

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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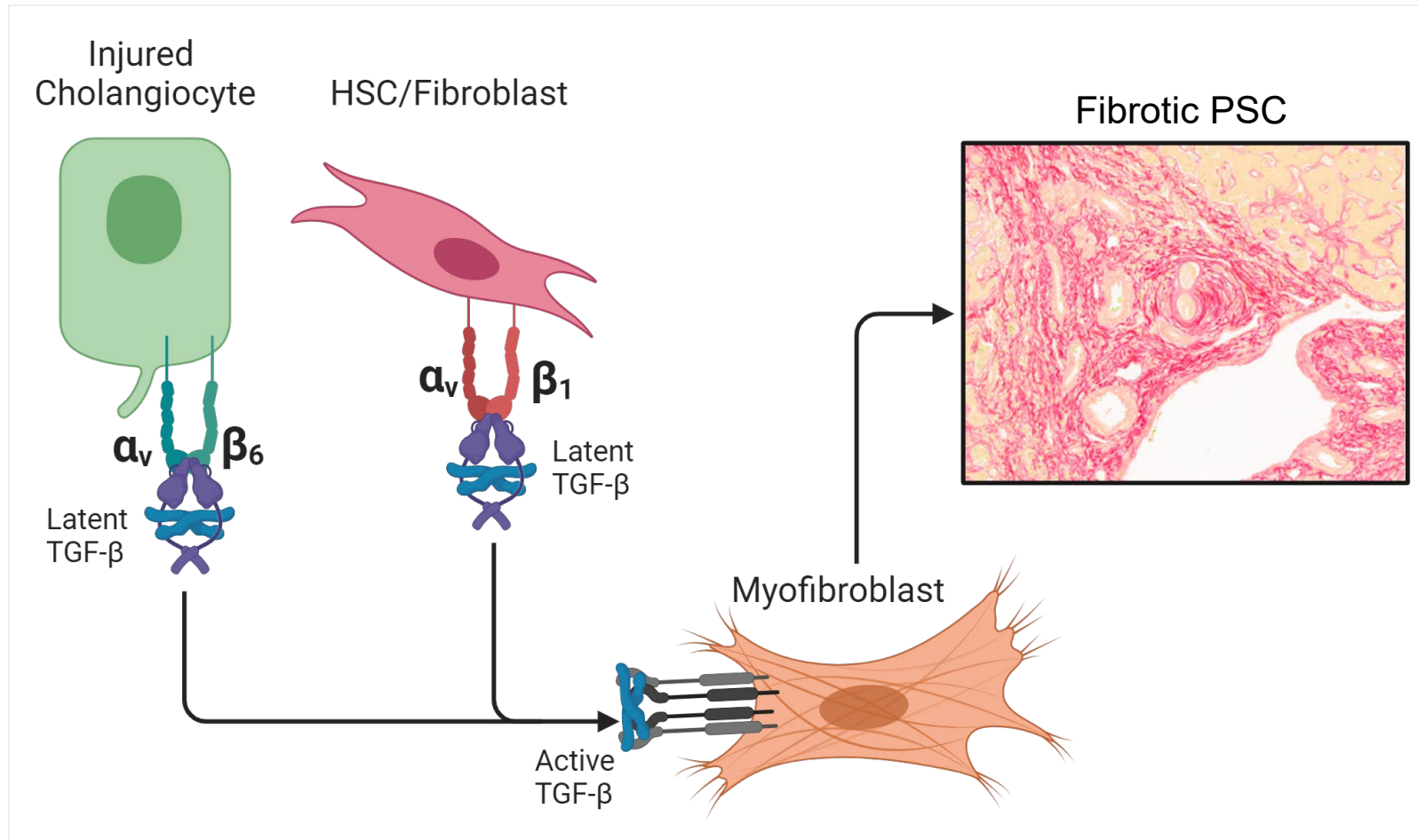


Disclosure Statement

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:

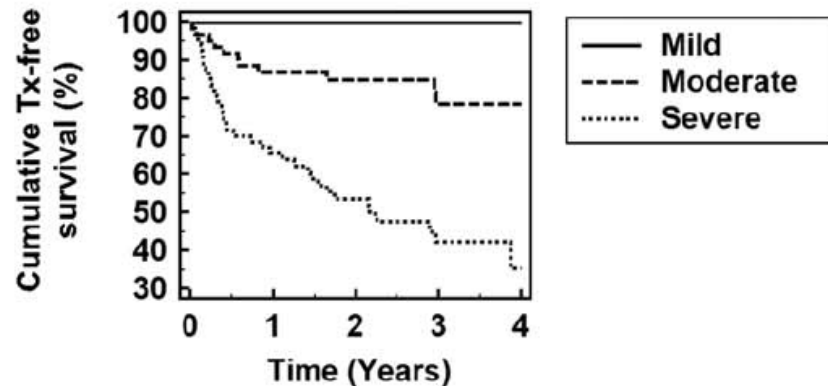
- $\alpha_v\beta_6$ is specifically expressed on injured cholangiocytes and $\alpha_v\beta_1$ on HSC/fibroblasts^{1,2}
- Loss or inhibition of $\alpha_v\beta_6$ or $\alpha_v\beta_1$ reduces fibrosis in preclinical models of biliary and hepatic fibrosis¹⁻⁵
- Therefore, localized TGF- β inhibition in the 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 ;

