BEXOTEGRAST IMPROVES MARKERS AND SYMPTOMS OF CHOLESTASIS AND STABILIZES MARKERS OF LIVER FIBROSIS IN PARTICIPANTS WITH PRIMARY SCLEROSING CHOLANGITIS

Palak J. Trivedi,[1,2] Kris V. Kowdley,[3,4] Bertus Eksteen,[5] Bilal Hameed,[6] Catherine Vincent,[7] Tianyan Chen,[8] Aparna Goel,[9] K. Gautham Reddy,[10] Eric Orman,[11] Deepak Joshi,[12] Éric A. Lefebvre,[13] Johanna Schaub,[13] Mahru An,[13] Annie Clark,[13] Chris N. Barnes,[13] Richard Pencek,[13] Douglas Thorburn,[14] Aldo J. Montano-Loza,[15] Christoph Schramm,[16] Christopher L. Bowlus,[17] Michael Trauner,[18] Cynthia Levy,[19] Gideon M. Hirschfield[20]

[1]NIHR Birmingham Biomedical Research Centre, Centre for Liver and Gastrointestinal Research, University of Birmingham, Birmingham, UK; [2]Liver Unit, University Hospitals Birmingham, Birmingham, UK; [3]Liver Institute Northwest, Seattle, WA, USA; [4]Elson S. Floyd College of Medicine, Washington State University, Seattle, WA, USA; [5]Aspen Woods Clinic, Calgary, AB, Canada; [6]University of California San Francisco School of Medicine, San Francisco, CA, USA; [7]Liver Unit, Centre hospitalier de l'Universite de Montreal (CHUM), Montreal, QC, Canada; [8]Department of Medicine, McGill University Health Centre, Montreal, QC, Canada; [9]Stanford University, Palo Alto, CA, USA; [10]Department of Medicine, University of Chicago, Chicago, IL, USA; [11]Indiana University School of Medicine, Indianapolis, IN, USA; [12]Institute of Liver Studies, King's College Hospital, London, UK; [13]Pliant Therapeutics, Inc, South San Francisco, CA, USA; [14]Sheila Sherlock Liver Centre and UCL Institute for Liver and Digestive Health, London, UK; [15]University of Alberta, Edmonton, AB, Canada; [16]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [17]University of California, Davis, Sacramento, CA, USA; [18]Division of Gastroenterology & Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [19]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA; [20]The Autoimmune and Rare Liver Disease Programme, Division of Gastroenterology and Hepatology, Toronto General Hospital, Toronto, Canada

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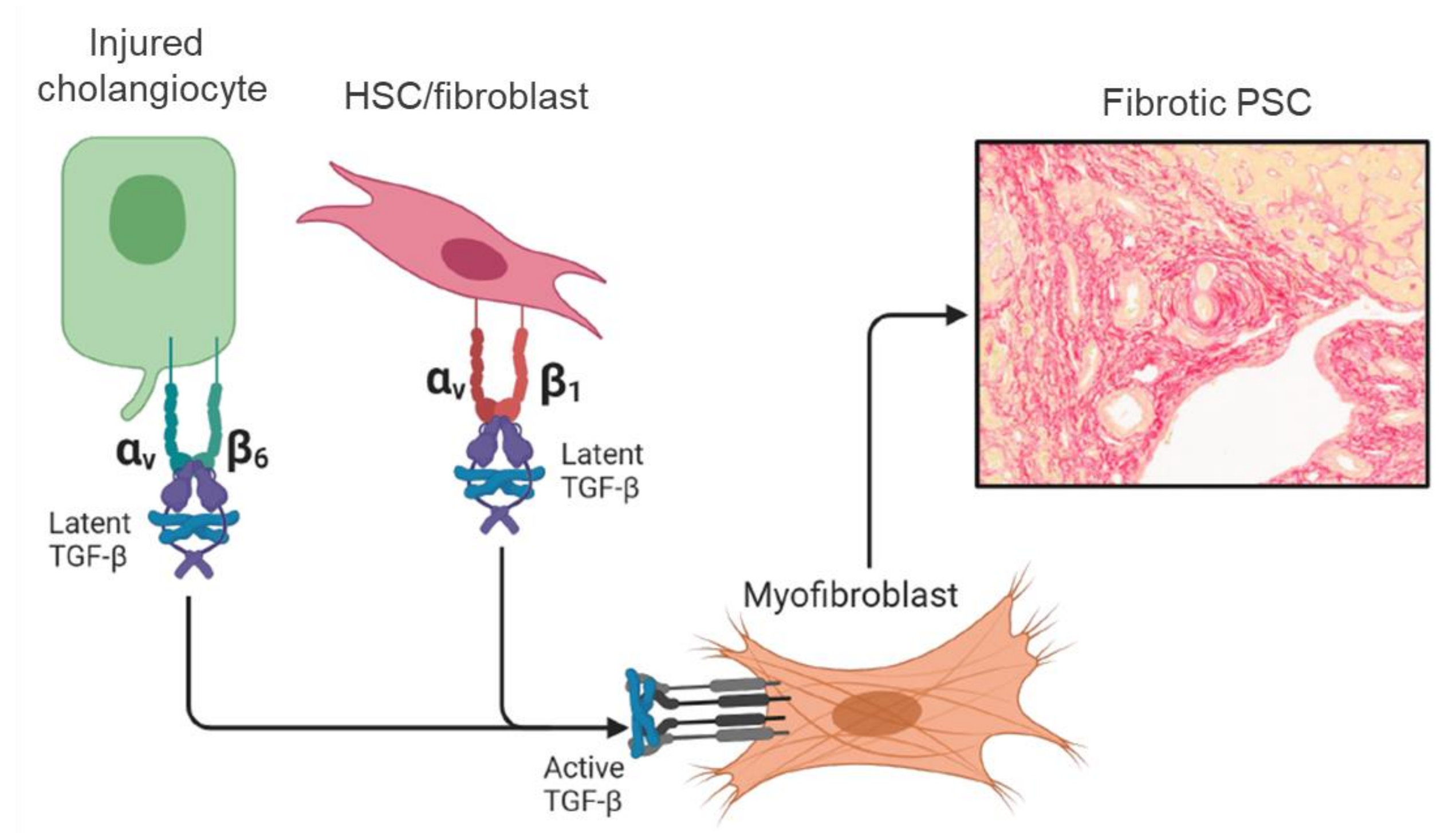
BACKGROUND

