ORAL ALPHA-V/BETA-6 AND ALPHA-V/BETA-1 INTEGRIN INHIBITOR BEXOTEGRAST IN PRIMARY SCLEROSING CHOLANGITIS: UPDATED 12-WEEK INTERIM SAFETY AND EFFICACY ANALYSIS OF THE INTEGRIS-PSC PHASE 2A TRIAL

Michael Trauner,[1] Kris V. Kowdley,[2,3] Gideon M. Hirschfield,[4] Éric A. Lefebvre,[5] Martin Decaris,[5] Johanna Schaub,[5] Annie Clark,[5] Mandy Lin,[5] Mahru An,[5] Aarthi Balasubramanyam,[5] Chris N. Barnes,[5] Richard Pencek,[5] Douglas Thorburn,[6] Aldo J. Montano-Loza,[7] Christopher L. Bowlus,[8] Christoph Schramm,[9] Cynthia Levy,[10] Palak J. Trivedi[11,12]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Liver Institute Northwest, Seattle, WA, USA; [3]Elson S. Floyd College of Medicine, Washington State University, Seattle, WA, USA; [4]Toronto Centre for Liver Disease, Toronto General Hospital, Toronto, ON, Canada; [5]Pliant Therapeutics, Inc, South San Francisco, CA, USA; [6]Sheila Sherlock Liver Centre and UCL Institute for Liver and Digestive Health, London, UK; [7]University of Alberta, Edmonton, AB, Canada; [8]University of California, Davis, Sacramento, CA, USA; [9]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [10]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA; [11]NIHR Birmingham Biomedical Research Centre, Centre for Liver and Gastrointestinal Research, University of Birmingham, Birmingham, UK; [12]Liver Unit, University Hospitals Birmingham, Birmingham, UK

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BACKGROUND

- Primary sclerosing cholangitis (PSC) is a rare, idiopathic, cholestatic 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]
  - $\alpha_v\beta_6$ is specifically expressed on injured cholangiocytes and $\alpha_v\beta_1$ on hepatic stellate cells/fibroblasts[4,5]
- 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

OBJECTIVE

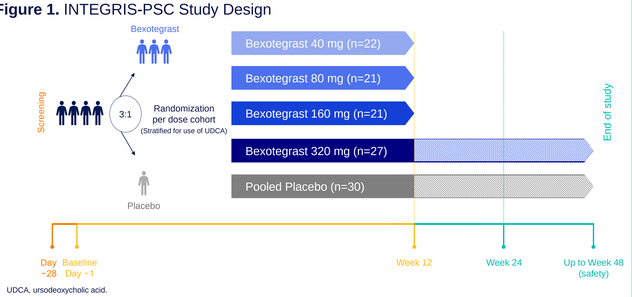
- We report interim results from the ongoing INTEGRIS-PSC study of bexotegrast for doses of 40 to 320 mg over 12 weeks of treatment

METHODS

Study Design

- INTEGRIS-PSC (NCT04480840) is an ongoing, double-blind, dose-ranging, randomized, placebo-controlled Phase 2a study of bexotegrast in participants with large duct PSC and evidence of liver fibrosis
- Participants were randomized 3:1 to receive once-daily bexotegrast or placebo in 3 cohorts (40 mg or placebo for 12 weeks; 80 mg, 160 mg or placebo for 12 weeks; 320 mg or placebo for ≥12 weeks and up to 48 weeks); participants in placebo group were pooled. The study design is summarized in **Figure 1**

Figure 1. INTEGRIS-PSC Study Design



UDCA, ursodeoxycholic acid.

