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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RATIONALE

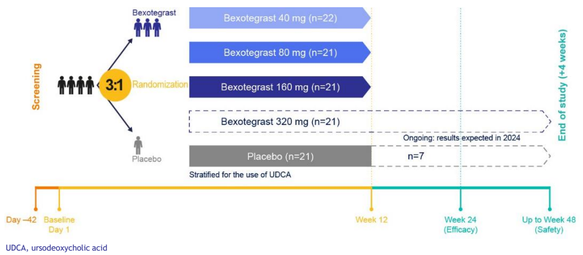
- Primary sclerosing cholangitis (PSC) is a rare, idiopathic, cholestatic liver disease characterized by biliary inflammation and progressive fibrosis[1,2]
- α_v integrins are key drivers of transforming growth factor-beta (TGF-β) signaling and fibrosis in the liver[3]
- Bexotegrast is an oral, once-daily, dual-selective inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ currently in development for the treatment of PSC
- Here, we report interim results from the ongoing INTEGRIS-PSC study of bexotegrast for doses of 40 to 160 mg over 12 weeks of treatment

METHODS

Study design

- INTEGRIS-PSC (NCT04480840) is an ongoing, double-blind, dose-ranging, randomized, placebo-controlled Phase 2a study of bexotegrast in participants with PSC and evidence of liver fibrosis
- The study design is summarized in **Figure 1**

Figure 1. INTEGRIS-PSC study design



UDCA, ursodeoxycholic acid

Key eligibility criteria

- Inclusion: large-duct PSC, suspected liver fibrosis (moderate to severe, with ≥1 of: enhanced liver fibrosis [ELF] score ≥7.7, transient elastography ≥8 to ≤14.4 kPa, magnetic resonance [MR] elastography ≥2.4 to ≤4.9 kPa, historical liver biopsy showing fibrosis without cirrhosis), stable inflammatory bowel disease (IBD) if present, ursodeoxycholic acid (UDCA) dose <25 mg/kg/day
- Exclusion: small-duct PSC, cirrhosis, worsening liver chemistry during screening, unstable IBD, known/suspected overlap with autoimmune hepatitis, historical or current cholangiocarcinoma, other hepatobiliary malignancy, colorectal cancer, or other abdominal malignancy

Study endpoints

- Primary endpoint: safety and tolerability
- Secondary endpoint: pharmacokinetics
- Exploratory endpoints: changes in liver fibrosis biomarkers (ELF score and neo-epitope pro-peptide of type III collagen formation [PRO-C3]), liver biochemistry, liver imaging, and patient-reported outcomes

RESULTS

Participants

- In total, 85 participants were randomized and treated
- For participants treated with bexotegrast (n=64):
  - Four discontinued treatment; three due to treatment-emergent adverse events (TEAEs; n=1 each in the 40 mg, 80 mg, and 160 mg arms) and one due to protocol deviation (n=1 in the 40 mg arm)
  - 42 received concomitant UDCA
  - All 64 participants were analyzed for safety and efficacy
- For participants treated with placebo (n=21):
  - Two discontinued treatment due to TEAEs
  - 13 received concomitant UDCA
  - All 21 participants were analyzed for safety and efficacy
- Participants in the bexotegrast- and placebo-treated groups were generally similar across Baseline characteristics and disease parameters (**Table 1**)

Table 1. Baseline demographics and disease parameters

Characteristic	Bexotegrast 40 mg (n=24)[a]	Bexotegrast 80 mg (n=20)[a]	Bexotegrast 160 mg (n=20)[a]	Bexotegrast All (n=64)	Placebo (n=21)
Male, n (%)	17 (70.8)	16 (80.0)	14 (70.0)	47 (73.4)	17 (81.0)
Age, mean years (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 (0.0)	1 (5.0)	0 (0.0)	1 (1.6)	1 (4.8)
Time since diagnosis of PSC,[b] mean years (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,[c] 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)
Serum liver tests, mean (SD)					
Alkaline phosphatase,[d] 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,[e] ng/mL	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]Two participants (80 mg and 160 mg) were dispensed an incorrect number of tablets and provided with 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; [b]duration since diagnosis at screening is calculated from the first reported date for preferred terms of PSC; [c]partial Mayo score only reported for those with active IBD at Baseline; [d]the study was initiated with an inclusion criterion of alkaline phosphatase >1.5x ULN for the 40 mg cohort, this was later removed; [e]PRO-C3 quantified using Roche COBAS platform (assay reports approximately 2x higher concentrations than previous generation PRO-C3 enzyme-linked immunosorbent assay)
ELF, enhanced liver fibrosis; IBD, inflammatory bowel disease; NRS, numerical rating scale; PRO-C3, neo-epitope pro-peptide of type III collagen formation; PSC, primary sclerosing cholangitis; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Safety and tolerability

- The incidence of TEAEs was similar between bexotegrast and placebo groups (**Table 2**)
- All treatment-related TEAEs were mild or moderate in severity and no serious treatment-related TEAEs were reported
- There was a low rate of discontinuations due to TEAEs and discontinuation rates were similar between the bexotegrast and placebo groups
- Cholangitis was less frequent with bexotegrast than with placebo