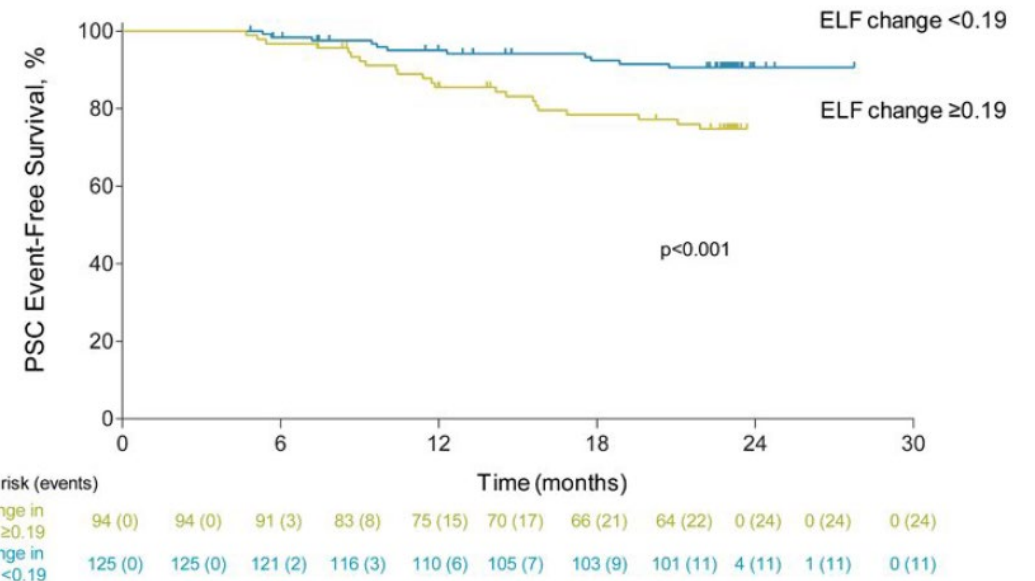
1. Peng Z-W, et al. *Hepatology* 2016;63(1):217–232; 2. Reed NI, et al. *Sci Transl Med* 2015;7(288):288ra279; 3. Popov Y, et al. *J Hepatol* 2008;48(3):453–464; 4. Patsenker E, et al. *Gastroenterology* 2008;135(2):660–670; 5. Schaub J, et al. *J Hepatol* 2019; 70(1): E57-E58

Enhanced Liver Fibrosis (ELF) Score Prognostic Biomarker

- Established ELF thresholds (7.7, 9.8) have been shown to predict transplant free survival in PSC¹
- Worsening of ELF associated with increased risk of PSC-related clinical events²
- Measuring ELF is suggested for annual surveillance of PSC³



