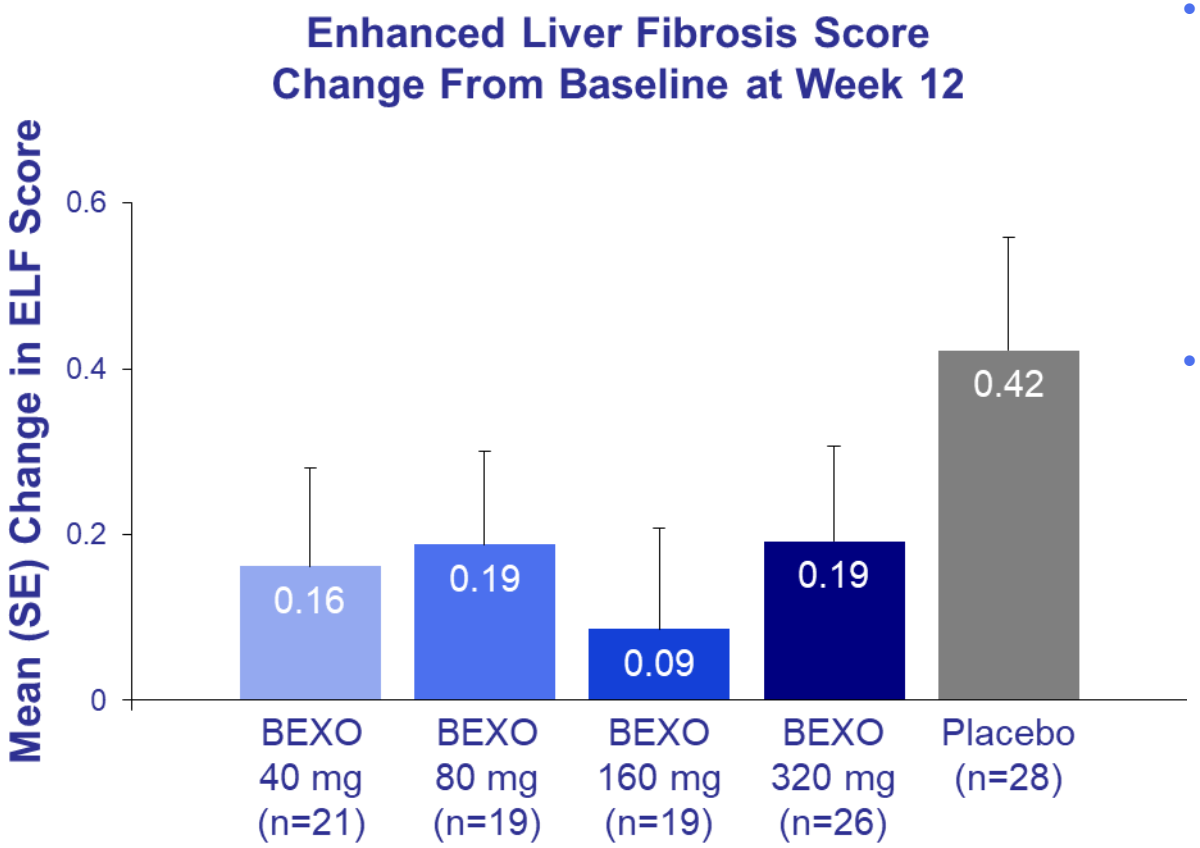
Key Exploratory Endpoints at Week 24

- Liver stiffness
- Liver function biomarkers
- ELF score
- Itch NRS score
- MRI gadoxetate time to arrival in the common bile duct
- MRI whole liver relative enhancement

ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NRS, numerical rating scale; PSC, primary sclerosing cholangitis; R, randomization; TE, transient elastography; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

[a] Due to the enrollment trajectory in the 320-mg cohort, the longest treatment duration was 40 weeks.

Phase 2a INTEGRIS-PSC Study: 12-Week Analysis and Current Objective[1]



