INTEGRIS-PSC PHASE 2A STUDY: EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF BEXOTEGRAST (PLN-74809) IN PARTICIPANTS WITH PRIMARY SCLEROSING CHOLANGITIS

Hirschfield G,[1] Kowdley K,[2] Levy C,[3,4] Schramm C,[5] Trivedi P,[6,7] Trauner M,[8] Pencek R,[9] Achneck H,[9] Lefebvre É[9]

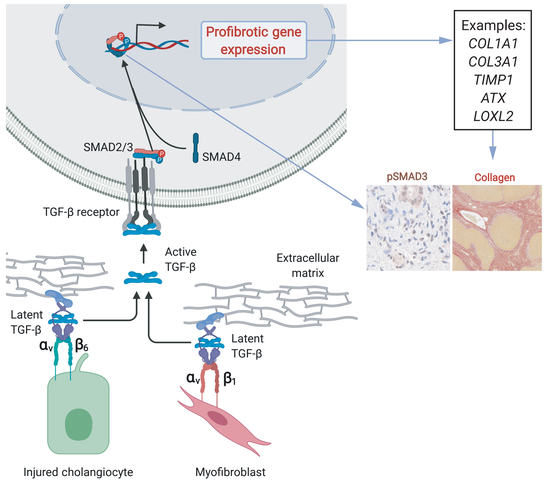
[1]Toronto Centre for Liver Disease, University of Toronto, ON, Canada; [2]Liver Institute Northwest, Seattle, WA, USA; [3]Division of Digestive Health and Liver Diseases, University of Miami, Miami, FL, USA; [4]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA; [5]Department of Medicine, Martin Zeitz Center for Rare Diseases, Hamburg Center for Translational Immunology (HCTI), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [6]National Institute for Health and Care Research, Birmingham Biomedical Research Centre, Centre for Liver and Gastroenterology Research, University of Birmingham, Birmingham, UK; [7]Liver Unit, University Hospitals Birmingham Queen Elizabeth, Birmingham, UK; [8]Medical University of Vienna, Vienna, Austria; [9]Pliant Therapeutics, Inc., South San Francisco, CA, USA

Poster no. WED-280

INTRODUCTION

- Primary sclerosing cholangitis (PSC) is a rare, idiopathic, cholestatic liver disease characterized by biliary inflammation and progressive fibrosis, which over time can lead to serious and often fatal liver complications[1–3]
- Transforming growth factor-beta (TGF-β) signaling, activated by α_v integrins, is a key driver of fibrosis in the liver[4,5]
- In PSC, $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins regulate TGF-β activity (**Figure 1**) and are present in the liver at elevated levels[6–8]
- For patients with PSC, disease management is confined to supportive measures, which fail to address disease progression. Thus, there remains a significant unmet medical need for effective therapies
- Localized TGF-β inhibition in the fibrotic liver, achieved by targeting $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, may provide a novel approach to treating PSC, without affecting systemic TGF-β signaling
- Bexotegrast (PLN-74809) is an oral, once-daily (QD), dual-selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins in development for the treatment of PSC
- INTEGRIS-PSC is an ongoing, randomized, placebo-controlled Phase 2a study evaluating the safety and tolerability of multiple doses of bexotegrast in participants with PSC (EudraCT: 2020-001428-33, NCT04480840)

Figure 1. Roles of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins in biliary fibrosis



This diagram has been developed by Pliant Therapeutics, Inc.
ATX, autotaxin; *COL1A1*, collagen type I alpha 1 chain; *COL3A1*, collagen type III alpha 1 chain; *LOXL2*, lysyl oxidase homolog 2; p, phosphorylated; SMAD, family of proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (*Mad*) and the *C. elegans* gene *Sma*; TGF-β, transforming growth factor-beta; *TIMP1*, tissue inhibitor metalloproteinase 1

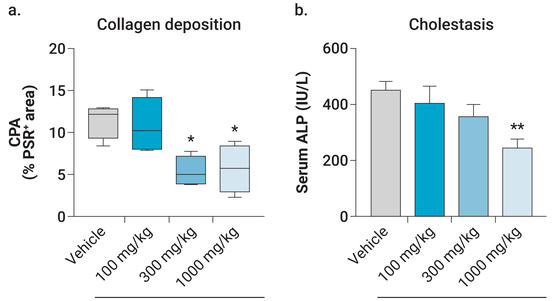
OBJECTIVES

- To present the supporting preclinical rationale for evaluating bexotegrast in PSC and provide an overview of the INTEGRIS-PSC study
- To present an update on the randomized study population