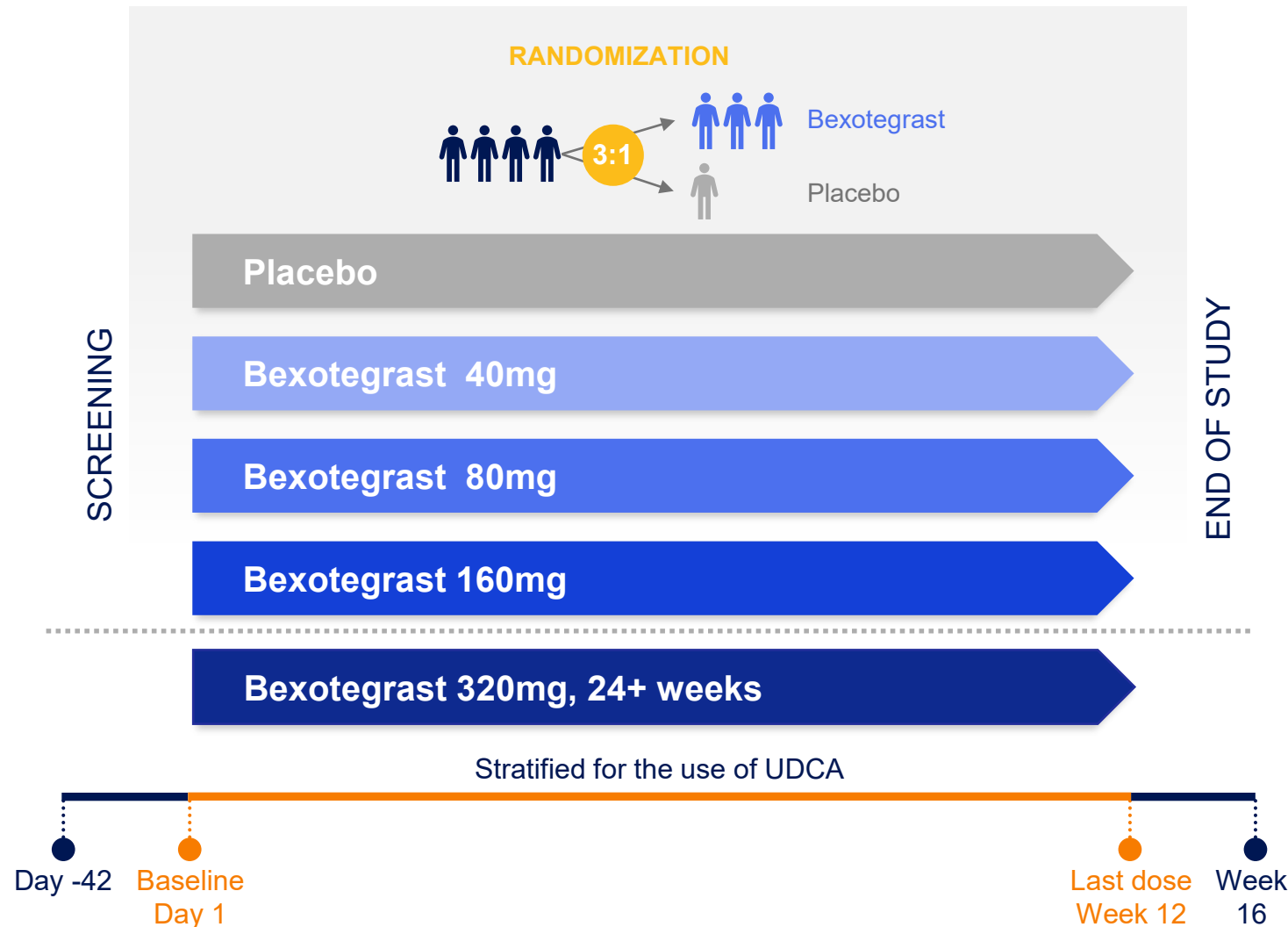
Number at risk					
	0	1	2	3	4
Mild	9	8	6	4	0
Moderate	62	50	38	25	0
Severe	67	41	28	15	0