- PSC is a rare, idiopathic, cholestatic liver disease characterized by biliary inflammation and progressive fibrosis[1]
  - A substantial proportion of participants 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 Fibrosis Through Activation of TGF-β[2-4]



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

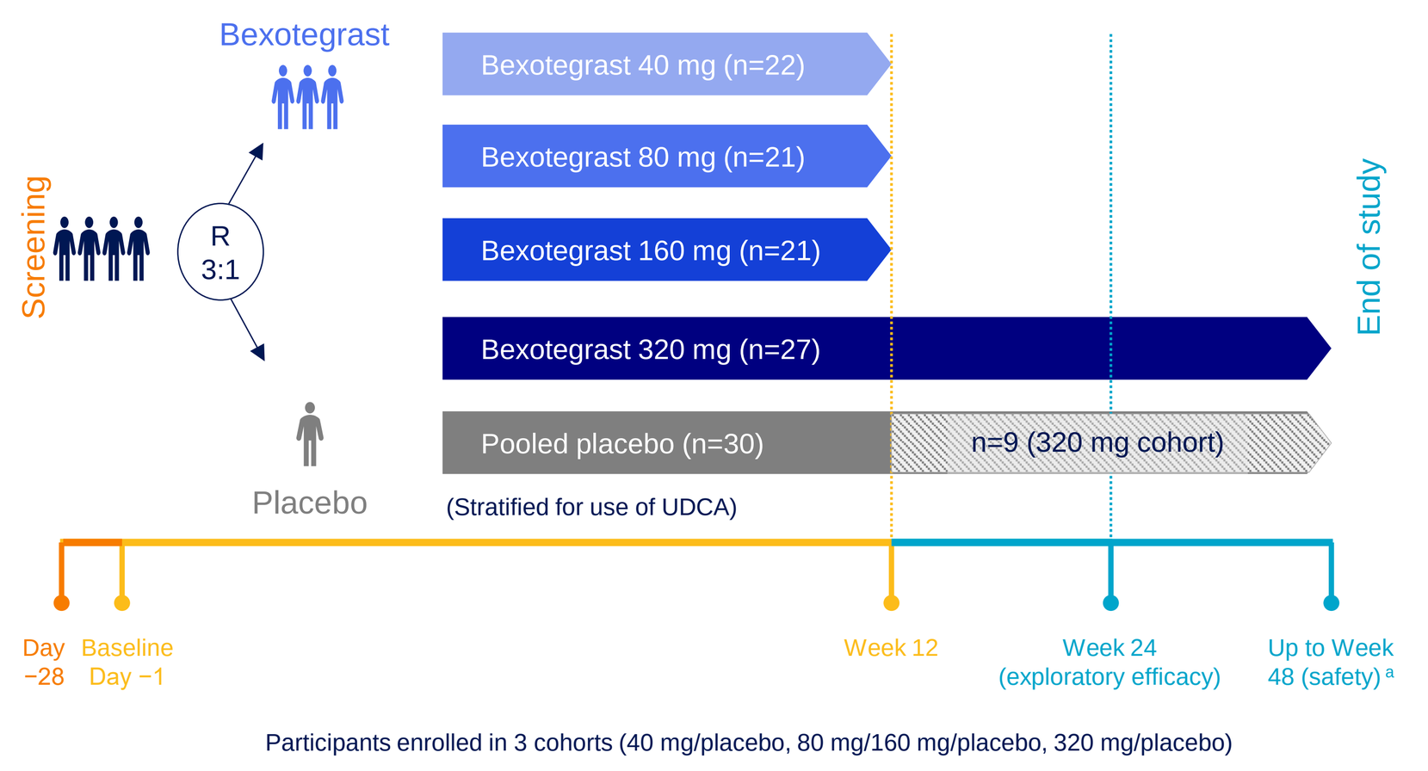
OBJECTIVE

- 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)

