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

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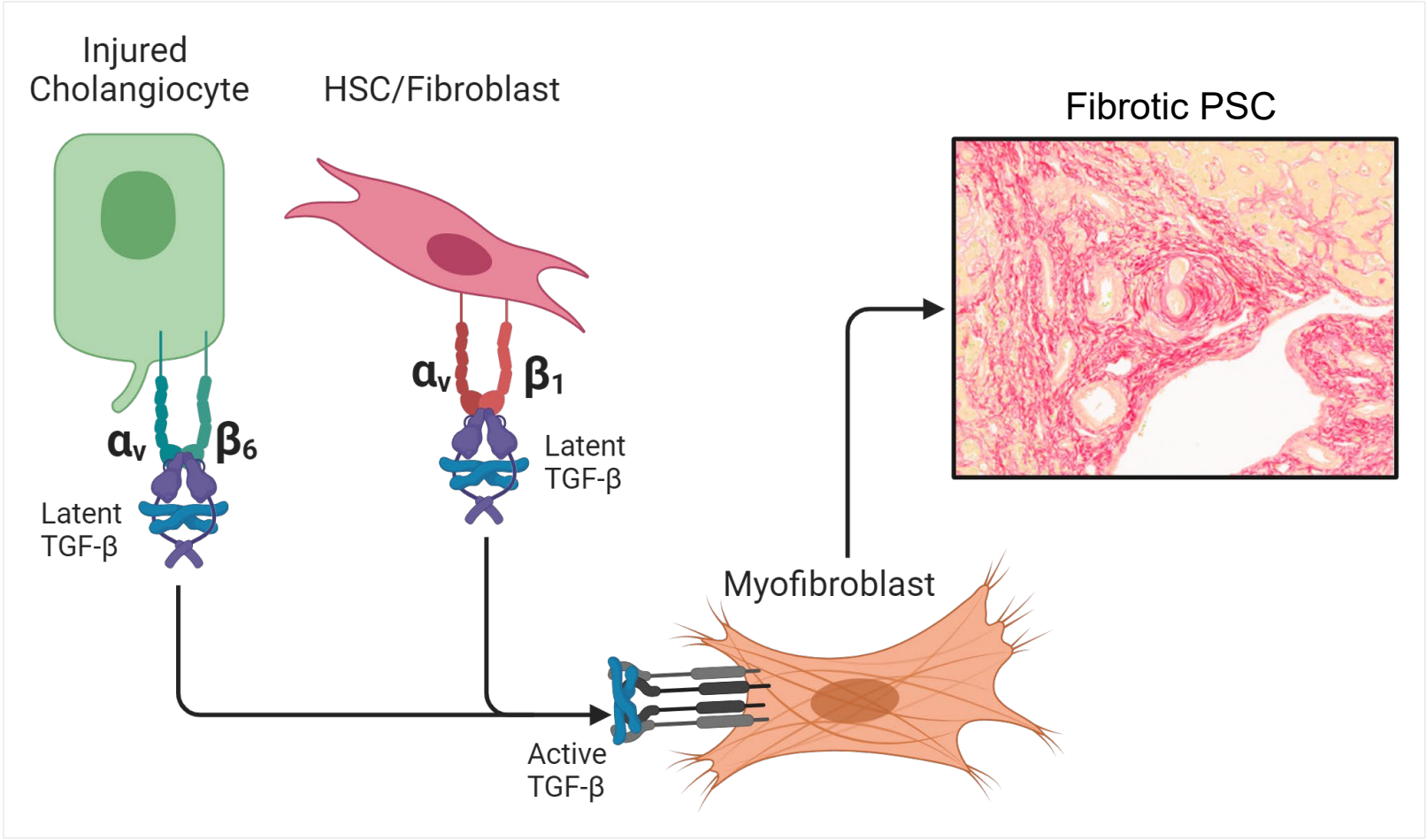
Disclosure Statement

Advisor

- Advanz Pharma
- CymaBay Therapeutics
- GSK
- Intercept Pharmaceuticals
- Ipsen
- Kowa Pharmaceuticals
- Mirum Pharmaceuticals
- Pliant Therapeutics

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



In PSC:

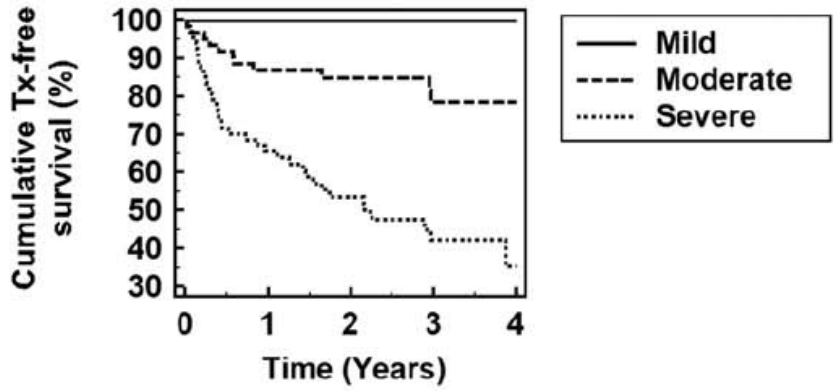
- $\alpha_V\beta_6$ is specifically expressed on injured cholangiocytes and $\alpha_V\beta_1$ on HSC/fibroblasts[1,2]
- Loss or inhibition of $\alpha_V\beta_6$ or $\alpha_V\beta_1$ reduces fibrosis in preclinical models of biliary and hepatic fibrosis[1-5]
- Therefore, localized TGF-β inhibition in the fibrotic liver may provide a novel approach to treat PSC, without affecting TGF-β signaling systemically