Key Eligibility Criteria

- Inclusion: large-duct PSC, stable inflammatory bowel disease (if present), ursodeoxycholic acid (UDCA) <25 mg/kg/day (if used), alkaline phosphatase (ALP) ≤10x upper limit of normal and suspected liver fibrosis (without cirrhosis) as evidenced by ≥1 of the following:
  - Enhanced liver fibrosis (ELF) score ≥7.7
  - Transient elastography ≥8 to ≤4.4 kPa
  - Magnetic resonance (MR) elastography ≥2.4 to ≤4.9 kPa
  - Historical biopsy indicating fibrosis

Endpoints

- Primary endpoint: safety and tolerability
- Secondary and exploratory endpoints: changes in ELF score, neo-epitope pro-peptide of type III collagen formation (PRO-C3) and gadoxetate contrast–enhanced MR imaging (MRI)

RESULTS

Summary of Participant Baseline Characteristics

- Of the 121 participants in the INTEGRIS-PSC study, 91 were randomized to bexotegrast treatment groups and 30 to placebo (**Table 1**)
- Participant disease characteristics were similar between treatment groups

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	BEXO 40 mg (n=24)[a]	BEXO 80 mg (n=20)[a]	BEXO 160 mg (n=20)[a]	BEXO 320 mg (n=27)	Placebo (n=30)
Male sex, n (%)	17 (70.8)	16 (80.0)	14 (70.0)	13 (48.1)	24 (80.0)
Age, mean (SD), years	46.9 (15.1)	40.5 (15.3)	45.1 (12.7)	47.1 (14.5)	45.2 (11.7)
Race, n (%)					
White	20 (83.3)	16 (80.0)	18 (90.0)	26 (96.3)	25 (83.3)
Black	2 (8.3)	2 (10.0)	1 (5.0)	0	2 (6.7)
Asian	2 (8.3)	1 (5.0)	1 (5.0)	1 (3.7)	1 (3.3)
Other/not reported/unknown	0	1 (5.0)	0	0	2 (6.7)
Time since diagnosis, mean (SD), years	11.1 (8.2)	8.3 (8.0)	7.8 (6.8)	9.7 (11.6)	9.1 (7.5)
Concomitant UDCA use, n (%)	14 (58.3)	15 (75.0)	13 (65.0)	18 (66.7)	19 (63.3)
IBD, n (%)	18 (75.0)	12 (60.0)	11 (55.0)	13 (48.1)	17 (56.7)
Ulcerative colitis	11 (45.8)	6 (30.0)	7 (35.0)	6 (22.2)	10 (33.3)
ALP[b], mean, (SD), U/L	315.1 (140.3)	199.2 (81.0)	273.8 (165.6)	190.6 (91.3)	277.4 (215.9)
ALT, mean (SD), U/L	91.5 (62.1)	67.6 (63.2)	98.4 (73.1)	60.4 (37.8)	73.1 (59.8)
AST, mean (SD), U/L	67.2 (49.3)	46.4 (30.1)	69.0 (39.6)	44.6 (24.7)	51.6 (37.1)
Total bilirubin, mean (SD), mg/dL	0.7 (0.3)	0.8 (0.5)	0.9 (0.4)	0.5 (0.2)	0.8 (0.4)
ELF score, mean (SD)	9.6 (0.8)	9.2 (1.0)	9.4 (0.8)	9.0 (0.8)	9.3 (1.0)
PRO-C3, ng/mL[c]	50.0 (13.8)	48.8 (42.8)	46.1 (11.7)	46.5 (19.5)	48.5 (24.3)
Bile duct gadoxetate time to arrival, mean (SD), seconds	542.4 (107.1)	514.7 (169.8)	527.3 (121.9)	550.3 (262.8)	500.3 (177.0)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEXO, bexotegrast; ELF, Enhanced Liver Fibrosis; ELISA, enzyme-linked immunosorbent assay; IBD, inflammatory bowel disease; PRO-C3, neo-epitope pro-peptide of type III collagen formation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
[a]Two participants (80 mg and 160 mg) received a dose ~40 mg/day due to site errors and were grouped with the 40 mg dose group for all summaries.
[b]The study was initiated with an inclusion criterion of ALP >1.5xULN for the 40 mg cohort, this was later removed.
[c]PRO-C3 quantified using Roche COBAS platform (assay reports approximately 2x higher concentrations than previous generation PRO-C3 ELISA).