METHODS

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


Bexotegrast
Screening
R 3:1
Placebo
Bexotegrast 40 mg (n=22)
Bexotegrast 80 mg (n=21)
Bexotegrast 160 mg (n=21)
Bexotegrast 320 mg (n=27)
Pooled placebo (n=30)
n=9 (320 mg cohort)
(Stratified for use of UDCA)
End of study
Day −28
Baseline Day ~1
Week 12
Week 24 (exploratory efficacy)
Up to Week 40 (safety)[a]
Participants enrolled in 3 cohorts (40 mg/placebo, 80 mg/160 mg/placebo, 320 mg/placebo)

Primary endpoint
- Treatment-emergent adverse events

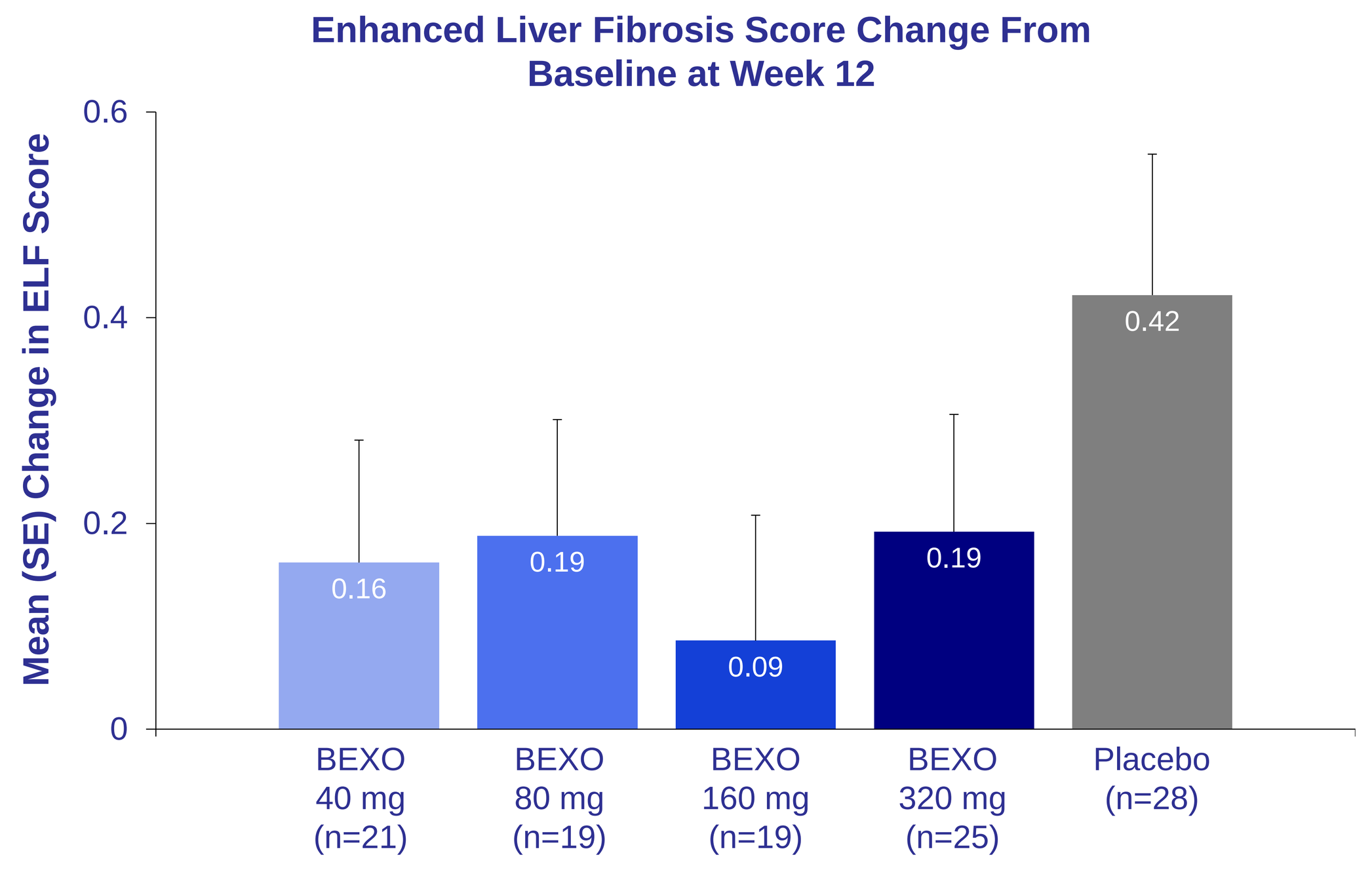
Key exploratory endpoints at Week 24
- Liver stiffness
- Liver function biomarkers
- ELF score
- Itch NRS score
- MRI gadoxetate time to arrival in the common bile duct
- MRI whole liver relative enhancement

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.