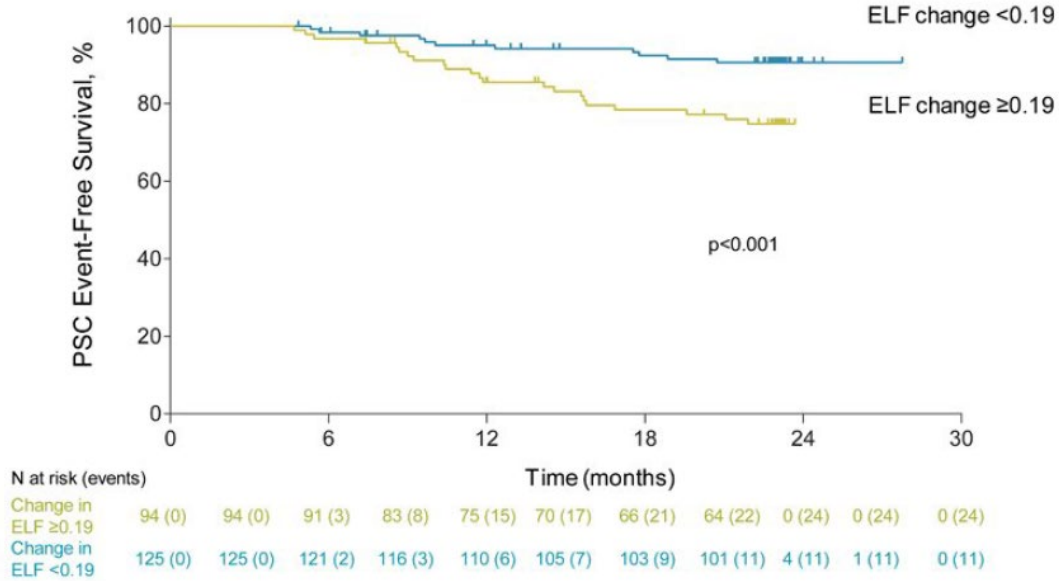
HSC, hepatic stellate cell; PSC, primary sclerosing cholangitis; TGF-β, transforming growth factor-β;

1. Peng Z-W, et al. *Hepatology* 2016;63(1):217–232; 2. Reed NI, et al. *Sci Transl Med* 2015;7(288):288ra279; 3. Popov Y, et al. *J Hepatol* 2008;48(3):453–464; 4. Patsenker E, et al. *Gastroenterology* 2008;135(2):660–670; 5. Schaub J, et al. *J Hepatol 2019;* 70(1): E57-E58

Enhanced Liver Fibrosis (ELF) Score
Prognostic Biomarker

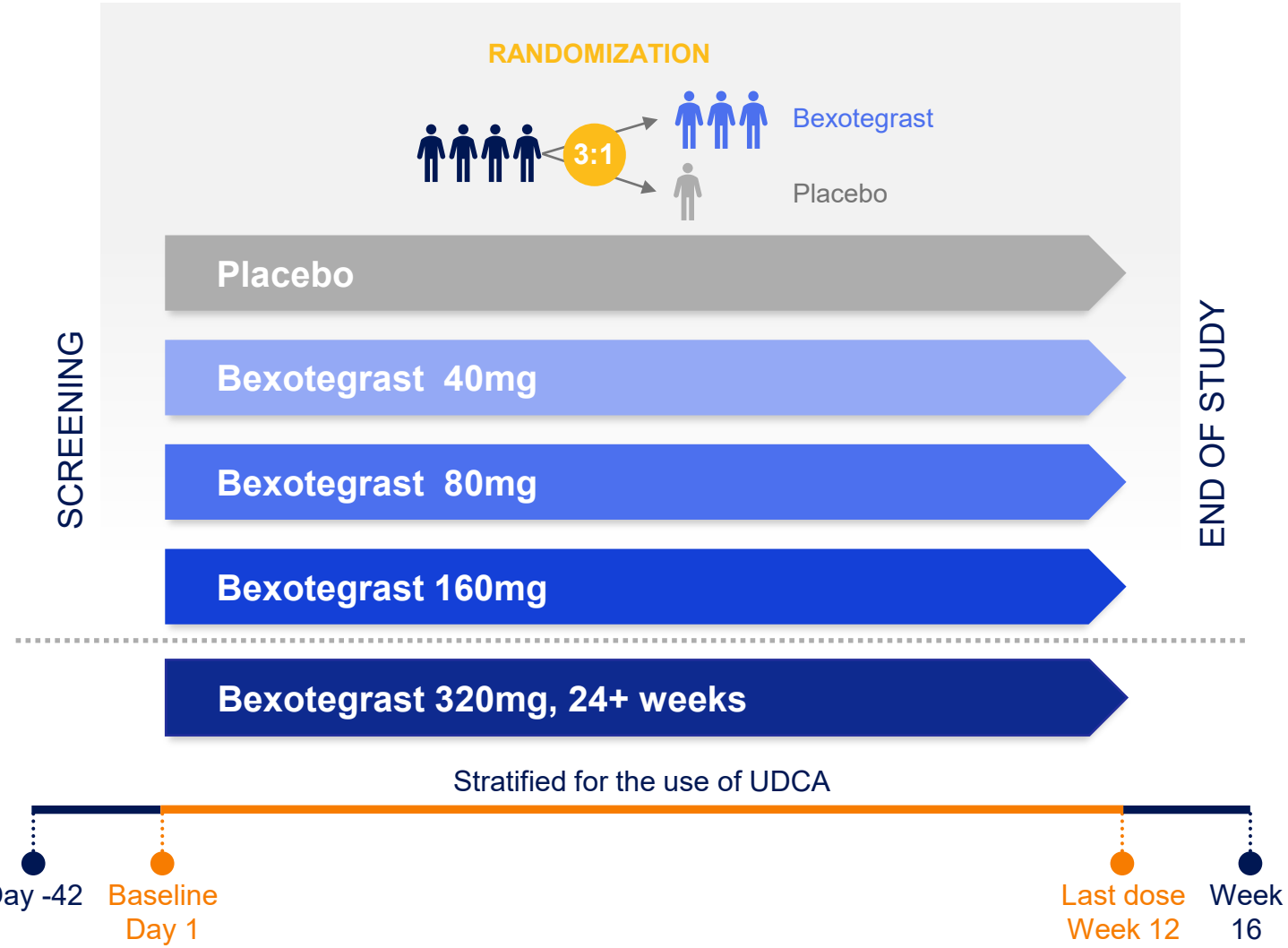
- Established ELF thresholds (7.7, 9.8) have been shown to predict transplant free survival in PSC[1]
- Worsening of ELF associated with increased risk of PSC-related clinical events[2]
- Measuring ELF is suggested for annual surveillance of PSC[3]