Safety Summary

- Treatment-emergent adverse events (TEAEs) were similar between bexotegrast- and placebo-treated participants, 67.0% and 66.7% respectively (**Table 2**)
  - No serious TEAEs were reported related to the study drug
- Most common TEAEs were fatigue, pruritus, headache, COVID-19 and nausea
  - Cholangitis and pruritis were less frequent with bexotegrast than with placebo
- Compared with placebo, the 320 mg dose group had lower proportions of participants with TEAEs classified as hepatobiliary (0% vs 16.7%) and gastrointestinal disorders (14.8% vs 36.7%)

Table 2. Proportion of Participants Reporting TEAEs Over 12 Weeks of Treatment

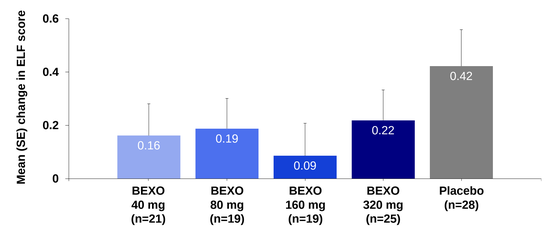
TEAE, n (%)	BEXO 40 mg (n=24)	BEXO 80 mg (n=20)	BEXO 160 mg (n=20)	BEXO 320 mg (n=27)	Placebo (n=30)
TEAE	10 (41.7)	16 (80.0)	15 (75.0)	20 (74.1)	20 (66.7)
Related to study drug	1 (4.2)	6 (30.0)	4 (20.0)	0	7 (23.3)
Serious TEAE	1 (4.2)[a]	1 (5.0)[b]	0	0	0
Related to study drug	0	0	0	0	0
Most frequent TEAEs[c]					
Fatigue	3 (12.5)	2 (10.0)	4 (20.0)	3 (11.1)	4 (13.3)
Pruritus[d]	2 (8.3)	4 (20.0)	3 (15.0)	2 (7.4)	6 (20.0)
Headache	1 (4.2)	2 (10.0)	3 (15.0)	2 (7.4)	4 (13.3)
COVID-19	2 (8.3)	1 (5.0)	0	4 (14.8)	3 (10.0)
Nausea	1 (4.2)	2 (10.0)	3 (15.0)	1 (3.7)	0
Frequent bowel movements	0	3 (15.0)	0	0	3 (10.0)
Cholangitis[e]	0	1 (5.0)	1 (5.0)	0	4 (13.3)
Pyrexia	1 (4.2)	0	0	0	3 (10.0)
Dyspepsia	0	0	0	0	3 (10.0)
Ocular icterus	0	0	0	0	3 (10.0)
TEAEs by system organ class					
Hepatobiliary disorders	1 (4.2)	2 (10.0)	2 (10.0)	0	5 (16.7)
GI disorders	5 (20.8)	7 (35.0)	7 (35.0)	4 (14.8)	11 (36.7)

BEXO, bexotegrast; COVID-19, coronavirus disease 2019, GI, gastrointestinal; TEAE, treatment-emergent adverse event.
[a]The participant reported Grade 3 cholecystitis, abdominal pain, and pancreatitis subsequent to endoscopic retrograde cholangiopancreatography procedure approximately 3-4 weeks after the last dose of study drug. The serious TEAEs were determined to not be study-drug related and the events recovered/resolved.
[b]The participant reported Grade 3 cholangitis, which was determined to not be related to the study drug. The event was recovered/resolved.
[c]≥3 in at least one arm.
[d]Pruritus includes preferred terms for pruritus and cholestatic pruritus.
[e]Cholangitis includes cholangitis/cholangitis sclerosing.