RESULTS

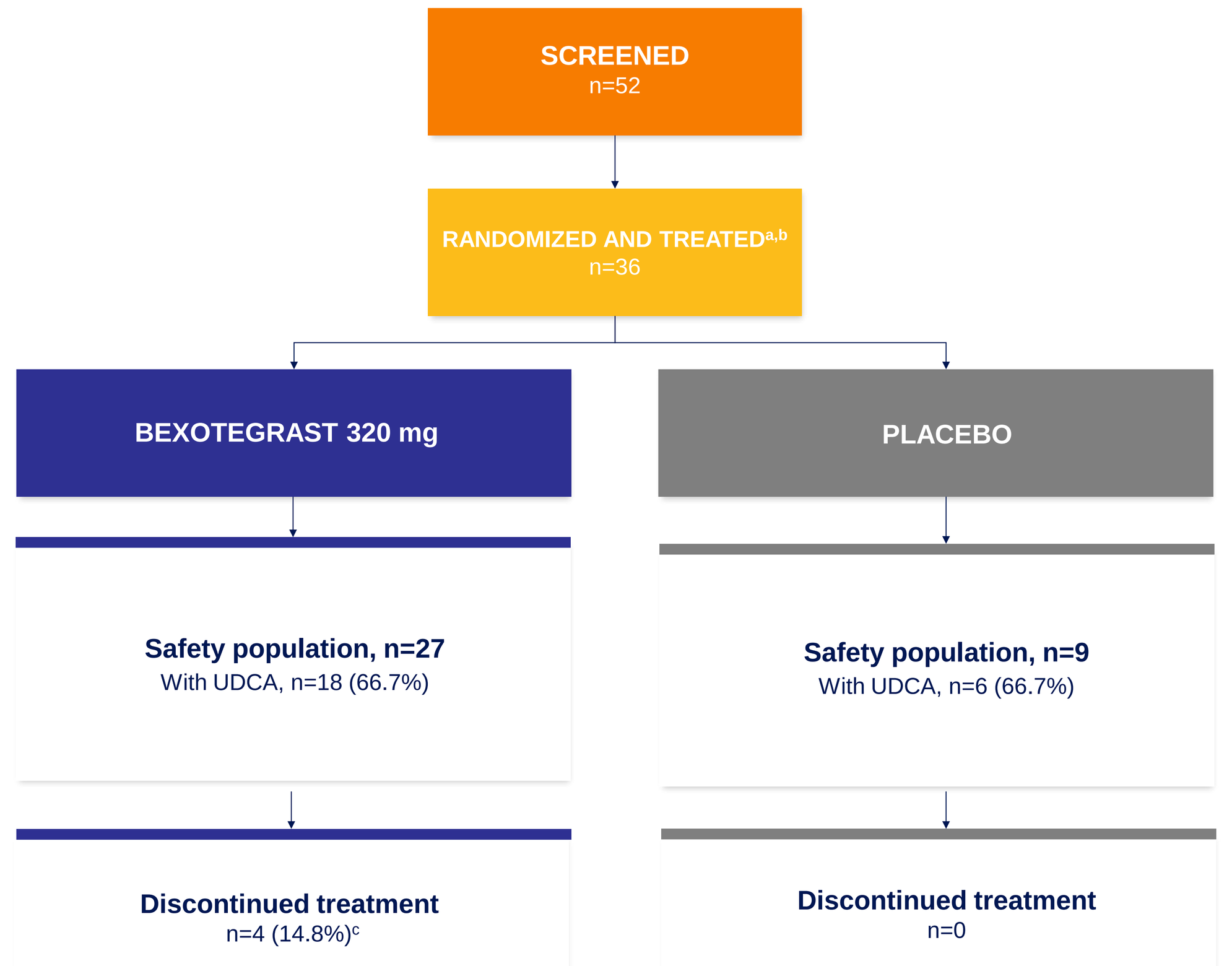
Phase 2a INTEGRIS-PSC Study: 12-Week Analysis[6]

- **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



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

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 Week 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)
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)