PRECLINICAL RESEARCH

- Bexotegrast or vehicle was administered orally for 6 weeks in BALBc.Mdr2$^{-/-}$ mice with established biliary fibrosis
- Hepatic collagen and cholestasis were quantified by collagen proportionate area (CPA) and serum alkaline phosphatase (ALP) levels, respectively
- Bexotegrast dose-dependently reduced CPA (up to ~50%; p<0.05) and serum ALP (46%; p<0.01) vs. vehicle in the BALBc.Mdr2$^{-/-}$ mouse model (**Figure 2**)

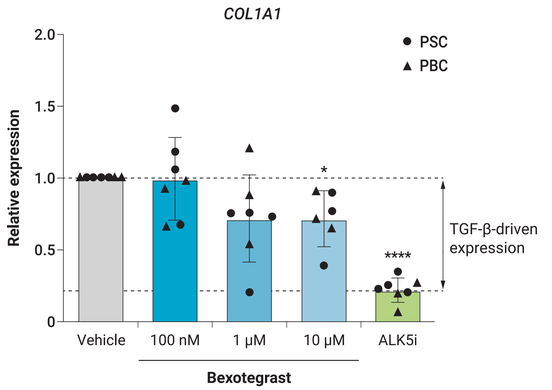
Figure 2. Effect of dual $\alpha_v\beta_6$ and $\alpha_v\beta_1$ inhibition with bexotegrast on collagen deposition and cholestasis in the BALBc.Mdr2$^{-/-}$ model



BALBc.Mdr2$^{-/-}$ mice were administered vehicle or bexotegrast 100 mg/kg, 300 mg/kg, or 1000 mg/kg QD for 6 weeks. Reduced collagen deposition was determined by PSR staining, with **a.** quantification as CPA. Reduced cholestasis was determined with an assay to assess **b.** serum ALP
Error bars represent standard deviation; *p<0.05; **p<0.01; vs. vehicle (phosphate-buffered saline)
+, positive; ALP, alkaline phosphatase; CPA, collagen proportionate area; PSR, picrosirius red; QD, once daily

- An *ex vivo* study showed that after 2 days in culture and incubation with bexotegrast, TGF-β-driven collagen type I alpha 1 chain (*COL1A1*) gene expression was dose-dependently reduced (up to ~35%; p<0.05) compared with vehicle (dimethylsulfoxide) (**Figure 3**)

Figure 3. Effect of bexotegrast and TGF-β receptor I kinase inhibitor (ALK5i; positive control) on collagen gene expression in PCLivS generated from liver explants from patients with biliary fibrosis (PSC n=4; PBC n=3)



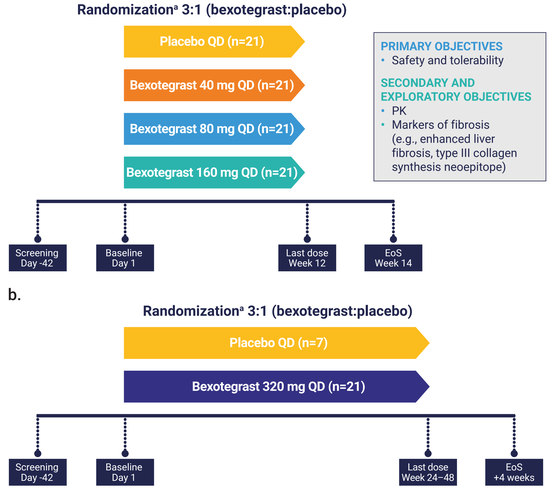
Error bars represent standard deviation; *p<0.05; ****p<0.0001 vs. vehicle (dimethylsulfoxide)
ALK5i, TGF-β receptor I kinase inhibitor; *COL1A1*, collagen type I alpha 1 chain; PBC, primary biliary cholangitis; PCLivS, precision-cut liver slices; PSC, primary sclerosing cholangitis; TGF-β, transforming growth factor-beta

INTEGRIS-PSC CLINICAL STUDY

Methods

- INTEGRIS-PSC is an ongoing, multinational, randomized, double-blind, dose-ranging, placebo-controlled Phase 2a study evaluating safety, tolerability, pharmacokinetics (PK), and markers of fibrosis following multiple doses of bexotegrast administered QD in participants with PSC (**Figure 4**)
  - Following review of safety data from the 40 mg, 80 mg, and 160 mg cohorts (**Figure 4a**), an additional 320 mg cohort was initiated with a longer treatment duration of at least 24 and up to 48 weeks (**Figure 4b**)