Markers of Fibrosis

- At Week 12, bexotegrast attenuated the increase in ELF score compared with placebo at all doses (**Figure 2**)

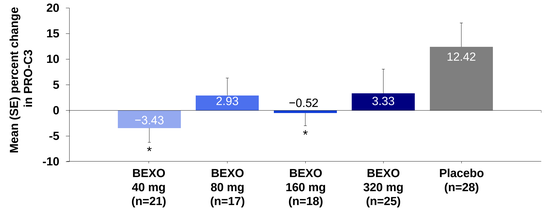
Figure 2. Mean (SE) Change from Baseline to Week 12 in ELF Score



BEXO, bexotegrast; ELF, enhanced liver fibrosis.

- All doses of bexotegrast attenuated the increase in collagen synthesis (PRO-C3) compared with placebo (**Figure 3**)
  - Bexotegrast 40 mg (*P*=0.01) and 160 mg (*P*=0.05) demonstrated statistically significant reductions in PRO-C3 compared with placebo

Figure 3. Mean (SE) Percent Change from Baseline to Week 12 in PRO-C3

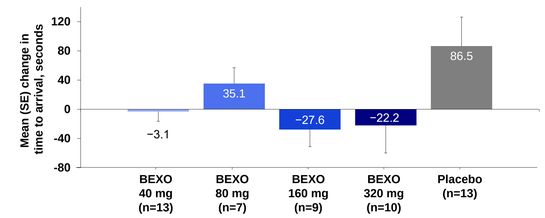


BEXO, bexotegrast; PRO-C3, neo-epitope pro-peptide of type III collagen formation.
*P<0.05 vs placebo.

Other Exploratory Endpoints

- Comparing baseline and Week 12 MRI scans, the mean time of arrival of the contrast agent gadoxetate in the common bile duct was faster (ie, improvement) for participants treated with bexotegrast 160 and 320 mg while was slower (ie, worsening) for the placebo-treated participants, suggesting improved hepatobiliary excretory function (**Figure 4**)

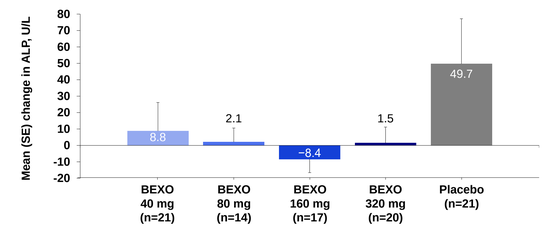
Figure 4. Mean (SE) Change From Baseline to Week 12 in Time to Arrival of Gadoxetate in the Common Bile Duct



BEXO, bexotegrast.

- In the subgroup of participants with elevated ALP at baseline, ALP was maintained at near baseline levels for the bexotegrast-treated participants while ALP increased in placebo-treated participants (**Figure 5**)

Figure 5. Mean (SE) Change From Baseline to Week 12 in ALP



ALP, alkaline phosphatase; BEXO, bexotegrast.

CONCLUSIONS

- Bexotegrast was well tolerated over 12 weeks of treatment in participants with PSC and evidence of liver fibrosis
  - The incidence of TEAEs was similar between bexotegrast and placebo and there were no serious TEAEs related to the study drug
  - Bexotegrast 320 mg was associated with fewer hepatobiliary and gastrointestinal TEAEs, providing preliminary evidence of the potential for reducing PSC-related clinical events
- Bexotegrast group had stable serum biomarkers of fibrosis compared with increases in the placebo group
- Preliminary MRI observations suggest that bexotegrast treatment may prevent the worsening of hepatobiliary excretory function
- This analysis supports proof of mechanism for targeting integrin-mediated TGF-β activation as a therapeutic approach for PSC

References: 1. Goode EC, Rushbrook SM. *Ther Adv Chronic Dis.* 2016;7(1):68-85. 2.Toy E, et al. *BMC Gastroenterol.* 2011;11:83. 3. Henderson NC, Sheppard D. *Biochim Biophys Acta.* 2013;1832(7):891-896. 4. Peng Z-W, et al. *Hepatology.* 2016;63(1):217-232. 5. Reed NI, et al. *Sci Transl Med.* 2015;7(288):288ra279.

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Contact information: rpencek@pliantrx.com

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