1.Vesterhus, et al. Enhanced liver fibrosis score predicts transplant-free survival in primary sclerosing cholangitis. Hepatology (AASLD). (2015) 62(1):188-197 https://journals.lww.com/hep/pages/articleviewer.aspx?year=2015&issue=07000&article=00025&type=Fulltext 2.Muir, et al. Simtuzumab for Primary Sclerosing Cholangitis: Phase 2 Study Results With Insights on the Natural History of the Disease. Hepatology (AASLD). (2019) 69(2):684-69 https://journals.lww.com/hep/fulltext/2019/02000/simtuzumab_for_primary_sclerosing_cholangitis_.19.aspx 3. EASL. *J Hepatology* 2022;77:761-806
ELF, enhanced liver fibrosis; PSC, primary sclerosing cholangitis; Tx, transplant

INTEGRIS-PSC: Study Design and Objectives



PRIMARY AND SECONDARY ENDPOINTS

- Safety and tolerability
- Pharmacokinetics[a]

EXPLORATORY ENDPOINTS

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

[a]Pharmacokinetics results are not presented but are available in the ePoster

ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; MR, magnetic resonance; NRS, numerical rating scale; PRO-C3, neo-epitope pro-peptide of type III collagen formation

Key Eligibility Criteria

Trial Enriched for Participants with Suspected Liver Fibrosis

INCLUSION

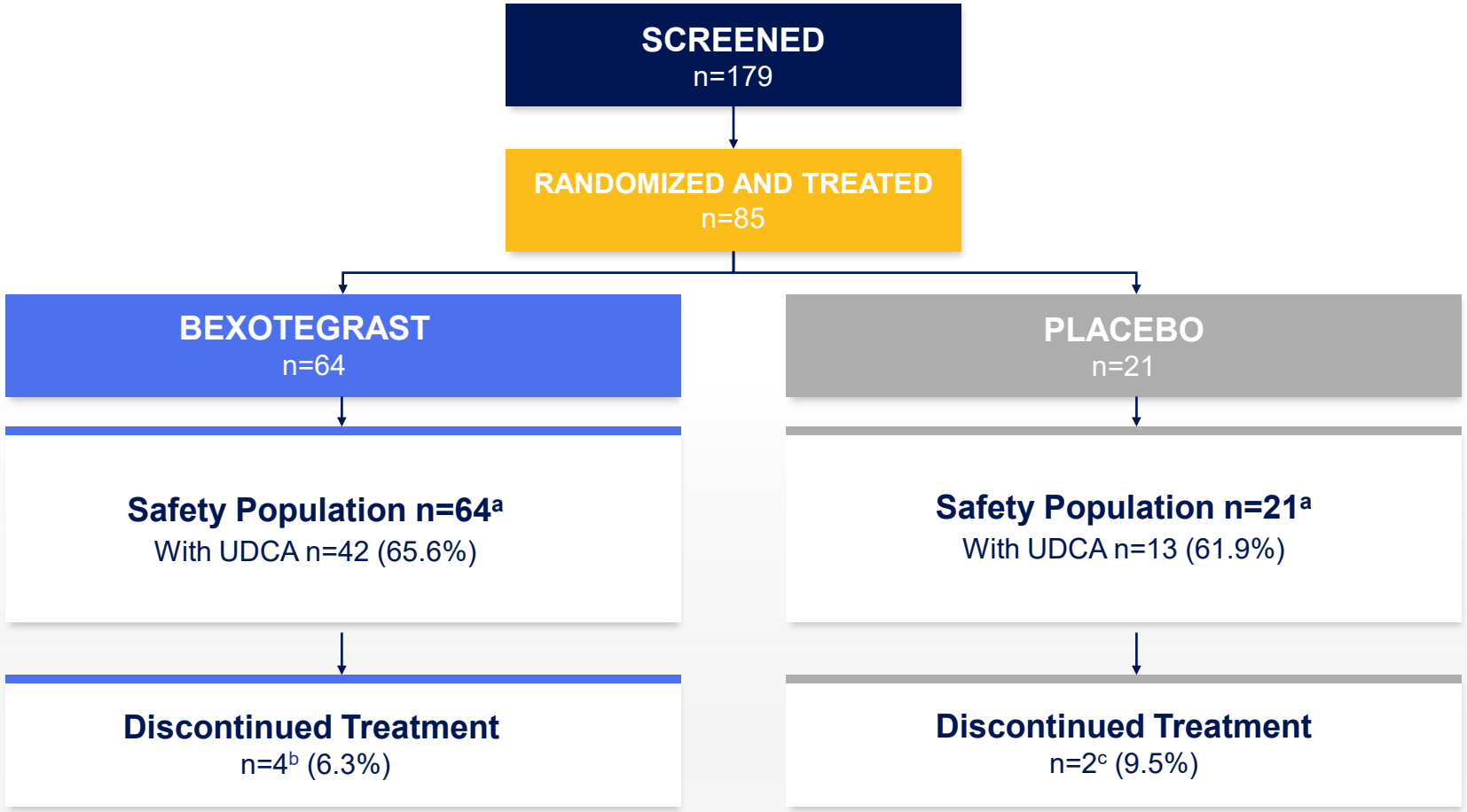
- Large duct PSC
- **Suspected liver fibrosis (moderate to severe) with at least one of the following:**
  - ELF score ≥7.7
  - Transient elastography ≥8 to ≤14.4 kPa
  - MR elastography ≥2.4 to ≤4.9 kPa
  - Historical liver biopsy showing fibrosis without cirrhosis
- Stable IBD, if present
- UDCA dose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