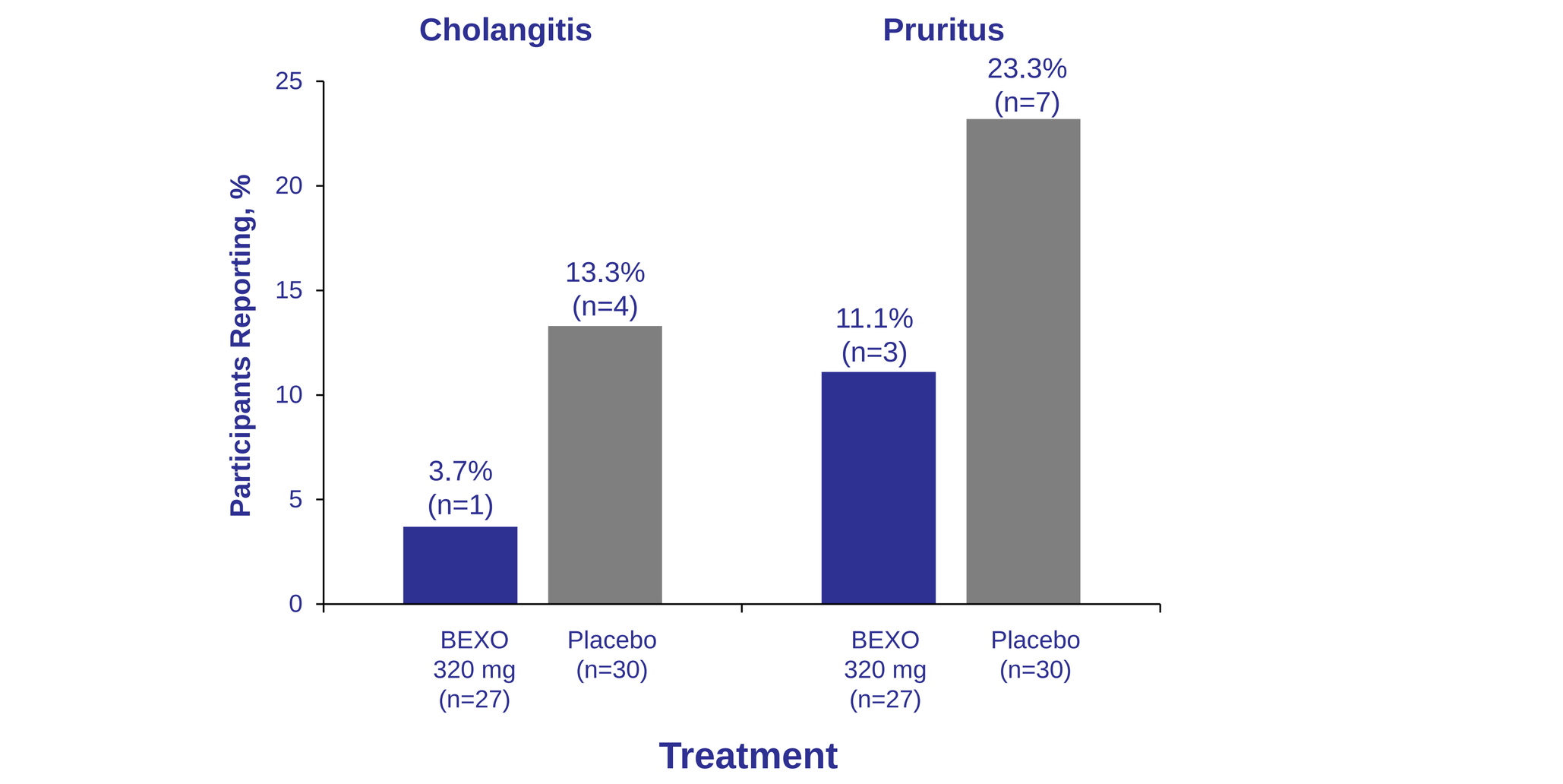
ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; NRS, numerical rating scale: PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN; upper limit of normal.
[a] Duration since diagnosis at screening is calculated from the first reported date for preferred terms of PSC.
[b]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

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 version 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.

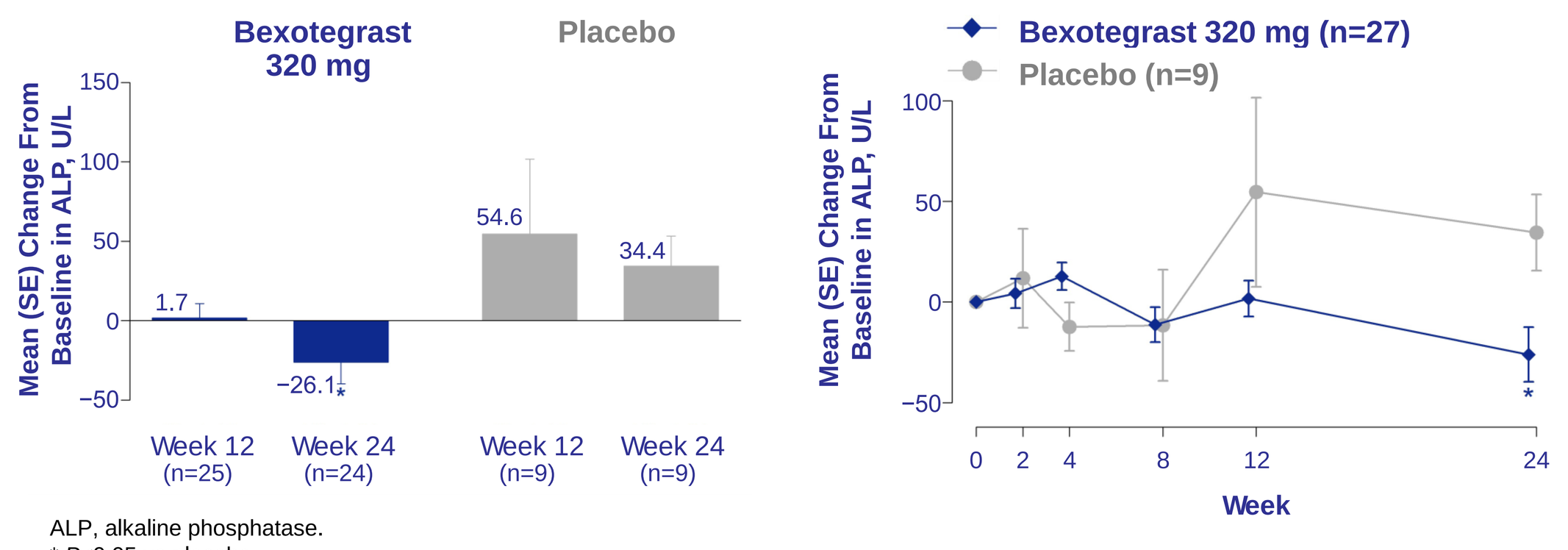
Bexotegrast Associated With Less Frequent Events of Cholangitis and Pruritus Through 40 Weeks of Treatment



BEXO, bexotegrast.

