SAFETY AND TOLERABILITY OF BEXOTEGRAST IN PHASE 2 TRIALS OF IDIOPATHIC PULMONARY FIBROSIS (IPF) AND PRIMARY SCLEROSING CHOLANGITIS (PSC)

Gregory P. Cosgrove,[1] Richard Pencek,[1] Chris N. Barnes,[1] Annie Clark,[1] Hardean E. Achneck,[2] Éric A. Lefebvre[1]

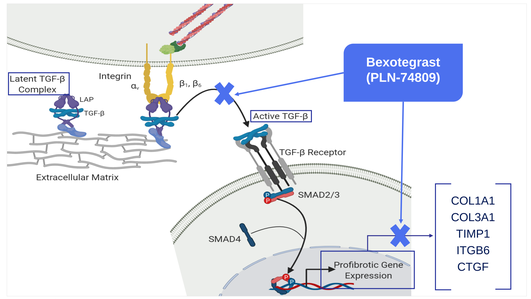
[1]Pliant Therapeutics, Inc., South San Francisco, CA, USA; [2]Former employee of Pliant Therapeutics, Inc., South San Francisco, CA, USA

Poster number: OA-2861

BACKGROUND

- TGF-β is a central driver of fibrosis[1,2]
- Systemic TGF-β blockade carries toxicity risks[2]
- Activation of latent TGF-β by $\alpha_v\beta_6$ (lung epithelial cells, injured cholangiocytes) and $\alpha_v\beta_1$ (lung fibroblasts, HSCs) is increased in fibrotic tissue[2-8]
- Localised TGF-β inhibition in fibrotic tissue, by targeting $\alpha_v\beta_6$ and $\alpha_v\beta_1$ with bexotegrast, may provide a novel approach to treat IPF and PSC without potentially affecting TGF-β signalling systemically

$\alpha_v\beta_6$ and $\alpha_v\beta_1$ Integrins Promote Fibrosis Through Activation of TGF-β[1,2,a]



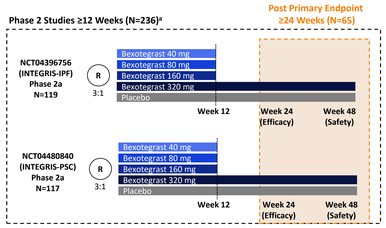
[a] This image is based off of preclinical models.
COL1A1, collagen type I alpha 1; COL3A1, collagen type III alpha 1; CTGF, connective tissue growth factor; HSC, hepatic stellate cell; IPF, idiopathic pulmonary fibrosis; ITGB6, integrin beta-6; LAP, latency-associated peptide; PSC, primary sclerosing cholangitis; SMAD, family of proteins similar to the gene products of the Drosophila gene "mothers against decapentaplegic homolog 1" (MAD) and the C elegans gene SMA; TGF-β, transforming growth factor-beta; TIMP1, tissue inhibitor matrix metalloproteinase 1.

OBJECTIVE

- To provide a comprehensive safety analysis of bexotegrast across Phase 2 clinical studies of 12 weeks or longer in IPF and PSC

STUDIES INCLUDED IN THE SAFETY POPULATION

- To date, over 700 participants have been exposed to bexotegrast in unblinded and blinded studies
- This safety analysis was performed on completed Phase 2 studies of ≥12 weeks treatment duration
- Bexotegrast doses ranged from 40 to 320 mg once daily