EXCLUSION

- Small duct PSC
- Cirrhosis
- Worsening liver chemistry during screening
- Known/suspected overlap with AIH
- Historical or current cholangiocarcinoma, other hepatobiliary malignancy, colorectal cancer, or other abdominal malignancy

AIH, autoimmune hepatitis; ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; MR, magnetic resonance; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid

Participant Disposition



[a]Safety population is the key population for both analysis of safety and efficacy; [b]Adverse Event (n=3; 40 mg, 80 mg, 160 mg) Protocol Deviation (n=1; 40 mg); [c]Adverse Event (n=2)
UDCA, ursodeoxycholic acid

Baseline Demographics

Characteristic	Bexotegrast 40 mg (n=24)[c]	Bexotegrast 80 mg (n=20)[c]	Bexotegrast 160 mg (n=20)[c]	Bexotegrast All (n=64)	Placebo (n=21)
Male sex, n (%)	17 (70.8)	16 (80.0)	14 (70.0)	47 (73.4)	17 (81.0)
Age (yr), mean (SD)	46.9 (15.06)	40.5 (15.32)	45.1 (12.65)	44.3 (14.46)	45.6 (12.48)
Race, n (%)					
White	20 (83.3)	16 (80.0)	18 (90.0)	54 (84.4)	18 (85.7)
Black	2 (8.3)	2 (10.0)	1 (5.0)	5 (7.8)	1 (4.8)
Asian	2 (8.3)	1 (5.0)	1 (5.0)	4 (6.3)	1 (4.8)
Other / Not Reported / Unknown	0	1 (5.0)	0	1 (1.6)	1 (4.8)
Time since diagnosis of PSC (yr)[a], mean (SD)	11.1 (8.15)	8.3 (7.97)	7.8 (6.78)	9.2 (7.72)	10.0 (7.95)
Concomitant UDCA use, n (%)	14 (58.3)	15 (75.0)	13 (65.0)	42 (65.6)	13 (61.9)
IBD, n (%)	18 (75.0)	12 (60.0)	11 (55.0)	41 (64.0)	12 (57.1)
Ulcerative colitis	11 (45.8)	6 (30.0)	7 (35.0)	24 (37.5)	7 (33.3)
Crohn's disease	6 (25.0)	4 (20.0)	2 (10.0)	12 (18.8)	4 (19.0)
IBD other	3 (12.5)	2 (10.0)	2 (10.0)	7 (10.9)	1 (4.8)
Partial Mayo score[b], mean (SD)	0.7 (1.08)	1.6 (2.54)	1.1 (1.27)	1.1 (1.70)	0.7 (1.56)
Itch NRS score, mean (SD)	1.8 (2.54)	2.1 (2.63)	1.4 (1.50)	1.7 (2.27)	1.1 (1.58)

[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
[c]Two participants (80 mg and 160mg) were dispensed incorrect number of tablets and provided incorrect dosing instructions for the full treatment period due to an error at a single site. The participants' daily dose corresponded to a ≤40 mg dose. These two participants are grouped in the 40 mg dose group for all summaries.
BMI, body mass index; IBD, inflammatory bowel disease; NRS, numerical rating scale; PSC, primary sclerosing cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid

Baseline Characteristics

	Bexotegrast 40 mg (n=24)	Bexotegrast 80 mg (n=20)	Bexotegrast 160 mg (n=20)	Bexotegrast All (n=64)	Placebo (n=21)
Serum liver tests, mean (SD)					
Alkaline phosphatase[a], U/L	315.1 (140.26)	199.2 (81.03)	273.8 (165.63)	266.0 (140.68)	259.7 (185.76)
Alanine aminotransferase, U/L	91.5 (62.08)	67.6 (63.15)	98.4 (73.11)	86.2 (66.25)	67.5 (49.19)
Aspartate aminotransferase, U/L	67.2 (49.34)	46.4 (30.12)	69.0 (39.62)	61.3 (41.70)	48.8 (30.57)
Total bilirubin, mg/dL	0.66 (0.307)	0.79 (0.493)	0.88 (0.396)	0.77 (0.405)	0.84 (0.357)
Direct bilirubin, mg/dL	0.27 (0.164)	0.26 (0.188)	0.31 (0.166)	0.28 (0.171)	0.30 (0.189)
Markers of fibrosis, mean (SD)					
ELF score	9.6 (0.77)	9.2 (1.01)	9.4 (0.79)	9.4 (0.86)	9.2 (1.08)
PRO-C3, ng/mL; (Roche COBAS)[b]	49.96 (13.844)	48.84 (42.790)	46.12 (11.670)	48.39 (25.904)	43.24 (10.828)
Transient elastography, kPa	10.1 (2.62)	9.1 (2.99)	8.2 (3.16)	9.2 (2.98)	8.5 (2.86)

[a]The study was initiated with an inclusion criterion of ALP >1.5xULN for the 40 mg cohort, this was later removed.
[b]PRO-C3 quantified using Roche COBAS platform (assay reports approximately 2x higher concentrations than previous generation PRO-C3 ELISA)
ALP, alkaline phosphatase; ELF, Enhanced Liver Fibrosis; PRO-C3, neo-epitope pro-peptide of type III collagen formation; SD, standard deviation; ULN, upper limit of normal