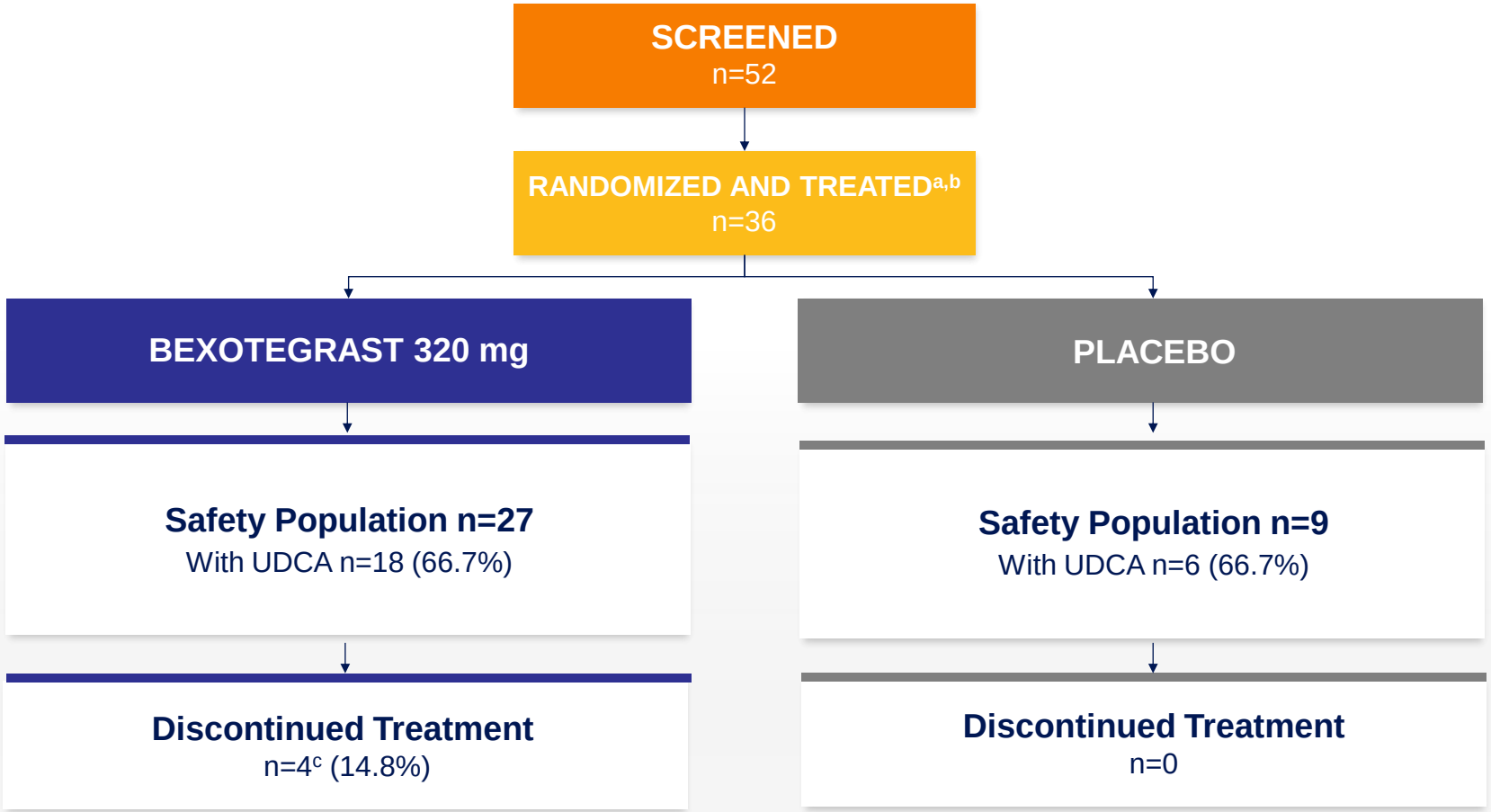
- **Safety results through 12 weeks of treatment**
  - Adverse events were well-balanced, 67.0% and 66.7%, in bexotegrast- and placebo-treated participants, respectively
  - No serious TEAEs related to the study drug
- **Efficacy summary at Week 12**
  - Bexotegrast attenuated the increase in ELF score compared with placebo at all doses
  - Bexotegrast attenuated ALP increases compared with placebo at all doses
  - Bexotegrast improved MRI parameters at all doses compared with placebo

We report the long-term (>12 weeks) safety and exploratory efficacy outcomes from a Phase 2, double-blind, randomized controlled trial of bexotegrast in PSC (INTEGRIS-PSC study, NCT04480840)

ALP, alkaline phosphatase; BEXO, bexotegrast; ELF, enhanced liver fibrosis; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis; TEAE, treatment-emergent adverse event.

1. Trauner M, et al. Trauner M, et al. *J Hepatol*. 2024;80(suppl):S97-S98.

INTEGRIS-PSC Participant Disposition: Bexotegrast 320-mg Cohort



UDCA, ursodeoxycholic acid.
[a] Treatment-emergent adverse event data include all available data up to 40 weeks of treatment.
[b] Exploratory efficacy data include data at Weeks 12 and/or Week 24.
[c] Adverse event (n=1), withdrawal by participant (n=2), other (n=1); one discontinuation occurred post Week 12 visit.

Baseline Demographics: Bexotegrast 320-mg Cohort Participants

Characteristic	Bexotegrast 320 mg (n=27)	Placebo (n=9)
Male, n (%)	13 (48.1)	7 (77.8)
Age, mean (SD), years	47.1 (14.47)	44.1 (10.04)
Race, n (%)		
White	26 (96.3)	7 (77.8)
Black	0	1 (11.1)
Asian	1 (3.7)	0
Other/not reported/unknown	0	1 (11.1)
Time since diagnosis of PSC, mean (SD), years[a]	9.4 (11.20)	6.7 (5.37)
Concomitant UDCA use, n (%)	18 (66.7)	6 (66.7)
IBD, n (%)	13 (48.1)	5 (55.6)
Ulcerative colitis	6 (22.2)	3 (33.3)
Crohn's disease	8 (29.6)	2 (40.0)
IBD other	0	0
Partial Mayo score, mean (SD)[b]	0.8 (1.17)	0
Itch NRS score, mean (SD)	0.9 (1.77)	0.9 (1.05)

IBD, inflammatory bowel disease; NRS, numerical rating scale: PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.
[a] Duration since diagnosis at screening is calculated from the first reported date for preferred terms of PSC.
[b] Partial Mayo score only reported for those with active IBD at baseline.

