UPDATE ON THE SAFETY AND TOLERABILITY OF BEXOTEGRAST, A DUAL-SELECTIVE INHIBITOR OF INTEGRINS $\alpha_v\beta_6$ and $\alpha_v\beta_1$, IN DEVELOPMENT FOR IDIOPATHIC PULMONARY FIBROSIS AND PRIMARY SCLEROSING CHOLANGITIS

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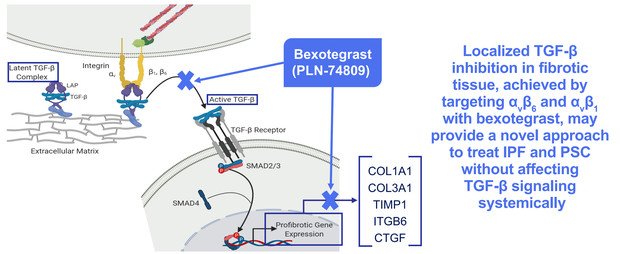
BACKGROUND

$\alpha_v\beta_6$ and $\alpha_v\beta_1$ Integrins Drive Cell-Matrix Interactions in Fibrosis

- Transforming growth factor-beta (TGF-β) is a central mediator 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, hepatic stellate cells) is increased in fibrotic tissue[2-8]

$\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins promote fibrosis through activation of TGF-β[1,2]



Localized TGF-β inhibition in fibrotic tissue, achieved by targeting $\alpha_v\beta_6$ and $\alpha_v\beta_1$ with bexotegrast, may provide a novel approach to treat IPF and PSC without affecting TGF-β signaling systemically

BCOL1A1, collagen type I alpha 1; COL3A1, collagen type III alpha 1; CTGF, connective tissue growth factor; 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' (Mad) and the C elegans gene Sma; TGF-β, transforming growth factor-beta; TIMP1, tissue inhibitor matrix metalloproteinase 1.

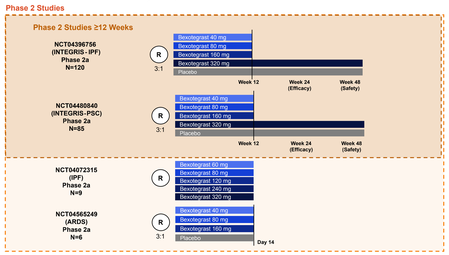
OBJECTIVE

- To provide a comprehensive safety analysis of bexotegrast across Phase 1 and Phase 2 clinical studies in idiopathic pulmonary fibrosis (IPF) and primary sclerosing cholangitis (PSC)

METHODS

- To date, over 700 participants have been exposed to bexotegrast in unblinded and blinded studies
- This safety analysis was performed on completed studies with unblinded data (cutoff date: August 16, 2023)
  - A total of 630 participants received bexotegrast and 113 received placebo
- This analysis included 523 unique participants from Phase 1 studies and 220 unique participants from Phase 2 studies[a]
- Bexotegrast doses ranged from 15 to 640 mg in single-dose studies and from 10 to 320 mg in multiple-dose studies
- In Phase 2 studies INTEGRIS-IPF and INTEGRIS-PSC, bexotegrast 320 mg QD was administered for ≥24 weeks and ≤48 weeks

Phase 2 Studies Included in the Safety Population

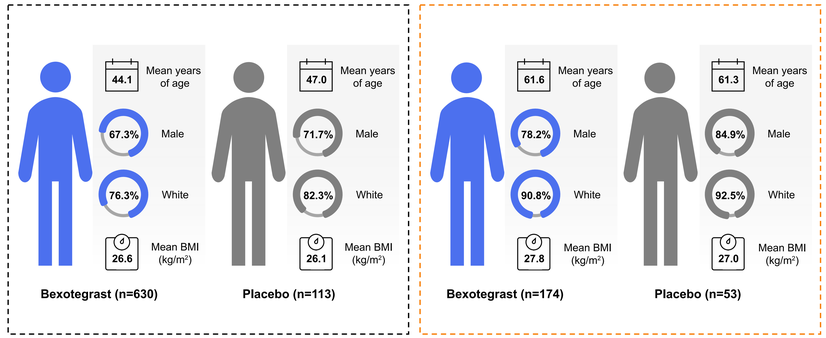


ARDS, acute respiratory distress syndrome; IPF, idiopathic pulmonary fibrosis; PSC, primary sclerosing cholangitis; QD, once daily; R, randomization.
[a]In NCT04072315, participants are counted for each unique dose level.