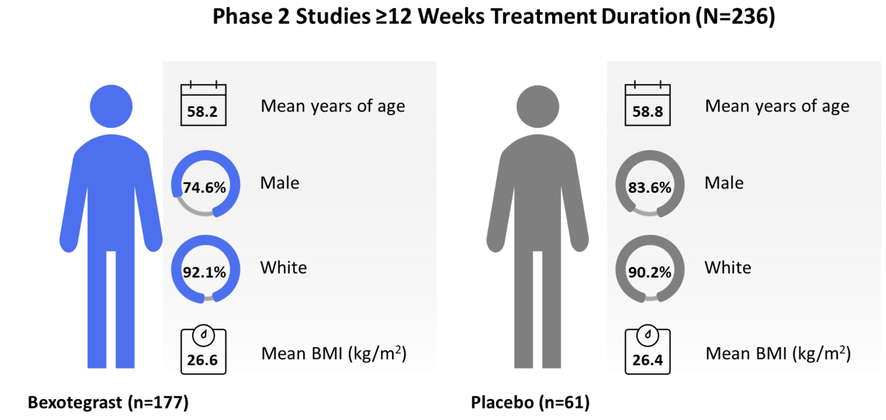


Number of participants (%)	Bexotegrast[a] (n=177)	Placebo[a] (n=61)
Safety ≤12 weeks	177 (98.3)	61 (100)
Safety data >12 weeks	167 (92.8)	58 (95.1)
Post primary endpoint ≥24 weeks	49 (27.7)	17 (27.9)

[a] Four participants in INTEGRIS-PSC participated in 2 cohorts; 3 participants received bexotegrast in both cohorts and are counted once in the all bexotegrast column; 1 participant received bexotegrast in one cohort and received placebo in the other cohort and is counted in both the bexotegrast column and in the placebo column. Each of the participants who repeated a cohort is counted once in the total column. One participant in INTEGRIS-IPF received both placebo and bexotegrast due to incorrect study drug dispensation and is counted in both treatment groups. The participant is counted once in the total column.
IPF, idiopathic pulmonary fibrosis; PSC, primary sclerosing cholangitis; R, randomisation.

RESULTS

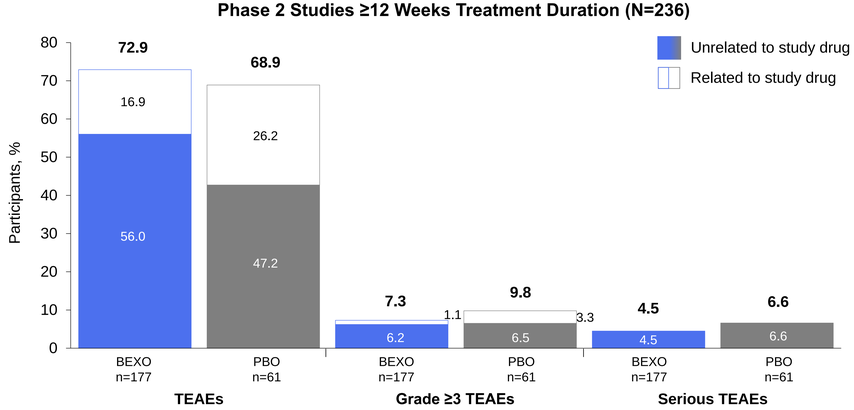
Baseline Demographics



BMI, body mass index.

Safety Summary

- Rates of discontinuation were similar between bexotegrast- and placebo-treated participants (2.3% vs 3.3%, respectively)
- Grade ≥3 TEAEs and serious TEAE rates were higher in the placebo group compared with the bexotegrast group
- No SAEs were considered related to the study drug