Baseline Disease Activity Markers: Bexotegrast 320-mg Cohort Participants

Characteristic	Bexotegrast 320 mg (n=27)	Placebo (n=9)
Liver biochemistry, mean (SD)		
Alkaline phosphatase, U/L	190.6 (91.29)	318.6 (282.73)
>ULN, n (%)	22 (81.5)	6 (66.7)
Alanine aminotransferase, U/L	60.4 (37.76)	85.8 (70.79)
Aspartate aminotransferase, U/L	44.6 (24.69)	58.2 (50.91)
Total bilirubin, mg/dL	0.53 (0.208)	0.76 (0.424)
Direct bilirubin, mg/dL	0.16 (0.062)	0.33 (0.341)
Markers of liver fibrosis, mean (SD)		
ELF score	9.0 (0.84)	9.5 (0.93)
Transient elastography, kPa	8.7 (3.14)	8.6 (2.85)

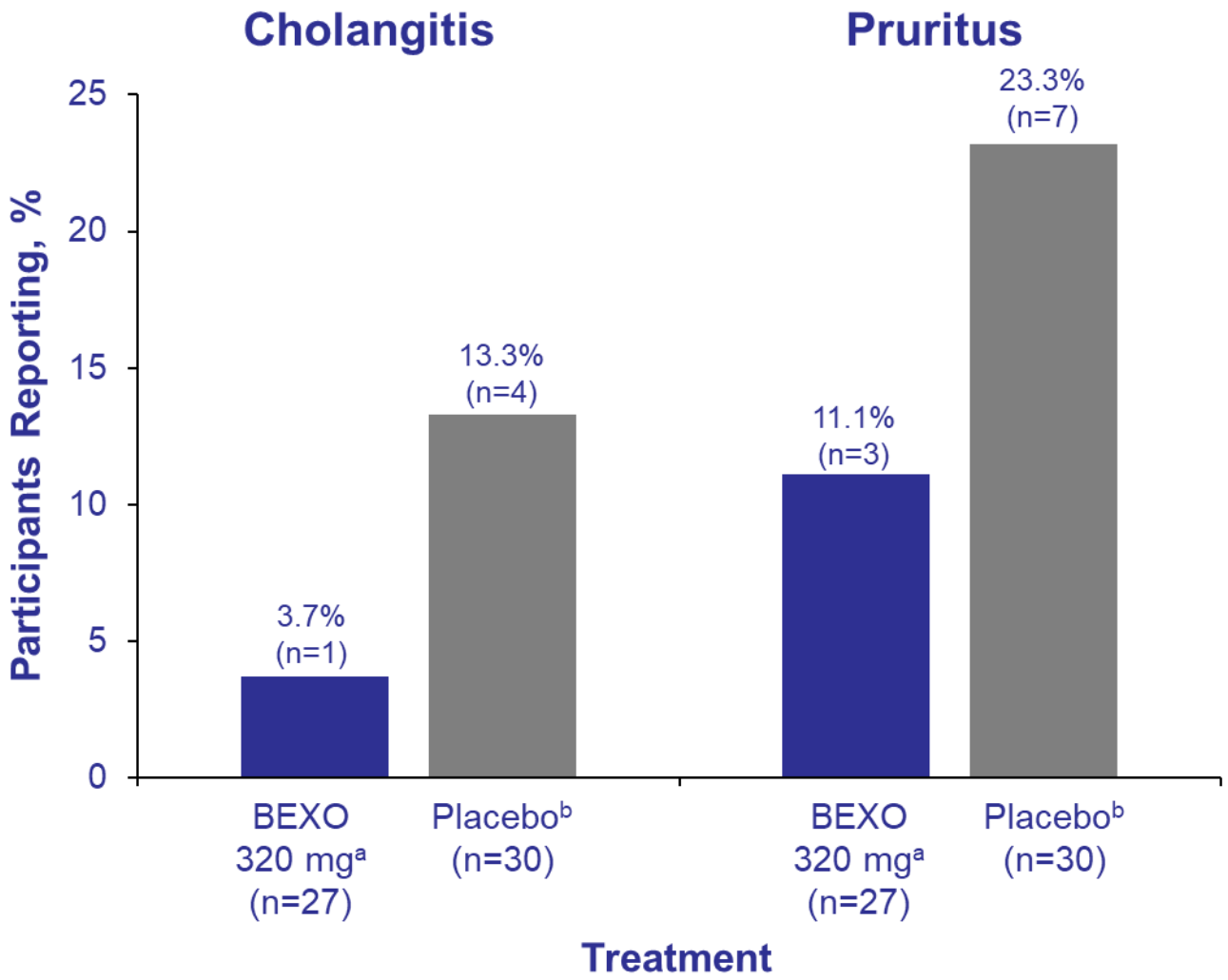
ELF, enhanced liver fibrosis; ULN, upper limit of normal.