Safety and Tolerability Summary

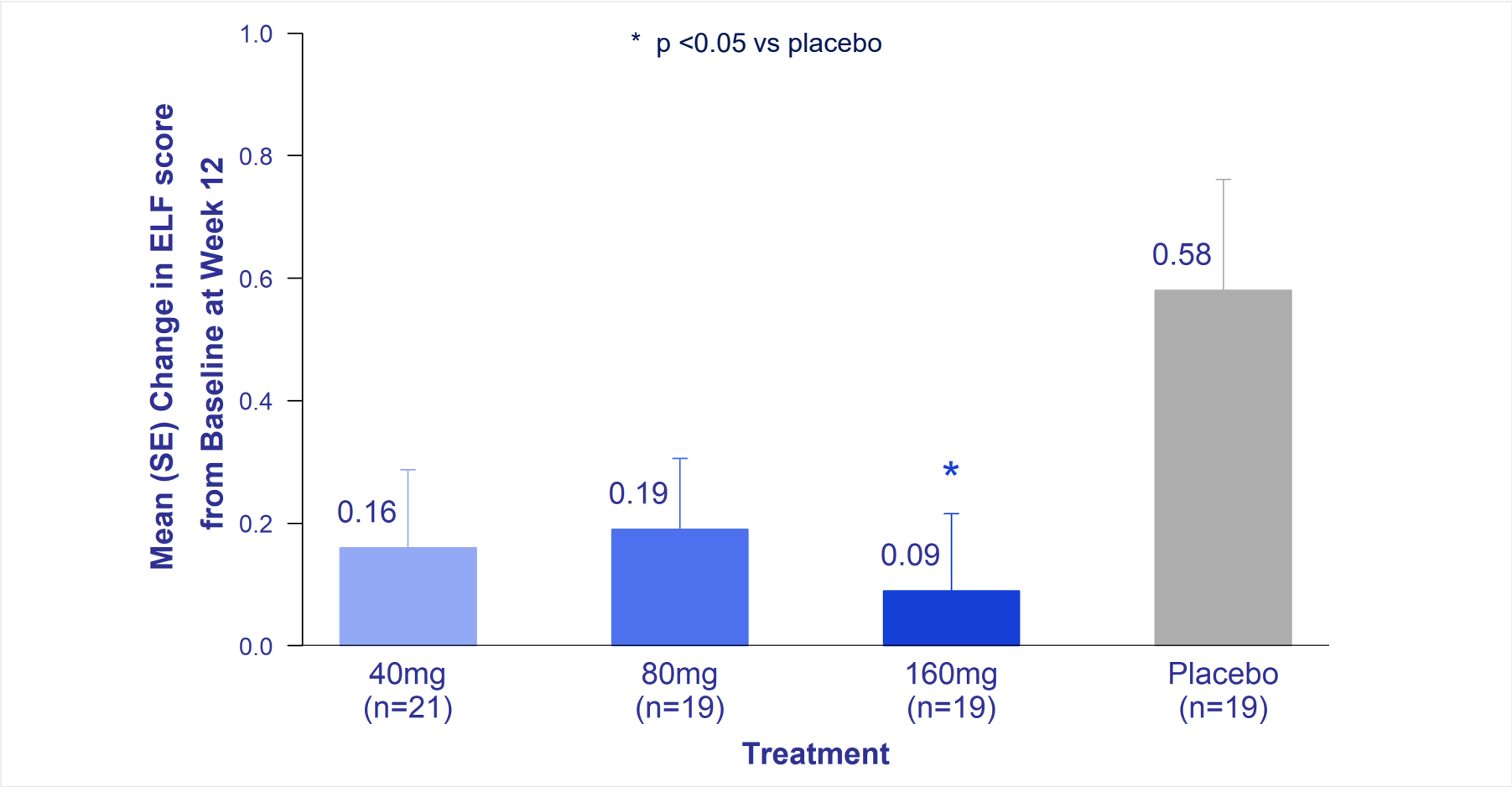
Bexotegrast was Well Tolerated over 12 Weeks

TEAE, n (%) of participants reporting	Bexotegrast 40 mg (n=24)	Bexotegrast 80 mg (n=20)	Bexotegrast 160 mg (n=20)	Bexotegrast All (n=64)	Placebo (n=21)
TEAE	10 (41.7)	16 (80.0)	15 (75.0)	41 (64.1)	16 (76.2)
Related to study drug	1 (4.2)	6 (30.0)	4 (20.0)	11 (17.2)	7 (33.3)
Serious TEAE	1 (4.2)	1 (5.0)	0	2 (3.1)	0
Related to study drug	0	0	0	0	0
Most frequent TEAEs (n ≥ 3 in at least one arm)					
Pruritus[a]	2 (8.3)	4 (20.0)	3 (15.0)	9 (14.1)	5 (23.8)
Fatigue	3 (12.5)	2 (10.0)	4 (20.0)	9 (14.1)	2 (9.5)
Headache	1 (4.2)	2 (10.0)	3 (15.0)	6 (9.4)	4 (19.0)
Nausea	1 (4.2)	2 (10.0)	3 (15.0)	6 (9.4)	0
COVID-19	2 (8.3)	1 (5.0)	0	3 (4.7)	3 (14.3)
Frequent bowel movements	0	3 (15.0)	0	3 (4.7)	3 (14.3)
Cholangitis	0	1 (5.0)	1 (5.0)	2 (3.1)	3 (14.3)

[a]Pruritus includes preferred terms for pruritus and cholestatic pruritus
AEs coded using MedDRA version 24.0.TEAE is defined as any AE starting (or worsening) on or after the date of first dose
AE, adverse event; TEAE, treatment emergent adverse event