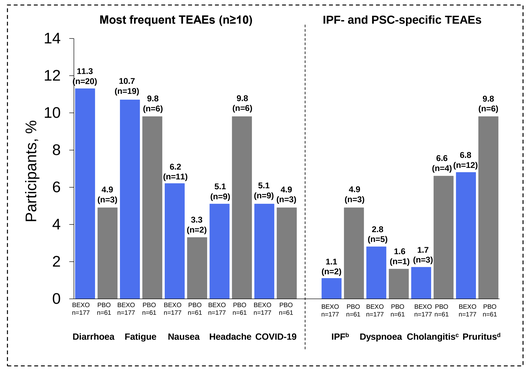


BEXO, bexotegrast; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

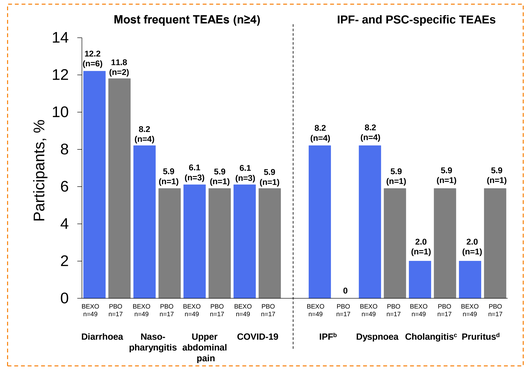
Most Frequently Reported TEAEs

- The proportion of bexotegrast-treated participants reporting TEAEs was similar regardless of time receiving study drug
- No more than 12% of participants reported any one TEAE across treatment durations

TEAEs In Participants with Treatment Duration ≤12 Weeks



TEAEs In Participants with Treatment Duration >12 Weeks[a]



[a] Treatment duration of >12 weeks and up to 40 weeks.
[b] Includes IPF and pulmonary fibrosis. After exposure adjustment across the full treatment duration, there was no difference between bexotegrast and placebo IPF rate per person year.
[c] Includes cholangitis and sclerosing cholangitis.
[d] Includes pruritis and cholestatic pruritis.
BEXO, bexotegrast; IPF, idiopathic pulmonary fibrosis; PBO, placebo; PSC, primary sclerosing cholangitis; TEAE, treatment-emergent adverse event.

CONCLUSIONS AND FUTURE RESEARCH

- Bexotegrast was well tolerated in participants in 2 Phase 2 studies ≥12 weeks in duration
  - The safety profile of bexotegrast was similar for participants treated for ≥12 weeks compared to those treated for a shorter duration
- The most frequently reported TEAE in bexotegrast-treated participants was diarrhoea
  - The most common TEAE ≤12 weeks was diarrhoea (11.3%)
  - The most common TEAEs >12 weeks was diarrhoea (12.2%)
- Most TEAEs were mild or moderate
  - Discontinuation rates were low in bexotegrast-treated participants (2.3%)
- Late-stage evaluation of bexotegrast in participants with IPF is currently underway (BEACON-IPF; NCT06097260)

References: 1. Saito A, et al. *Int J Mol Sci*. 2018;19(8):2460; 2. Decaris ML, et al. *Respir Res*. 2021;22(1):265; 3. Reed NI, et al. *Sci Transl Med*. 2015;7(288):288ra79; 4. Munger JS, et al. *Cell*. 1999;96(3):319-328; 5. Horan GS, et al. *Am J Respir Crit Care Med*. 2008;177(1):56-65; 6. Sato D, et al. *Eur Respir J*. 2015;46(2):448-454; 7. Peng Z-W, et al. *Hepatology*. 2014;63(1):217-232; 8. Schuppan J, et al. *J Hepatol*. 2018;70(1):157-158.

Disclosures: **GP Cosgrove, R Pencek, CN Barnes, A Clark,** and **EA Lefebvre** were employees of Pliant Therapeutics, Inc., at the time of this analysis. **HE Achneck** is a former employee of Pliant Therapeutics, Inc

Presented at European Respiratory Society (ERS) Congress 2024; September 7-11, 2024; Vienna, Austria.

Acknowledgments: This study was sponsored by Pliant Therapeutics, Inc. Support for third-party writing assistance for this presentation, furnished by Samantha O'Dwyer, PhD, of Nucleus Global, was provided by Pliant Therapeutics, Inc. This poster was developed in accordance with Good Publication Practice (GPP 2022) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication. Bexotegrast is an investigational drug in which safety and efficacy are still being evaluated and is not approved by any health authority.

Contact information: gcosgrove@pliantrx.com

Miscellaneous: Copyright © 2024 Pliant Therapeutics, Inc. | All Rights Reserved