Figure 4. INTEGRIS-PSC study design



INTEGRIS-PSC study design for **a.** the 40, 80, and 160 mg dose groups and **b.** the 320 mg dose group
[a]Randomization stratified by use of UDCA (yes/no) at Baseline
EoS, end of study; PK, pharmacokinetics; PSC, primary sclerosing cholangitis; QD, once daily; UDCA, ursodeoxycholic acid

- Key inclusion criteria:
  - 18–75 years of age
  - Established clinical diagnosis of large-duct PSC with evidence of hepatic fibrosis based on one of the following:
    - Historical biopsy
    - Enhanced liver fibrosis score ≥7.7
    - Transient elastography >8 kPa
    - Magnetic resonance elastography >2.4 kPa
  - Stable inflammatory bowel disease (IBD)
  - Normal or elevated serum ALP
  - Serum aspartate aminotransferase and serum alanine aminotransferase concentration ≤5 × upper limit of normal (ULN)
  - Total bilirubin ≤1.5 × ULN
  - Participants were allowed to receive ursodeoxycholic acid treatment, provided it was administered at a stable dose of <25 mg/kg/day for ≥3 months before screening and was expected to remain unchanged during the study
- Safety assessments included type, incidence, and severity of adverse events, laboratory tests, vital signs, electrocardiograms, and physical examinations

Update on trial in progress

- Here, we present a summary of the randomized participants to date in the ongoing, blinded INTEGRIS-PSC study
  - Enrolment of the 40 mg, 80 mg, and 160 mg cohorts is complete and is ongoing for the 320 mg cohort
    - A total of 85 participants had been randomized at last review
  - Baseline demographics and disease characteristics are summarized in **Table 1**
  - The most common comorbidity at Baseline was IBD, with ulcerative colitis being the most common form

Table 1. INTEGRIS-PSC Baseline demographics and disease characteristics

Baseline demographics and disease characteristics	Participants (n=85)
Male sex, n (%)	64 (75)
Median age, years (range)	45 (18, 71)
Median BMI, kg/m^2 (range)	26.8 (19.3, 47.7)
Median time since PSC diagnosis, years (range)	7 (<1, 35)
Concomitant UDCA use, n (%)	55 (65)
Median duration of UDCA use, years (range)	4 (<1, 25)
Median Baseline transient elastography, kPa (range)	8.9 (3.6, 14.4)
Most common comorbidities occurring in >10% of participants, n (%)	
IBD	55 (65)
GERD	14 (17)
Vitamin D deficiency	13 (15)
Hypertension	12 (14)
Seasonal allergy	11 (13)
Fatigue	10 (12)
Pruritus	10 (12)
Median Baseline liver chemistry (range)	
ALP, U/L	225 (62, 856)
ALT, U/L	62 (13, 310)
AST, U/L	45 (16, 256)
Total bilirubin, mg/dL	0.7 (0.29, 2.1)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid

CONCLUSIONS

- The INTEGRIS-PSC Phase 2a study evaluating the safety, tolerability, and pharmacokinetics of bexotegrast in participants with PSC continues without modification by an independent data safety monitoring board
- Twelve-week results from this study (40 mg, 80 mg, and 160 mg vs. placebo) are expected in Q3 2023

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. Chapman R, et al. *Hepatology* 2010;51(2):660–678; 4. Henderson NC, Sheppard D. *Biochim Biophys Acta* 2013;1832(7):891–896; 5. Xu F, et al. *J Histochem Cytochem* 2016;64(3):157–167; 6. Turner S, et al. *Hepatology* 2019;70(S1):794A–795A. Abstract 1308; 7. Popov Y, et al. *J Hepatol* 2008;48(3):453–464; 8. Wang B, et al. *Hepatology* 2007;46(3):1404–1412

Contact information: gideon.hirschfield@uhn.ca

Poster presented at the European Association for the Study of the Liver™ (EASL) Congress, 21–24 June 2023, Vienna, Austria

Disclosures: This study was funded by Pliant Therapeutics, Inc. RP, HA, and ÉL were employed by Pliant Therapeutics, Inc., and owned stock at the time of the study. CL and KK received a research grant and consulting fees from Pliant Therapeutics, Inc. GH and CS have been consultants for Pliant Therapeutics, Inc. MT has advised for Pliant Therapeutics, Inc. PT received speaker fees from Pliant Therapeutics, Inc.

Acknowledgments: Thank you to the patients who participated in this study. Thank you to Theresa Thuener, Mandy Lin, Kanyetta Wansley, and Fiona Cilli for their oversight of the conduct of the study. Thank you to Johanna Schaub for her input and review of the preclinical rationale. Editorial assistance was provided by Alpharmaxim Healthcare Communications and funded by Pliant Therapeutics, Inc.