ELF Score

Lower Mean Change in ELF with Bexotegrast vs Placebo



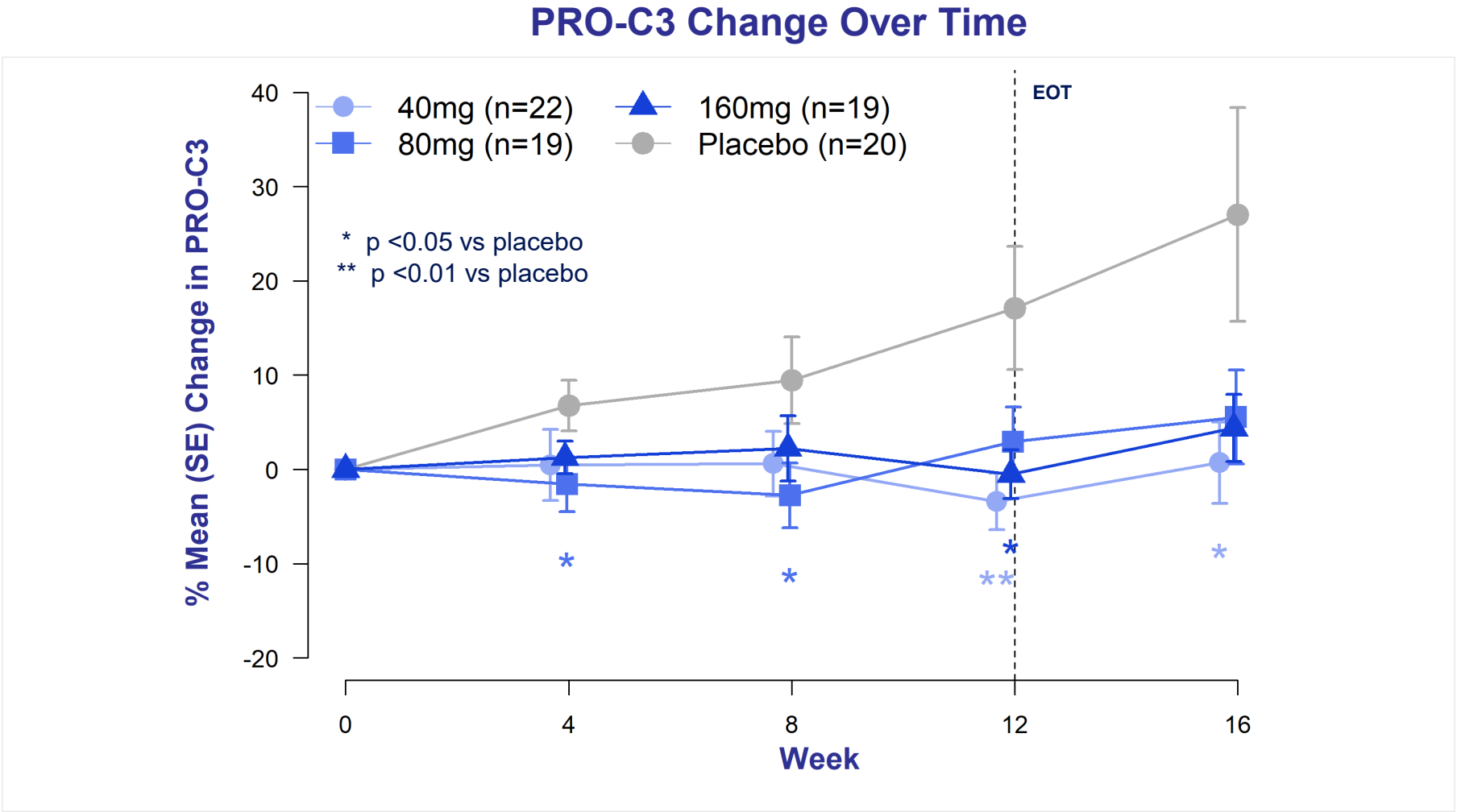
All participants had baseline ELF ≥ 7.7 (moderate to severe liver fibrosis)[1]

1. Vesterhus M et al. *Hepatology* 2015 62(1):188-197

ELF, enhanced liver fibrosis; SE, standard error

PRO-C3: Dynamic marker of collagen formation

Lower Mean Change in PRO-C3 with Bexotegrast vs Placebo



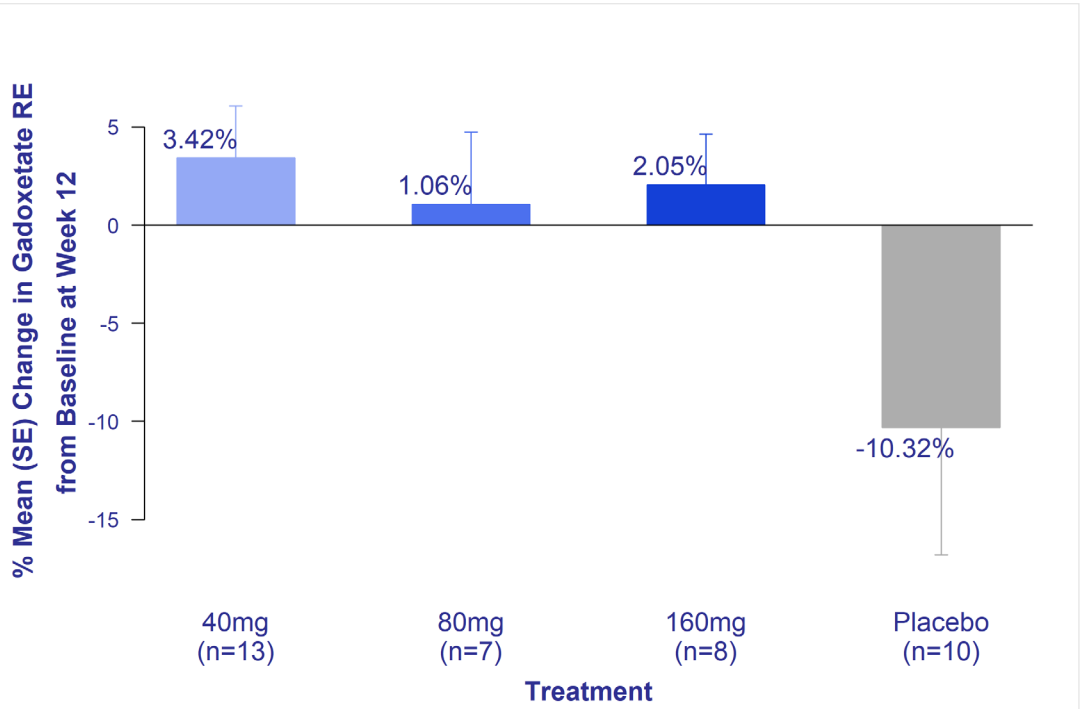
At 12 weeks, PRO-C3 change from baseline was significant for 40 mg and 160 mg