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

^aPharmacokinetics 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

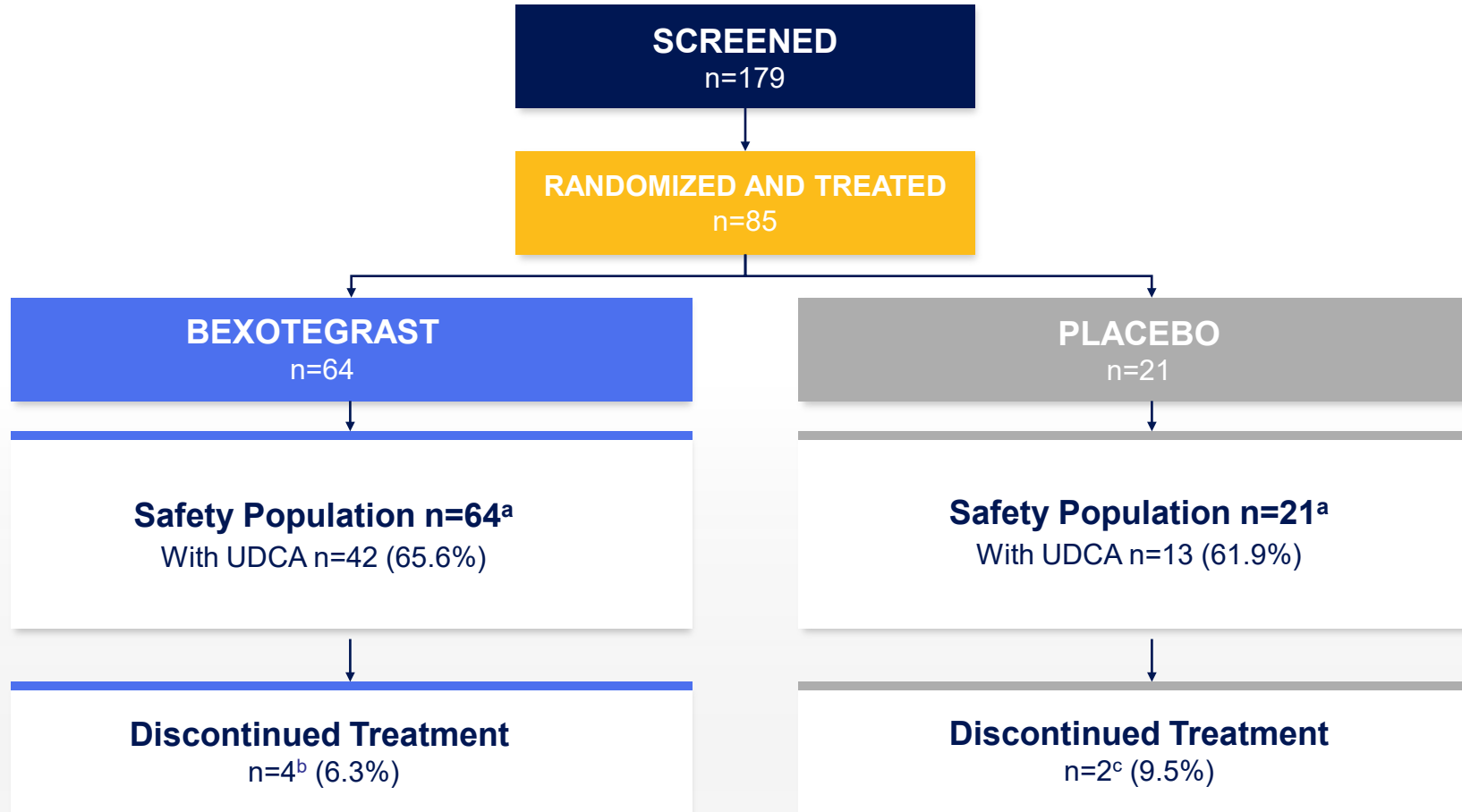
INCLUSION

- 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

Participant Disposition



^aSafety population is the key population for both analysis of safety and efficacy; ^bAdverse Event (n=3; 40 mg, 80 mg, 160 mg) Protocol Deviation (n=1; 40 mg);

^cAdverse 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)

^aDuration since diagnosis at screening is calculated from the first reported date for preferred terms of PSC.

^bPartial Mayo score only reported for those with active IBD at Baseline