Bexotegrast Reduced ALP at Weeks 12 and 24

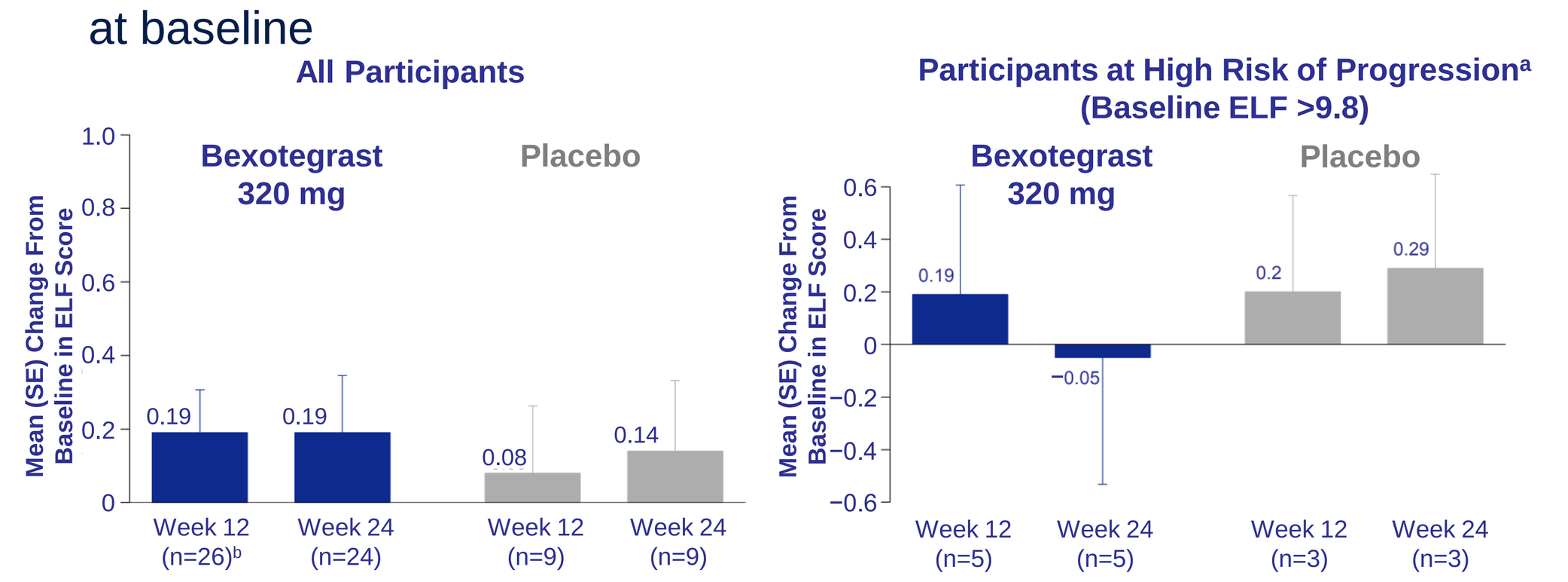
- Bexotegrast lowered ALP values from baseline to Week 24 compared with an increase with placebo (*P*<0.05)



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

Bexotegrast ELF Score Stable From Weeks 12 to 24

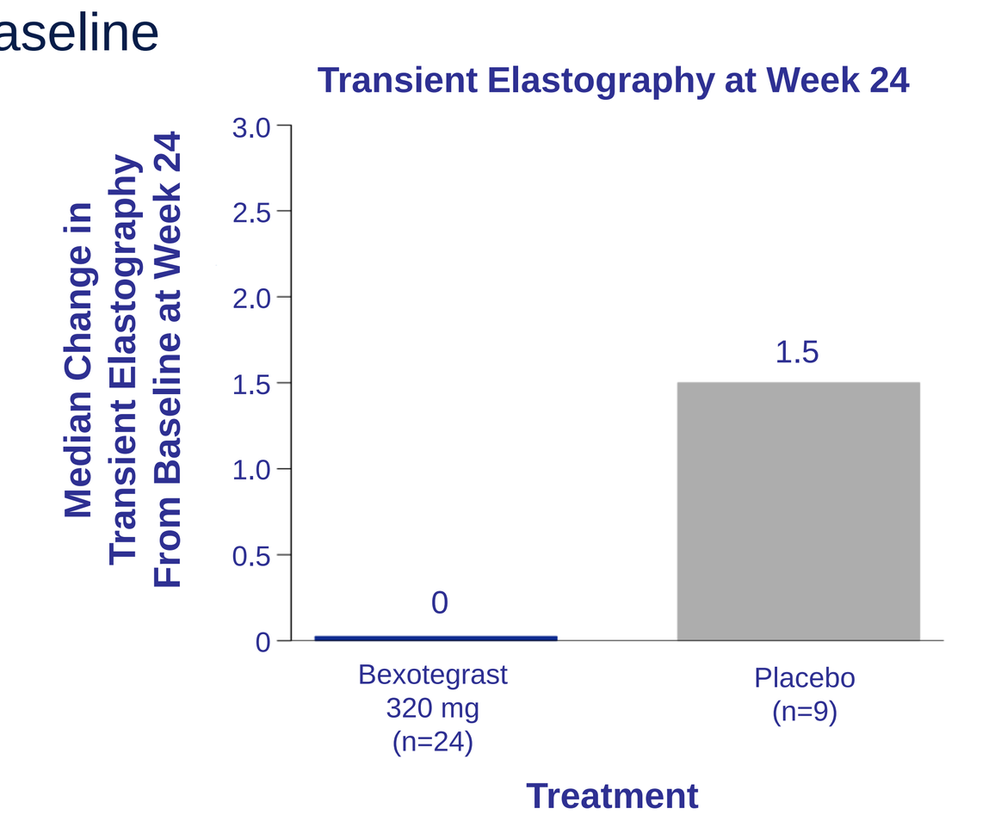
- Bexotegrast treatment resulted in a stable ELF score from Week 12 to Week 24, with a reduction in participants with an ELF score of >9.8 at baseline