Bexotegrast Safety and Tolerability Maintained Over Longer-Term Dosing

AEs in Participants Reported After Week 12, n (%)	Bexotegrast 320 mg (n=27)	Placebo (n=9)
TEAE	16 (59.3)	5 (55.6)
Related to study drug	**0**	**0**
Serious TEAE	1 (3.7)[a]	1 (11.1)[b]
Related to study drug	**0**	**0**
Most frequent TEAEs (≥10% in the 320-mg treatment group)		
COVID-19	5 (18.5)	1 (11.1)
Nasopharyngitis	5 (18.5)	1 (11.1)
Diarrhea	4 (14.8)	0
Colitis ulcerative	3 (11.1)	0
Fatigue	3 (11.1)	2 (22.2)
Headache	3 (11.1)	0
Pruritus[c]	3 (11.1)	2 (22.2)

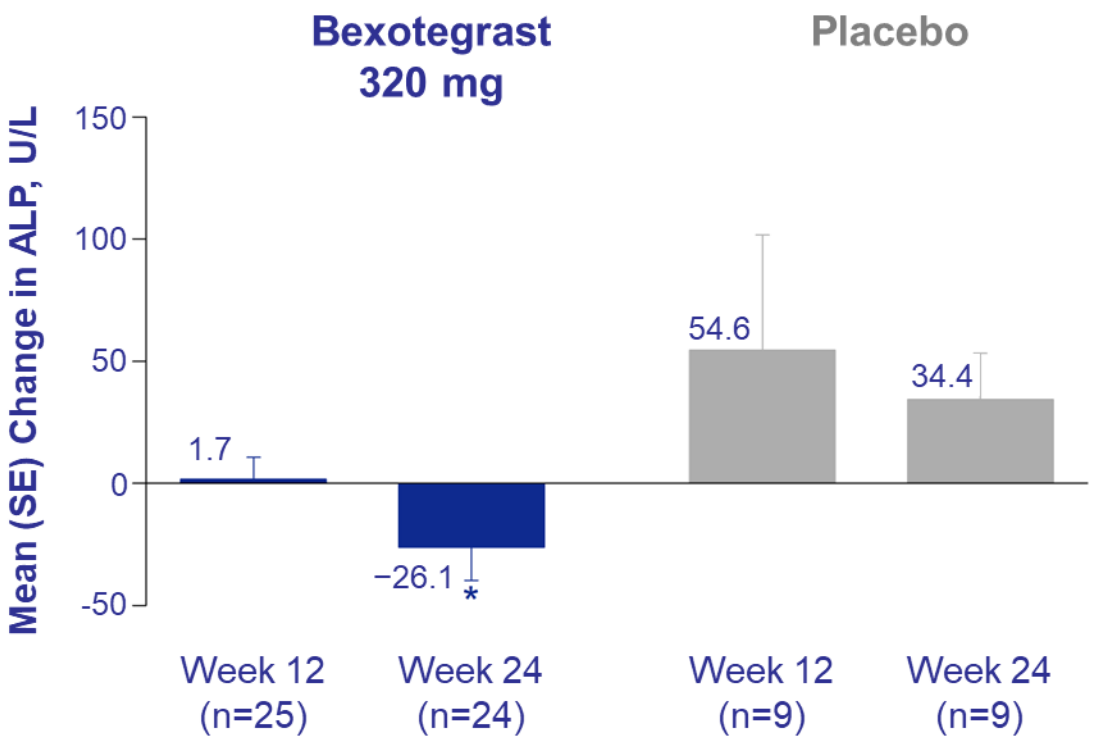
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment emergent adverse event.
AEs coded using MedDRA v. 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose.
[a] Cholangitis/*Enterobacter* bacteremia (n=1).
[b] Cholangitis (n=1).
[c] Pruritus includes preferred terms for pruritus and cholestatic pruritus.

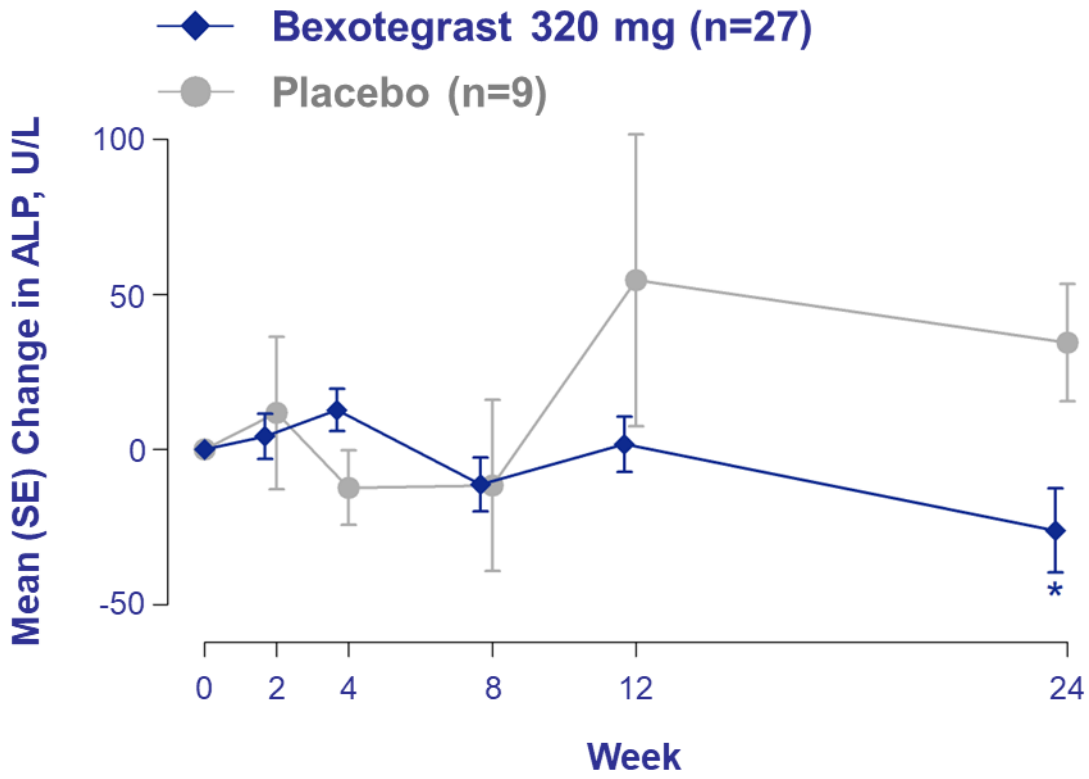
Bexotegrast Associated With Less Frequent Events of Cholangitis and Pruritus