^cTwo 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)

^aThe study was initiated with an inclusion criterion of ALP >1.5xULN for the 40 mg cohort, this was later removed.

^bPRO-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

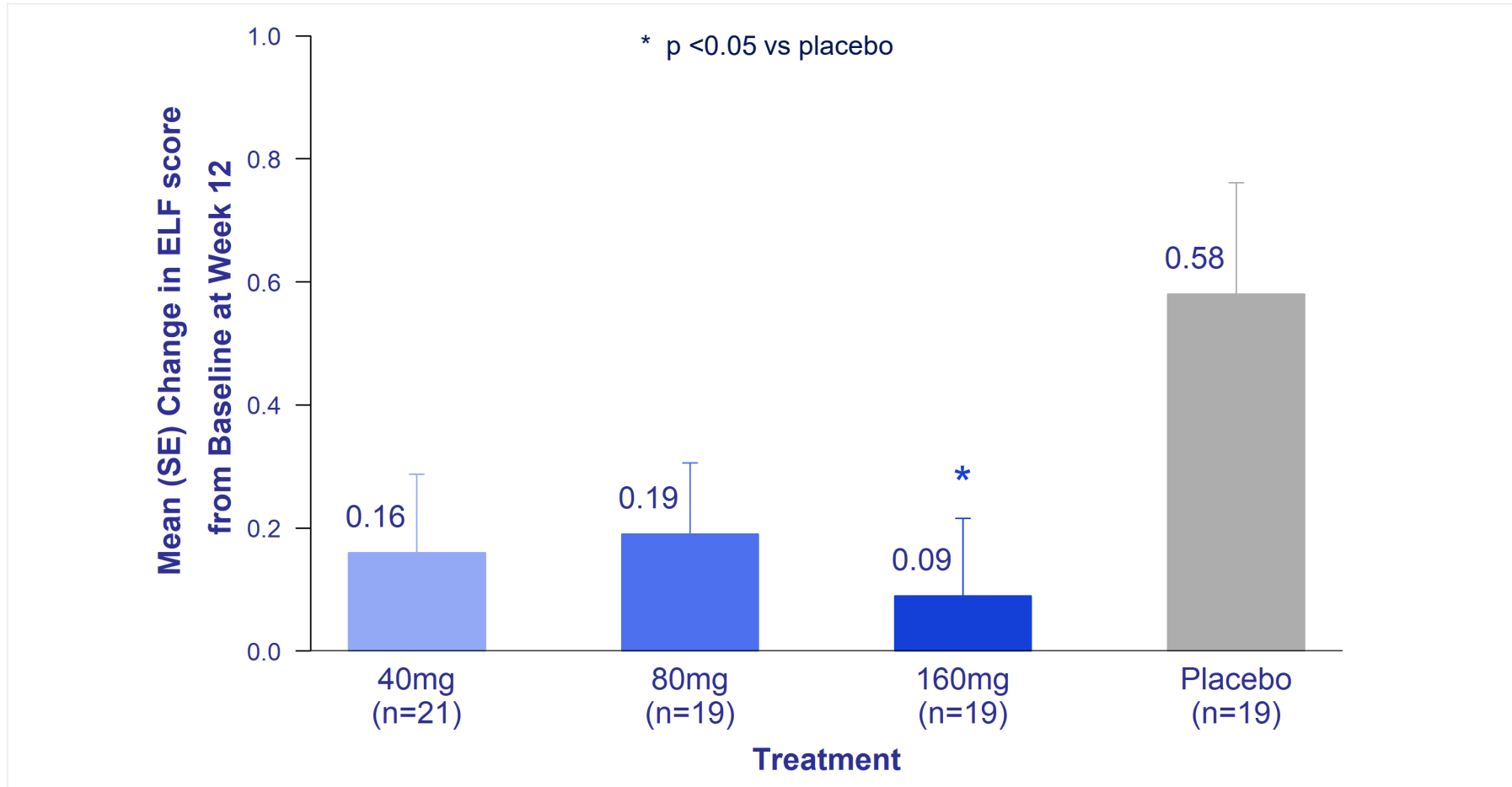
TEAE, n (%) of participants reporting	Bexotegrast 40 mg (n=24)	Bexotegrast 80 mg (n=20)	Bexotegrast 160 mg (n=20)	Bexotegrast All (n=64)	Placebo (n=21)
TEAE	10 (41.7)	16 (80.0)	15 (75.0)	41 (64.1)	16 (76.2)
Related to study drug	1 (4.2)	6 (30.0)	4 (20.0)	11 (17.2)	7 (33.3)
Serious TEAE	1 (4.2)	1 (5.0)	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)