All Participants
Participants at High Risk of Progression[a] (Baseline ELF >9.8)
Bexotegrast 320 mg
Placebo
Mean (SE) Change From Baseline in ELF Score
0.19
0.19
0.08
0.14
−0.05
0.2
0.29
Week 12 (n=26)[b]
Week 24 (n=24)
Week 12 (n=9)
Week 24 (n=9)
Week 12 (n=5)
Week 24 (n=5)
Week 12 (n=3)
Week 24 (n=3)

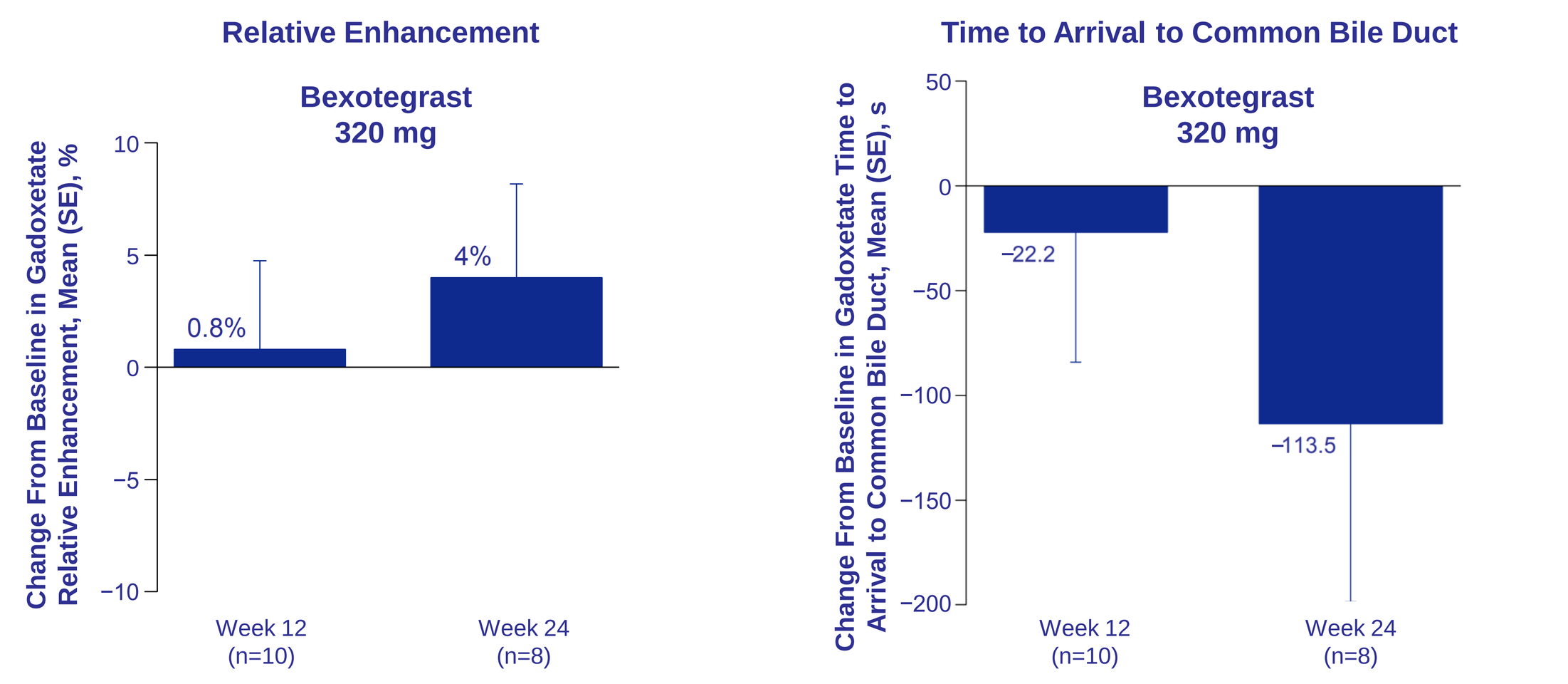
ELF, enhanced liver fibrosis.
[a] Includes 1 participant who was not included in 12-week interim analysis due to sample unavailability at the time of interim analysis.
[b] ELF score >9.8 is associated with increased risk for advanced liver fibrosis and disease progression.