Only participants with both a baseline and post baseline are summarized
EOT, end of treatment; PRO-C3, neo-epitope pro-peptide of type III collagen formation; SE, standard error

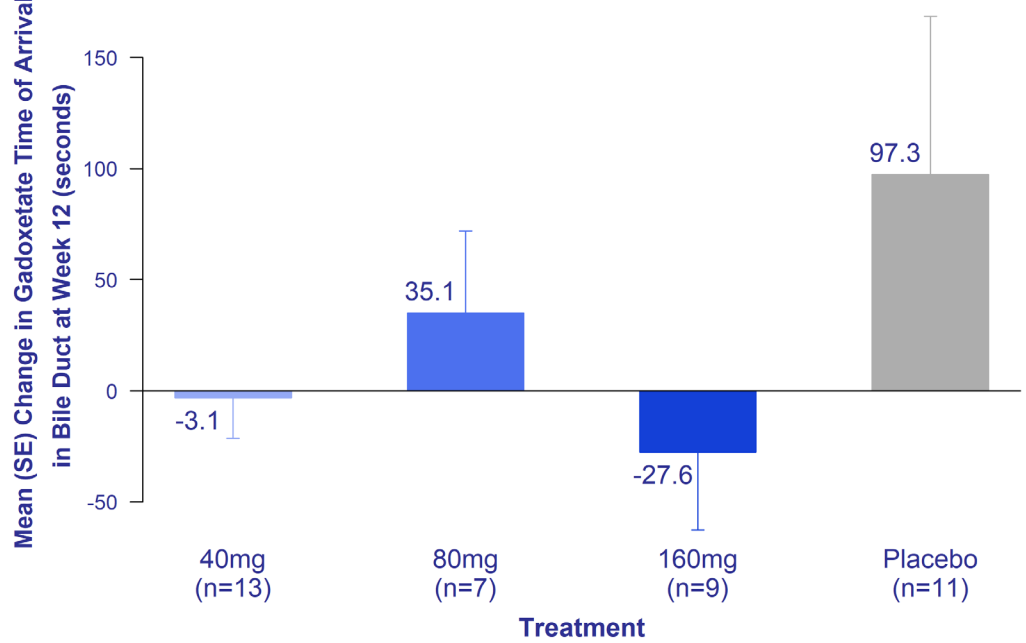
Gadoxetate-Enhanced MR of the Liver (Sub-Study)

- Using the MR contrast agent gadoxetate, relative enhancement is a measure of hepatocyte function[1,2]
- Time of arrival of gadoxetate to the common bile duct is an exploratory measure of excretory flow
- Findings are suggestive of improved hepatocyte function and excretory flow relative to placebo

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



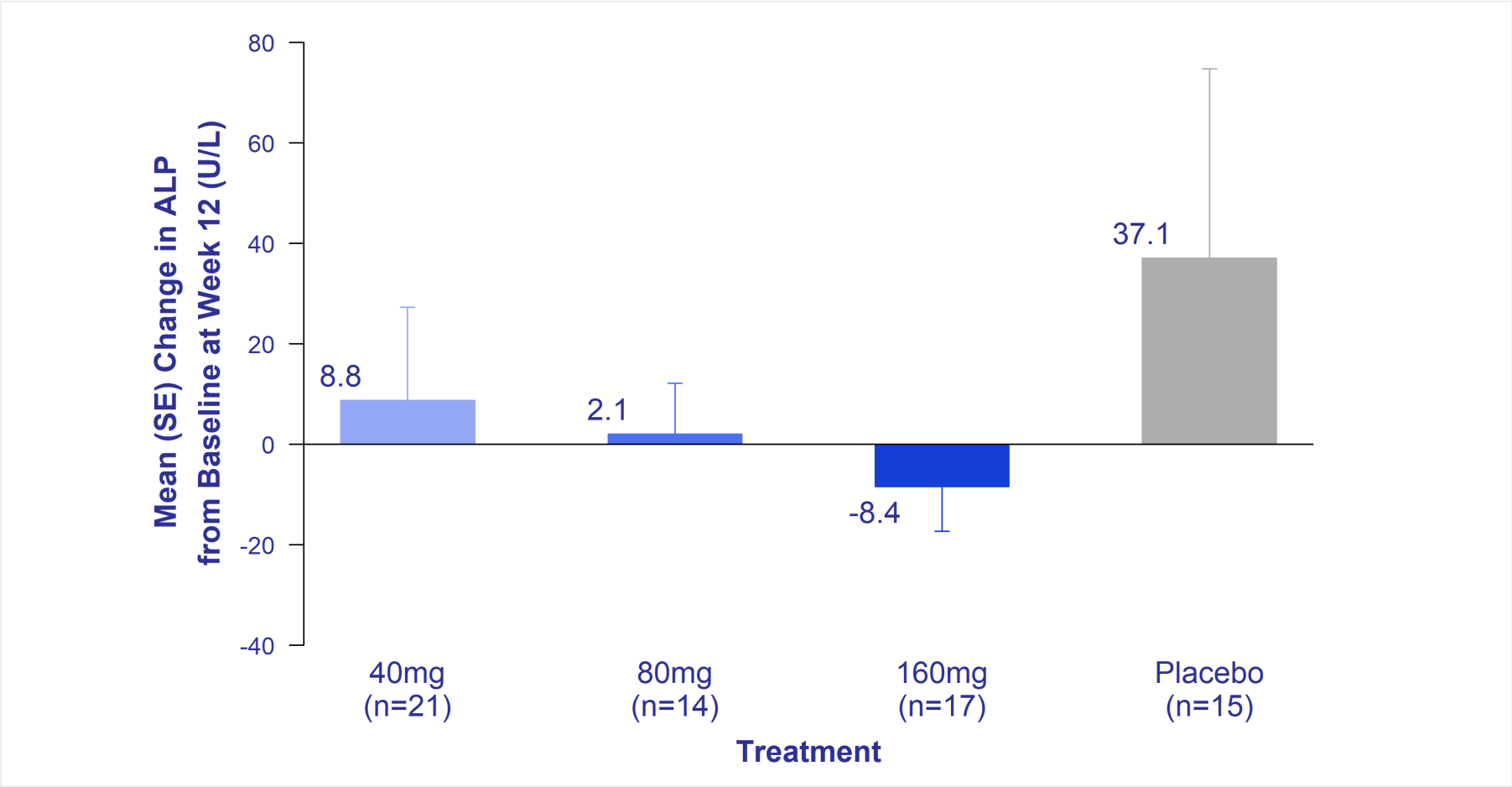
Time of Arrival in Common Bile Duct (sec): Change from Baseline at Week 12