RESULTS

Baseline Demographics

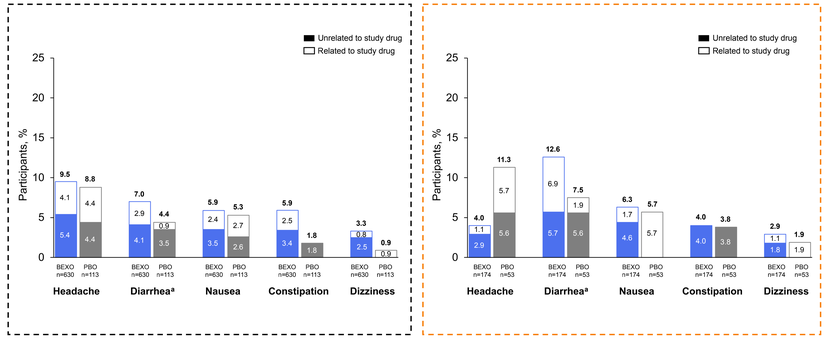
- The population from all completed studies was 67.3% male and 76.3% White, with a mean age of 44.1 years and a mean body mass index of 26.6 kg/m^2



BMI, body mass index.

Most Frequently Reported TEAEs

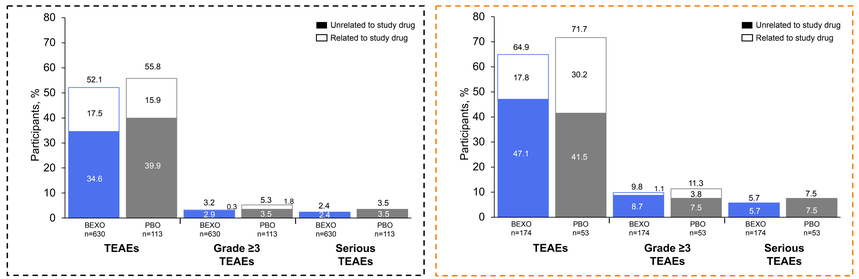
- The most common reported TEAEs in all completed studies (bexotegrast/placebo) were headache (9.5%/8.8%), diarrhea (7.0%/4.4%), nausea (5.9%/5.3%) and constipation (5.9%/1.8%)



BEXO, bexotegrast; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Nineteen participants in the all bexotegrast group had a TEAE of diarrhea; nintedanib was background therapy in 16 participants, pirfenidone was background therapy in 2 participants, and 1 participant with a medical history of ulcerative colitis was not receiving background therapy.

Safety Summary

- Rates of discontinuation were similar between bexotegrast-treated participants in all completed and all Phase 2 studies (2.2% vs 2.9%); 4.4% and 7.5% of PBO-treated participants discontinued from all completed and all Phase 2 studies, respectively
- TEAE (overall and by grade category) 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; TEAE, treatment-emergent adverse event.

CONCLUSIONS AND FUTURE RESEARCH

- Bexotegrast was well tolerated in participants in 11 Phase 1 and 4 Phase 2 studies
- The most frequently reported TEAE was headache
  - The most common system organ class TEAEs were gastrointestinal related, including diarrhea, nausea and constipation
- Most TEAEs were mild to moderate
  - Discontinuation rates were low
- These findings support the continued development of bexotegrast in IPF and PSC

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. Saini G, et al. *Eur Respir J.* 2015;46(2):486-494; 7. Peng Z-W, et al. *Hepatology.* 2016;63(1):217-232; 8. Schaub J, et al. *J Hepatol.* 2019;70(1):E57-E58.

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