^aPruritus 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

ELF Score Change from Baseline at Week 12



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

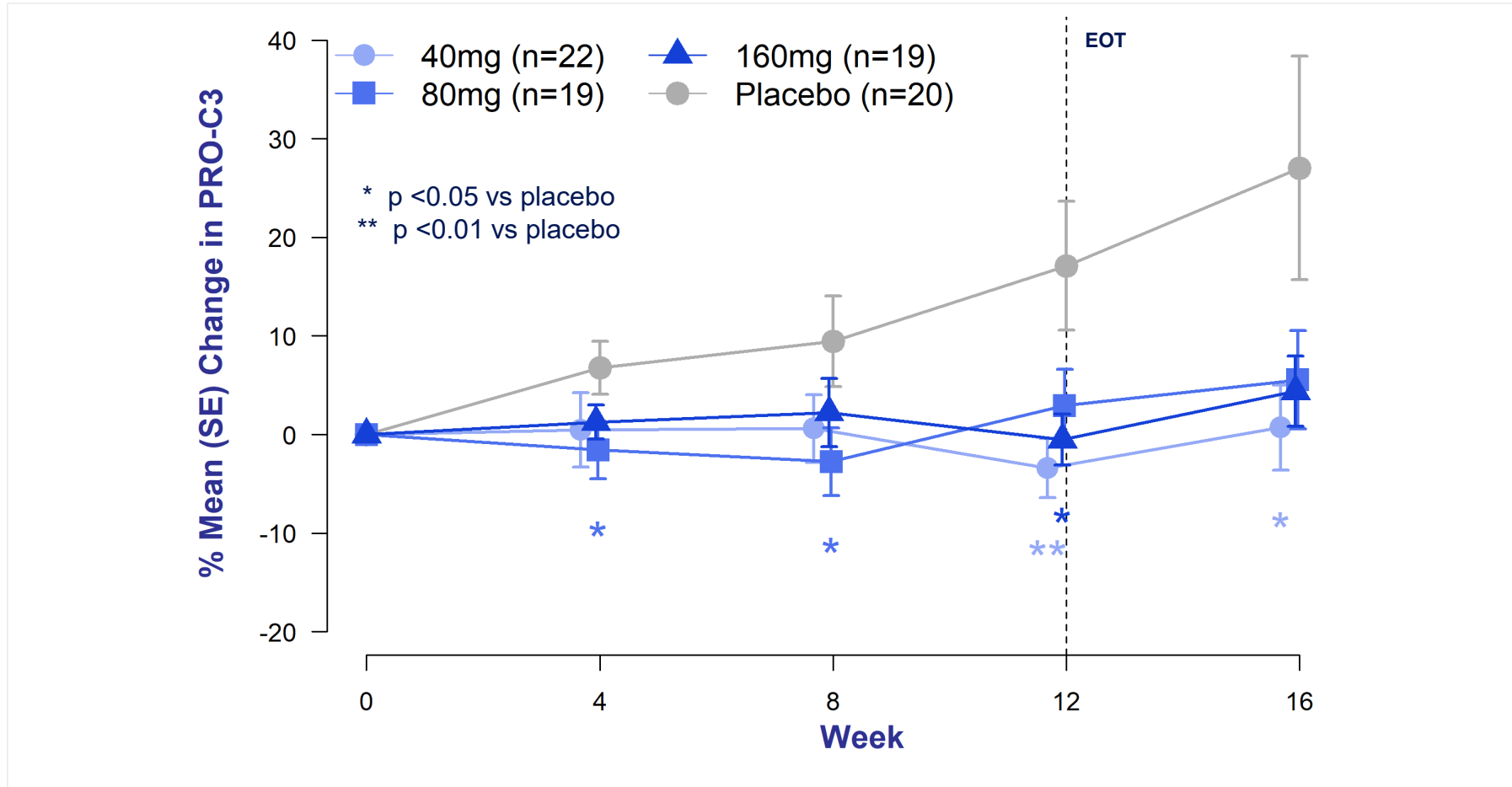
1. Vesterhus M et al. *Hepatology* 2015 62(1):188-197