BEXO, bexotegrast.
[a] Bexotegrast 320 mg includes participants with up to 40 weeks' treatment duration.
[b] Placebo includes all participants who received placebo (n=21 for up to 12 weeks, n=9 for up to 40 weeks' treatment duration).

Bexotegrast Associated With a Reduction in ALP Over 24 Weeks

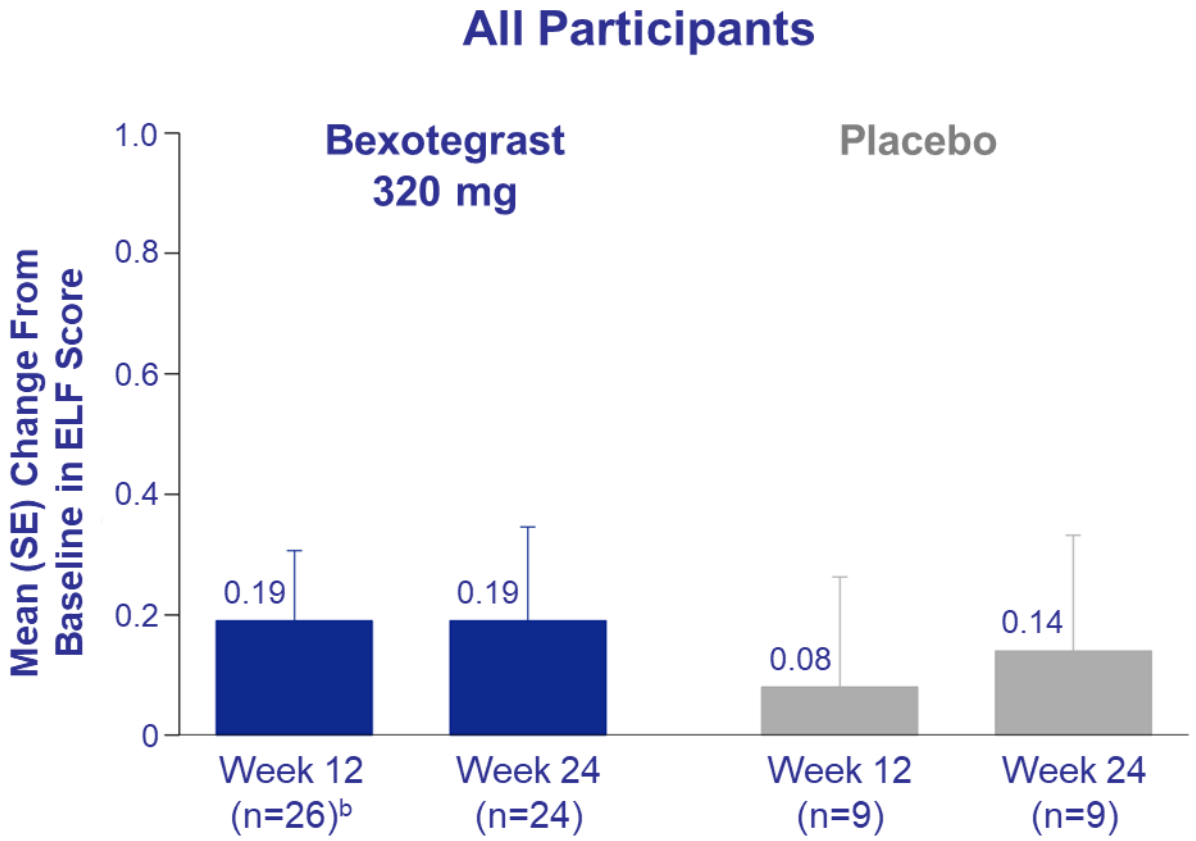


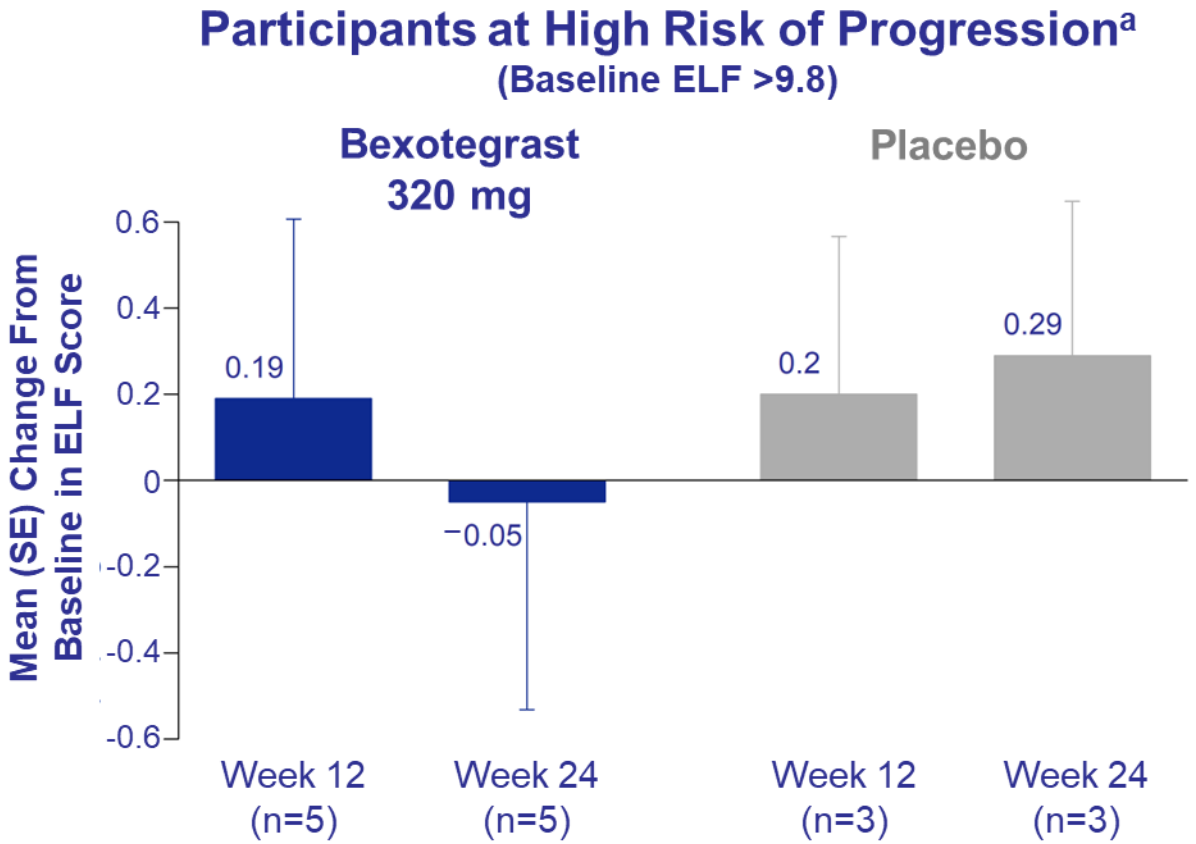


Bexotegrast significantly lowered ALP values from baseline to Week 24 compared with an increase with placebo (*P*<0.05)

ALP, alkaline phosphatase.
* *P*<0.05 vs placebo.