Table 2. Safety summary

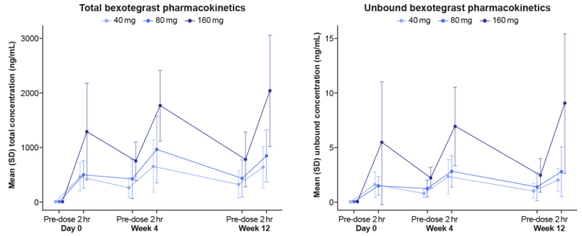
TEAE,[a] n (%)	Bexotegrast 40 mg (n=24)	Bexotegrast 80 mg (n=20)	Bexotegrast 160 mg (n=20)	Bexotegrast All (n=64)	Placebo (n=21)
TEAE	10 (41.7)	16 (80.0)	15 (75.0)	41 (64.1)	16 (76.2)
TEAE related to study drug	1 (4.2)	6 (30.0)	4 (20.0)	11 (17.2)	7 (33.3)
Serious TEAE	1 (4.2)	1 (5.0)	0 (0.0)	2 (3.1)	0 (0.0)
Serious TEAE related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most frequent TEAEs (n≥3 in any arm)					
Pruritus[b]	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 (0.0)
COVID-19	2 (8.3)	1 (5.0)	0 (0.0)	3 (4.7)	3 (14.3)
Frequent bowel movements	0 (0.0)	3 (15.0)	0 (0.0)	3 (4.7)	3 (14.3)
Cholangitis	0 (0.0)	1 (5.0)	1 (5.0)	2 (3.1)	3 (14.3)

[a]AEs were coded using MedDRA version 24.0 and TEAEs were defined as any AE starting (or worsening) on or after the date of first dose; [b]pruritus includes preferred terms for pruritus and cholestatic pruritus
AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Pharmacokinetics

- Bexotegrast total and unbound plasma concentrations increased with dose (**Figure 2**)

Figure 2. Pre- and post-dose bexotegrast concentrations

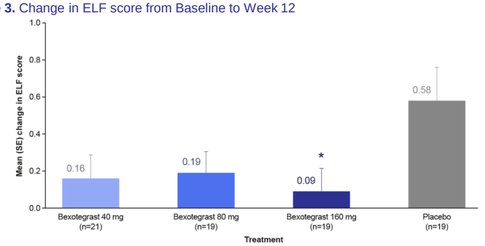


hr, hour; SD, standard deviation

ELF

- At Week 12, the mean change in ELF score in participants receiving bexotegrast 160 mg was 84% lower than that in participants receiving placebo (p<0.05) (**Figure 3**)

Figure 3. Change in ELF score from Baseline to Week 12

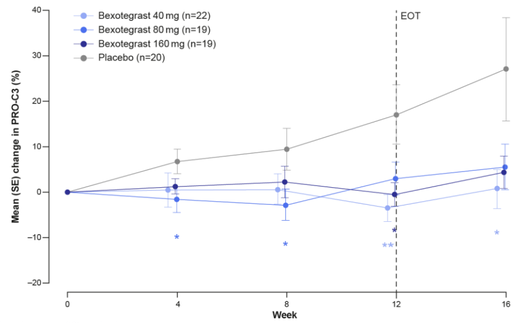


All participants had Baseline ELF score ≥7.7 (moderate-to-severe liver fibrosis)
*p<0.05 vs. placebo
ELF, enhanced liver fibrosis; SE, standard error

PRO-C3

- The mean percentage change in PRO-C3 levels from Baseline to Week 12 was significantly lower with bexotegrast 40 mg (p<0.01) and 160 mg (p<0.05) compared with placebo (**Figure 4**)

Figure 4. Change in PRO-C3 levels from Baseline to Week 12



*p<0.05 vs. placebo; **p<0.01 vs. placebo
EOT, end of treatment; PRO-C3, neo-epitope pro-peptide of type III collagen formation; SE, standard error

Other exploratory endpoints

- Relative liver enhancement of gadoxetate contrast MR imaging from Baseline to Week 12 suggested improvements in hepatocyte function in participants receiving bexotegrast compared with those receiving placebo, but this improvement did not reach statistical significance
- Similarly, time to arrival of gadoxetate contrast in the common bile duct was shorter in participants receiving bexotegrast compared with those receiving placebo, suggesting improved biliary flow, but this difference did not reach statistical significance
- Based on mean change in itch numerical rating scale score, participants receiving placebo had significant worsening in pruritus from Baseline to Week 12 compared with those receiving bexotegrast 160 mg (p<0.05)

CONCLUSIONS

- Bexotegrast was well tolerated over 12 weeks of treatment in participants with PSC and suspected moderate-to-severe liver fibrosis
  - The incidence of TEAEs was similar between bexotegrast and placebo groups and there were no severe or serious treatment-related TEAEs
- Bexotegrast total and unbound plasma concentrations increased with dose
- In exploratory analyses, bexotegrast reduced changes in serum biomarkers of liver fibrosis over 12 weeks, compared with placebo
  - All doses reduced changes in ELF score and PRO-C3 from Baseline relative to placebo, with statistically significant differences for both parameters observed with the 160 mg dose
- These results support proof of concept for targeting integrin-mediated TGF-β activation as a potential antifibrotic approach for PSC

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