ELF, enhanced liver fibrosis; SE, standard error

PRO-C3: Dynamic marker of collagen formation

Lower Mean Change in PRO-C3 with Bexotegrist vs Placebo

PRO-C3 Change Over Time

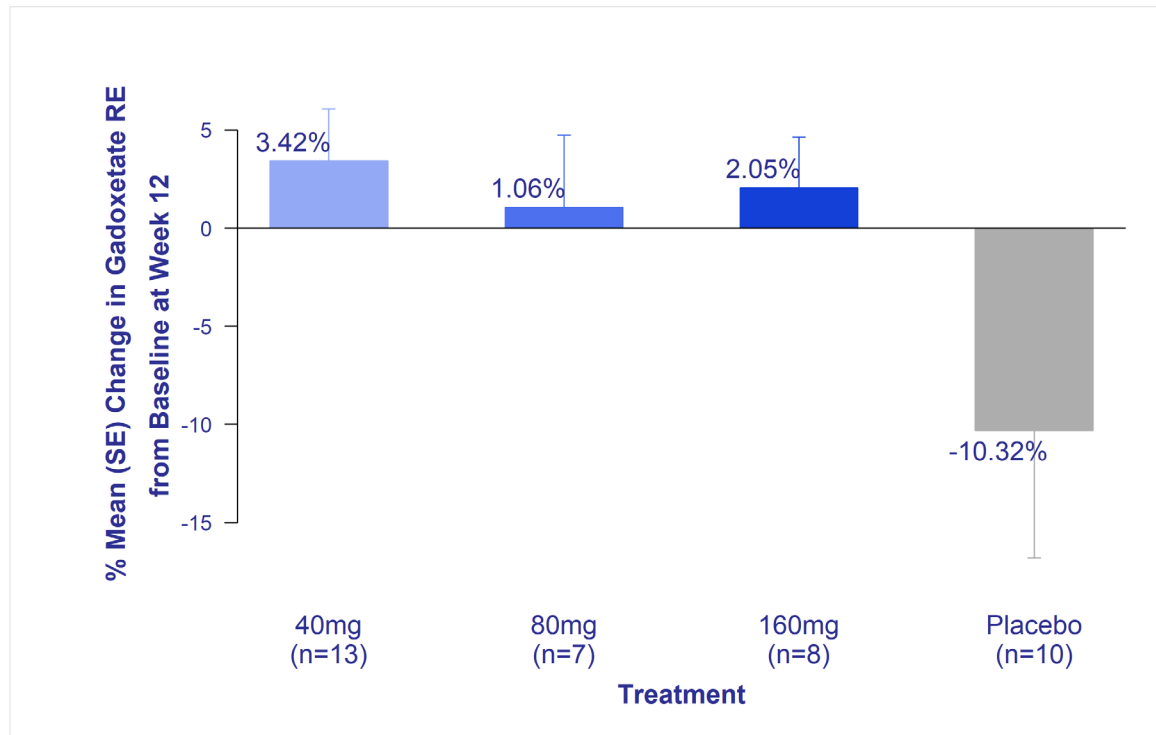


At 12 weeks, PRO-C3 change from baseline was significant for 40 mg and 160 mg

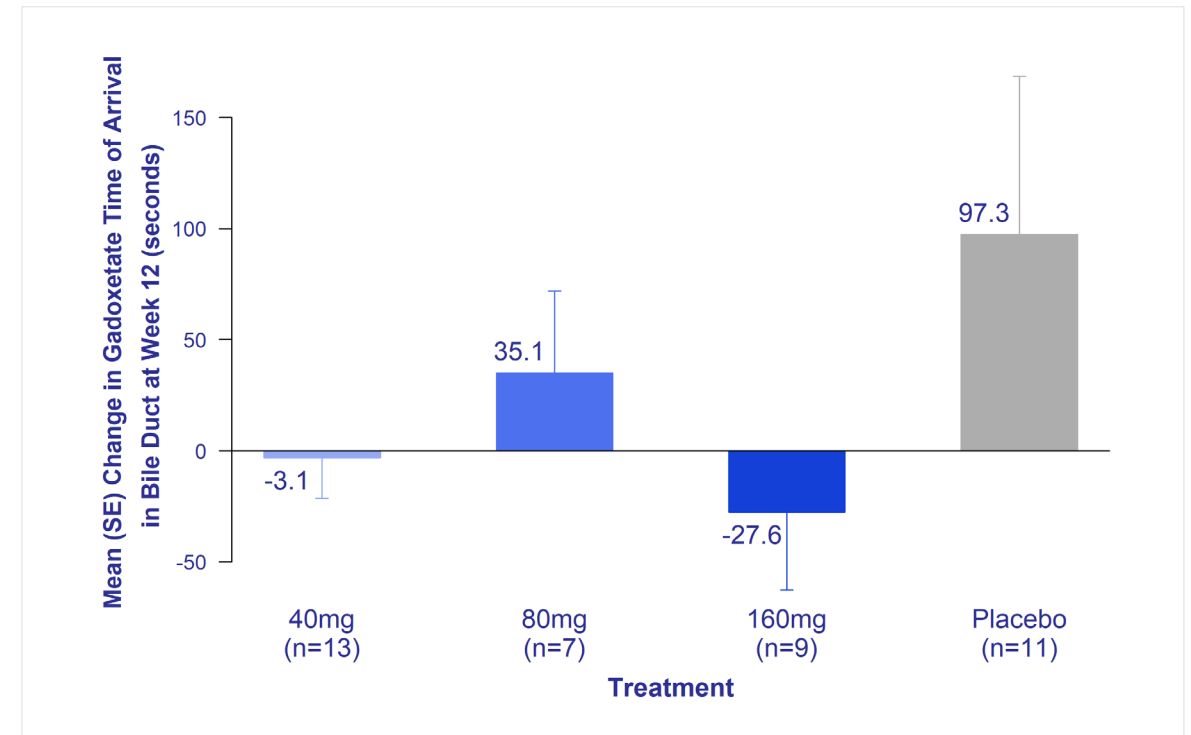
Gadoxetate-Enhanced MR of the Liver (Sub-Study)