Bexotegrast ELF Score Stable From Weeks 12 to 24

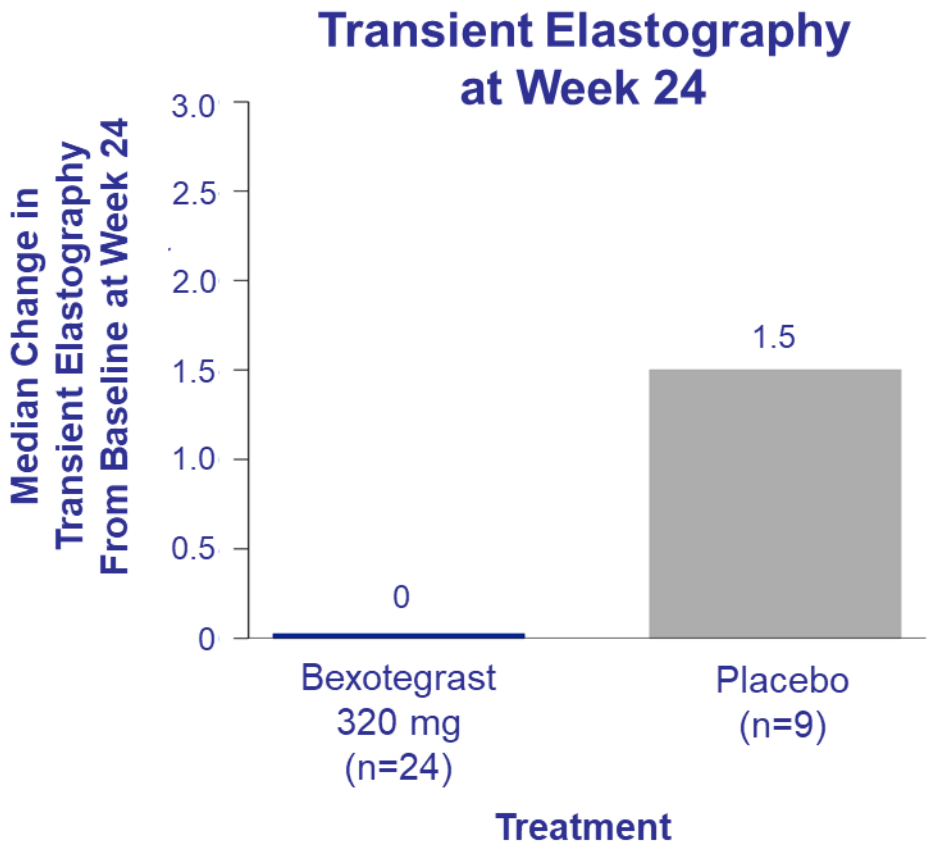




Bexotegrast treatment resulted in a stable ELF score from Week 12 to Week 24, with a reduction in participants with an ELF score of >9.8 at baseline

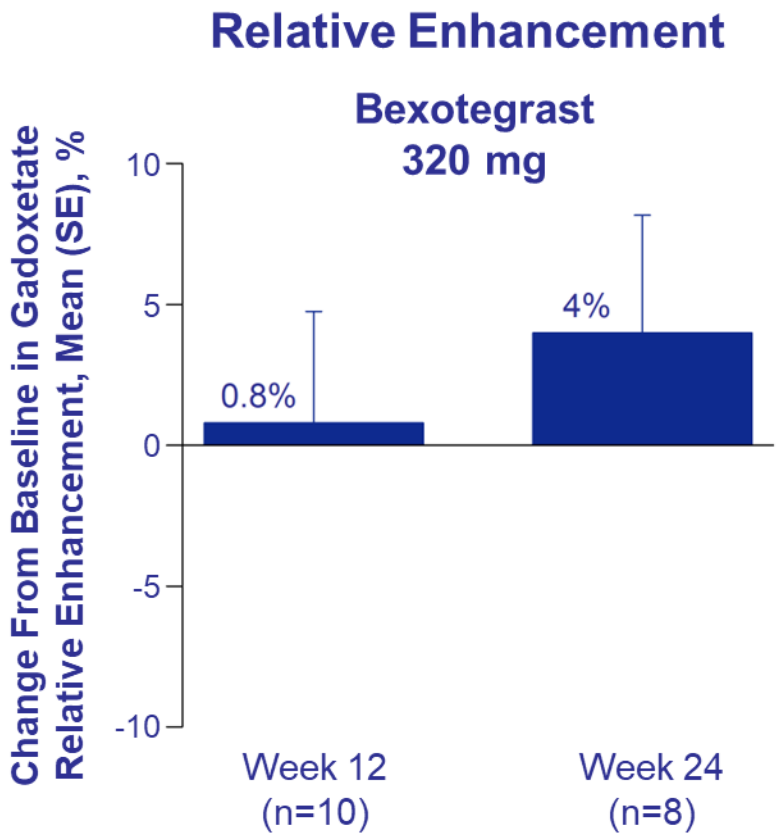
ELF, enhanced liver fibrosis.