Liver Stiffness Measured by Transient Elastography

- Liver stiffness findings indicate the potential for stabilization of liver fibrosis in bexotegrast-treated participants after 24 weeks compared with baseline



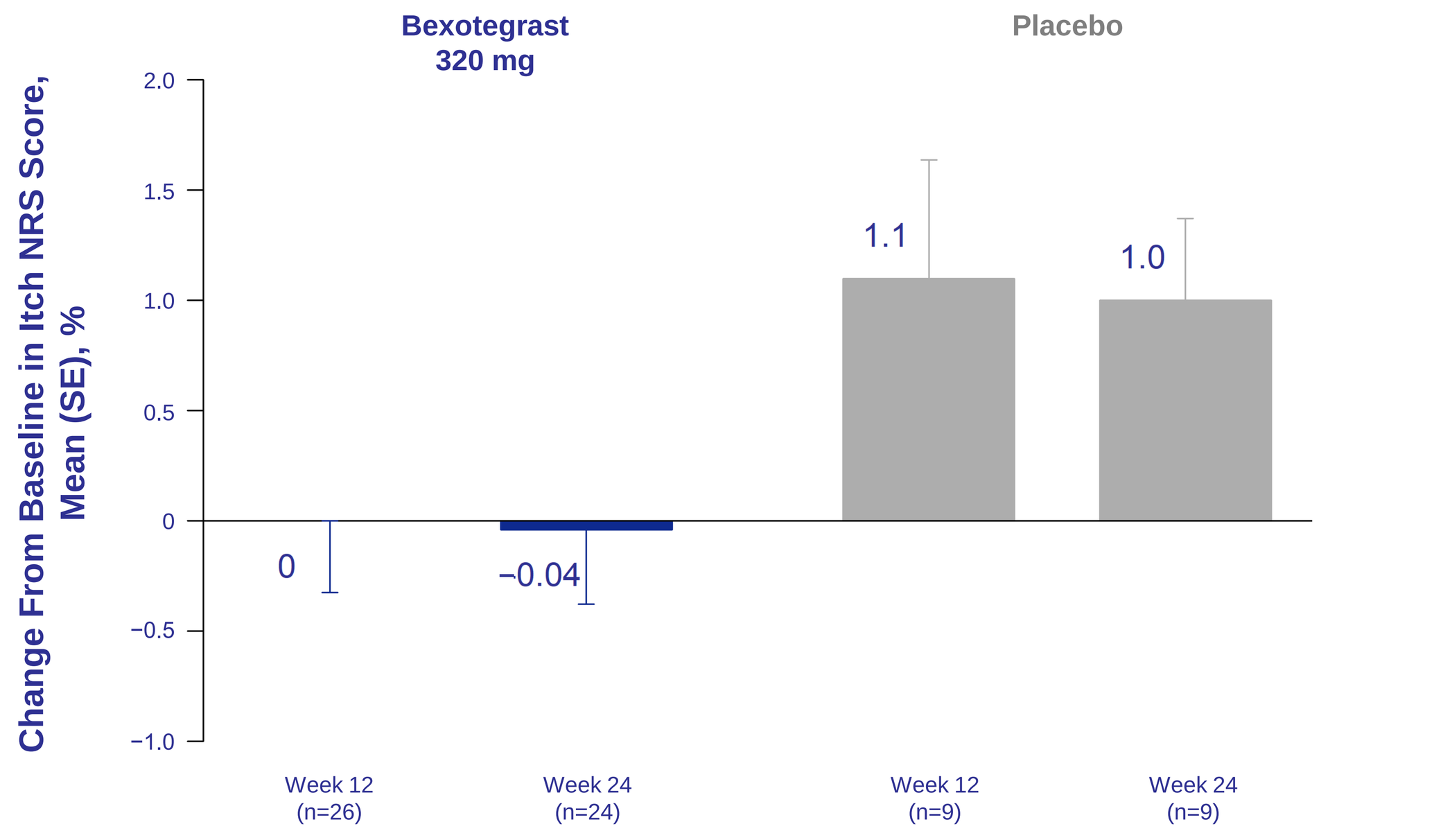
MRI Parameters Continued to Improve From Weeks 12 to 24 With Bexotegrast


Relative Enhancement
Time to Arrival to Common Bile Duct
Bexotegrast 320 mg
Change From Baseline in Gadoxetate Relative Enhancement, Mean (SE), %
Change From Baseline in Gadoxetate Time to Arrival to Common Bile Duct, Mean (SE), s
0.8%
4%
−22.2
−113.5
Week 12 (n=10)
Week 24 (n=8)

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.

Itch NRS Score was Unchanged with Bexotegrast Treatment

- Itch NRS score was unchanged 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

References: 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. 6. Trauner M, et al. *J Hepatol*. 2024;80(suppl):S97-S98.

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Contact information: ELefebvre@pliantrx.com