- 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**

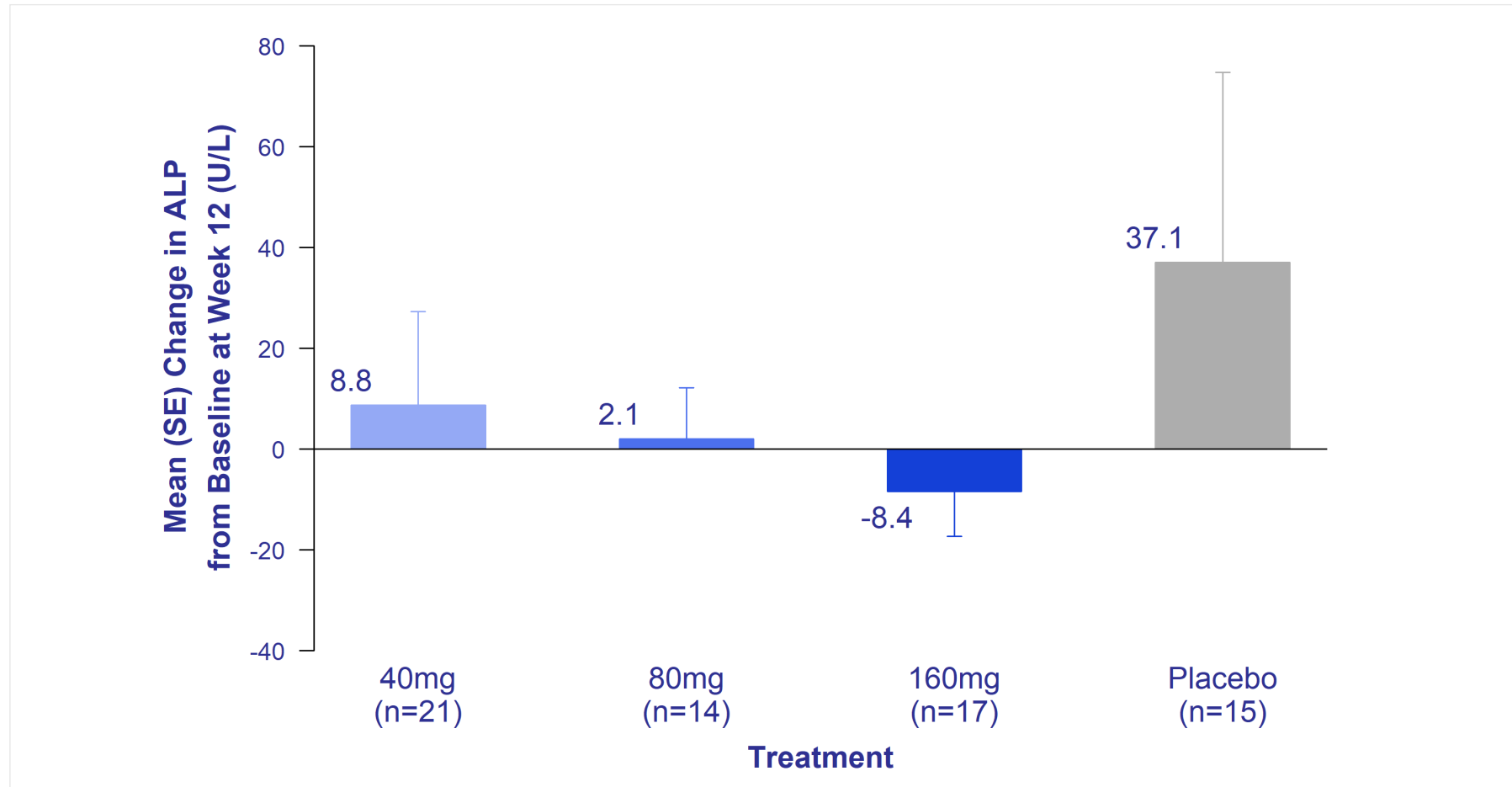


¹Elkilany A, et al. *Abdominal Radiology*. 2021 46:979-991. ²Schulze J, et al. *Clin. Gastroenterol. Hepatol*. 2019 17:192-199.
MR, magnetic resonance; RE, relative enhancement; SE, standard error

Alkaline Phosphatase

Participants with Baseline ALP > ULN

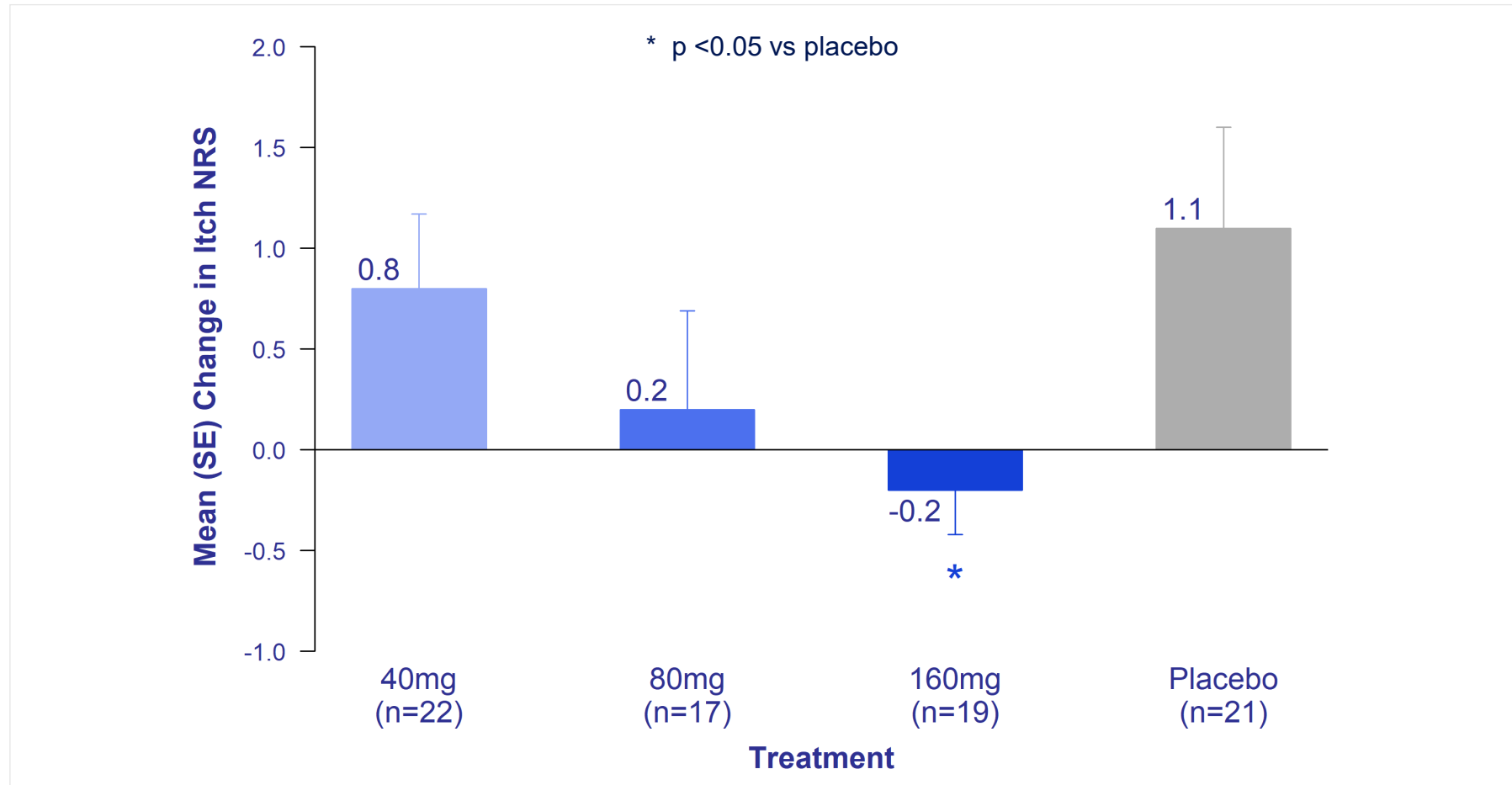
ALP (U/L) Change from Baseline at Week 12



Itch

Numerical Rating Scale

Itch NRS Score Change from Baseline at Week 12



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)

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