[1]Elkilany A, et al. *Abdominal Radiology*. 2021 46:979-991. [2]Schulze J, et al. *Clin. Gastroenterol. Hepatol*. 2019 17:192-199.
MR, magnetic resonance; RE, relative enhancement; SE, standard error

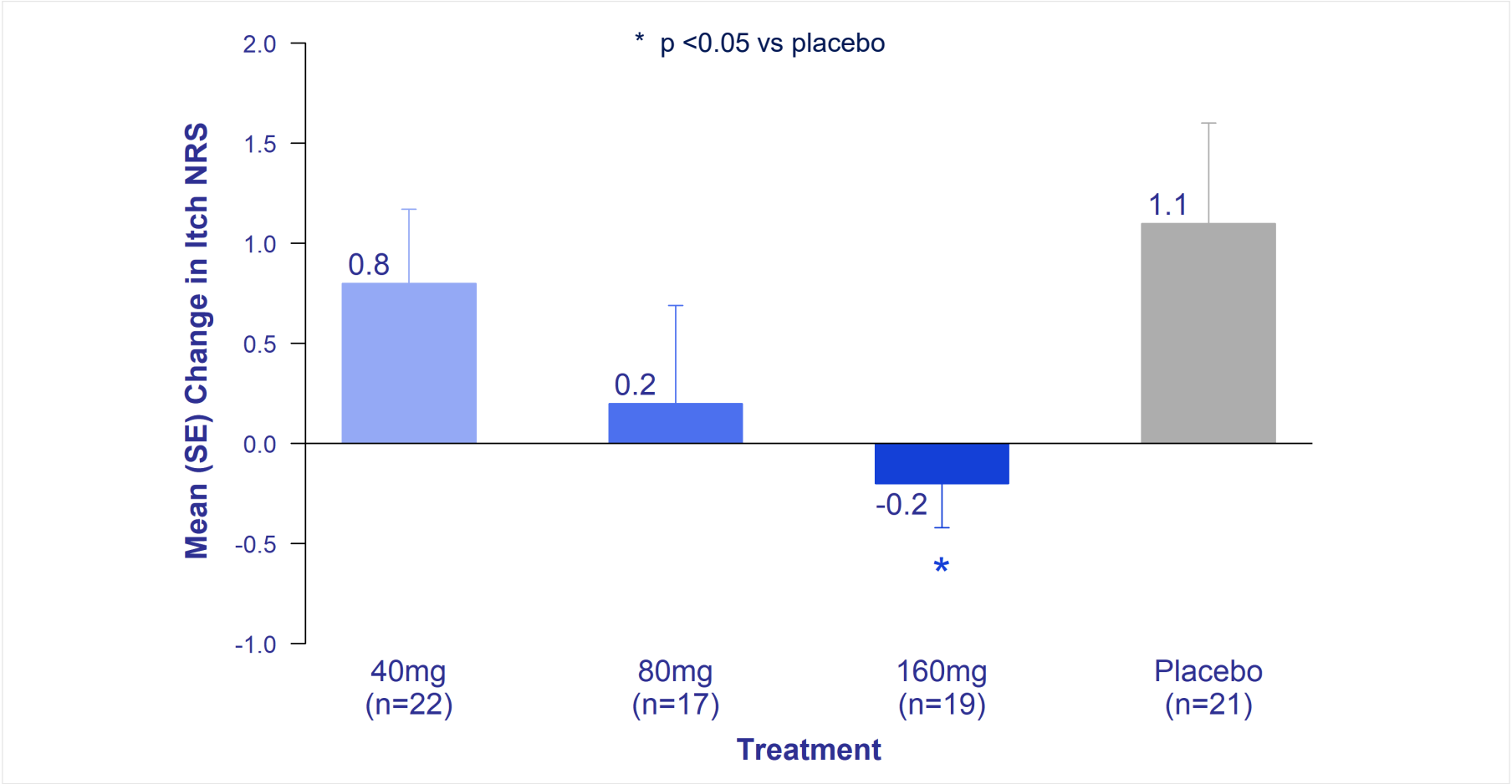
Alkaline Phosphatase

Participants with Baseline ALP > ULN



ALP, alkaline phosphatase; EOT, end of treatment; SE, standard error; ULN, upper limit of normal

Itch
Numerical Rating Scale



Itch NRS is a patient reported outcome which assesses severity of itch, over the last 24 hours, on a scale of 0 (no itch) to 10 (worst imaginable itching)
NRS: numerical rating scale; SE, standard error

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

Bexotegrast was well tolerated over 12 weeks of treatment

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

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

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

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

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

AE, adverse event; ELF, enhanced liver fibrosis, MR, magnetic resonance; PRO-C3, neo-epitope pro-peptide of type III collagen formation; PSC, primary sclerosing cholangitis

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