[a] ELF score >9.8 is associated with increased risk for advanced liver fibrosis and disease progression.
[b] Includes 1 participant who was not included in 12-week interim analysis due to sample unavailability at the time of interim analysis.

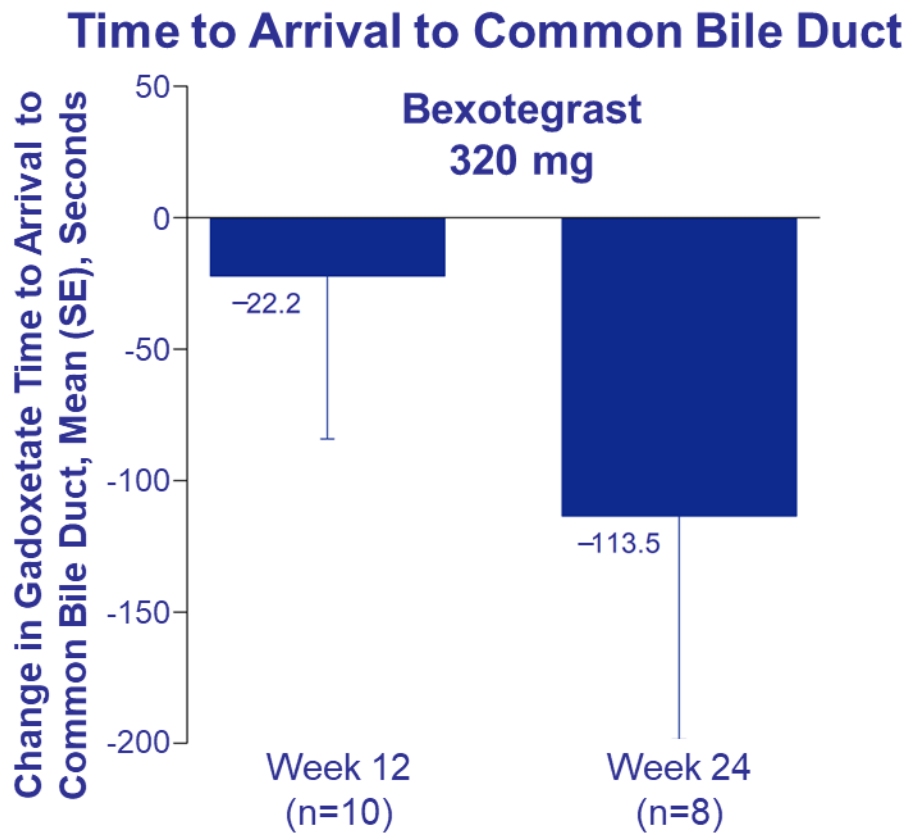
Liver Stiffness Measured by Transient Elastography



Liver stiffness findings indicate the potential for stabilization of liver fibrosis in bexotegrast-treated participants

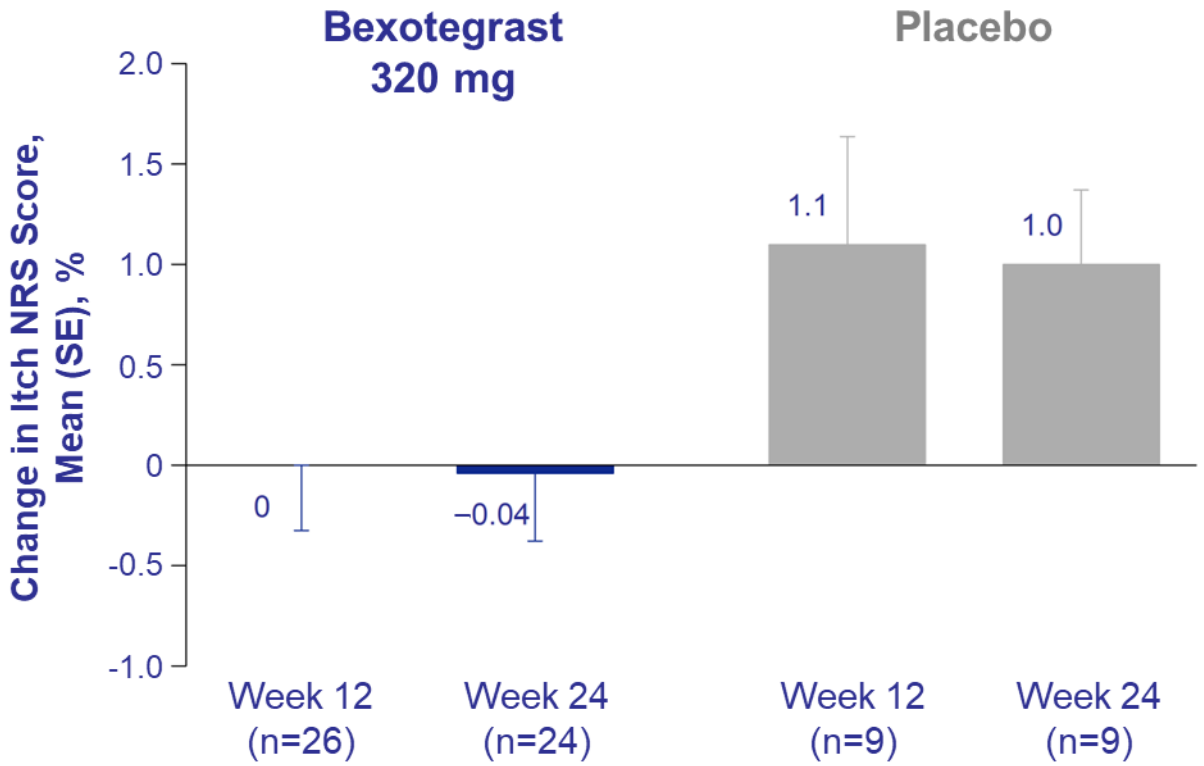
MRI Parameters Continued to Improve From Weeks 12 to 24 With Bexotegrast





MRI, magnetic resonance imaging.
Placebo not shown due to small n. Placebo for relative enhancement, n=1; placebo for time to arrival to common bile duct, n=2.
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 bile flow/excretory function.
MRI was an optional substudy to main study.

Bexotegrast Associated With Stable Itch NRS Score



Itch NRS score was stable from baseline to Week 24 in bexotegrast-treated participants compared with an increase with placebo

NRS, numerical rating scale.
Itch NRS is a patient-reported outcome that assesses severity of itch over the last 24 hours on a scale of 0 (no itch) to 10 (worst imaginable itching).

Conclusions

Bexotegrast 320 mg was generally well tolerated for up to 40 weeks of treatment

- Discontinuation rates were low, and no serious TEAEs were reported that were related to the study drug
- TEAEs of pruritus and cholangitis were observed less frequently with bexotegrast than placebo

Bexotegrast was shown to improve ALP and stabilize symptoms associated with cholestasis compared with placebo

Bexotegrast demonstrated potential antifibrotic activity, suggesting disease stabilization as evidenced by liver stiffness, ELF, and MRI measures

This study supports targeting integrin-mediated TGF-β activation as a potential therapeutic approach for PSC

- Due to the limited sample size and duration of the current study, late-stage evaluation is needed to confirm this approach

ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis; TEAE, treatment-emergent adverse event; TGF-β, transforming growth factor-beta.

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