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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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American Thoracic Society 2024

May 21, 2024

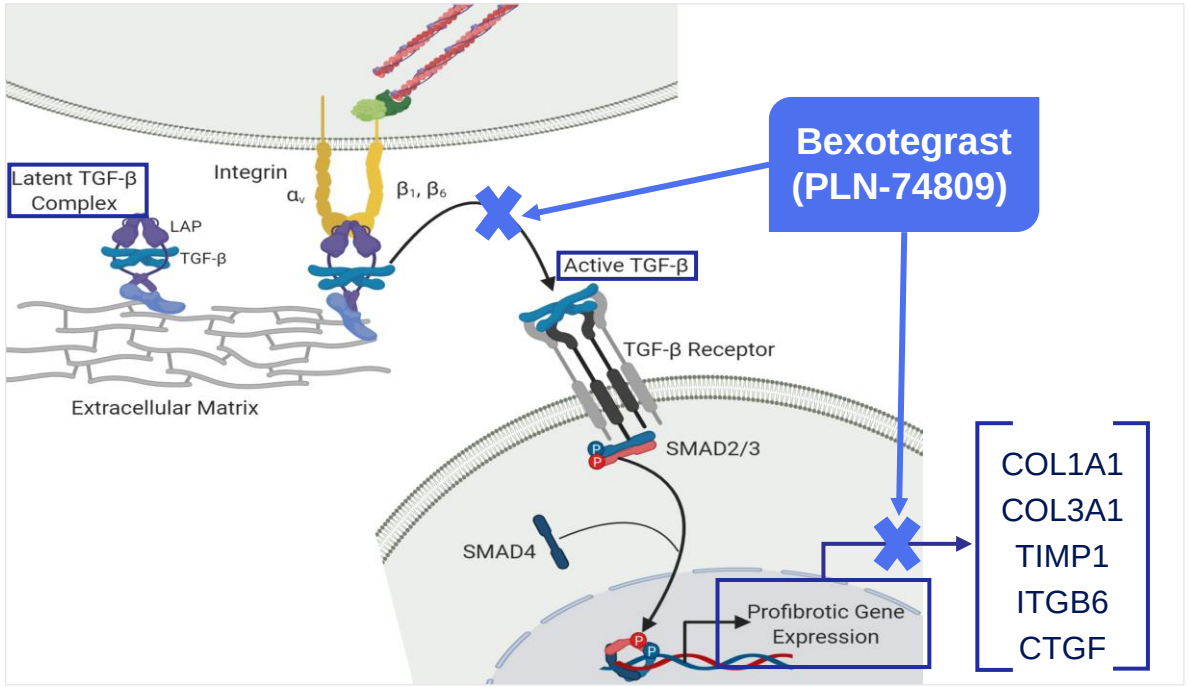
Disclosures and Acknowledgments

G. P. Cosgrove, R. Pencek, A. Clark, C. N. Barnes, H. E. Achneck, and É. A. Lefebvre were employees and shareholders of Pliant Therapeutics, Inc, at the time of this analysis.

This study was sponsored by Pliant Therapeutics, Inc. Editorial assistance was provided by Samantha O'Dwyer, PhD, of Nucleus Global and funded by Pliant Therapeutics, Inc. This presentation 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 presentation.

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

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



- 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, HSCs) is increased in fibrotic tissue[2-8]

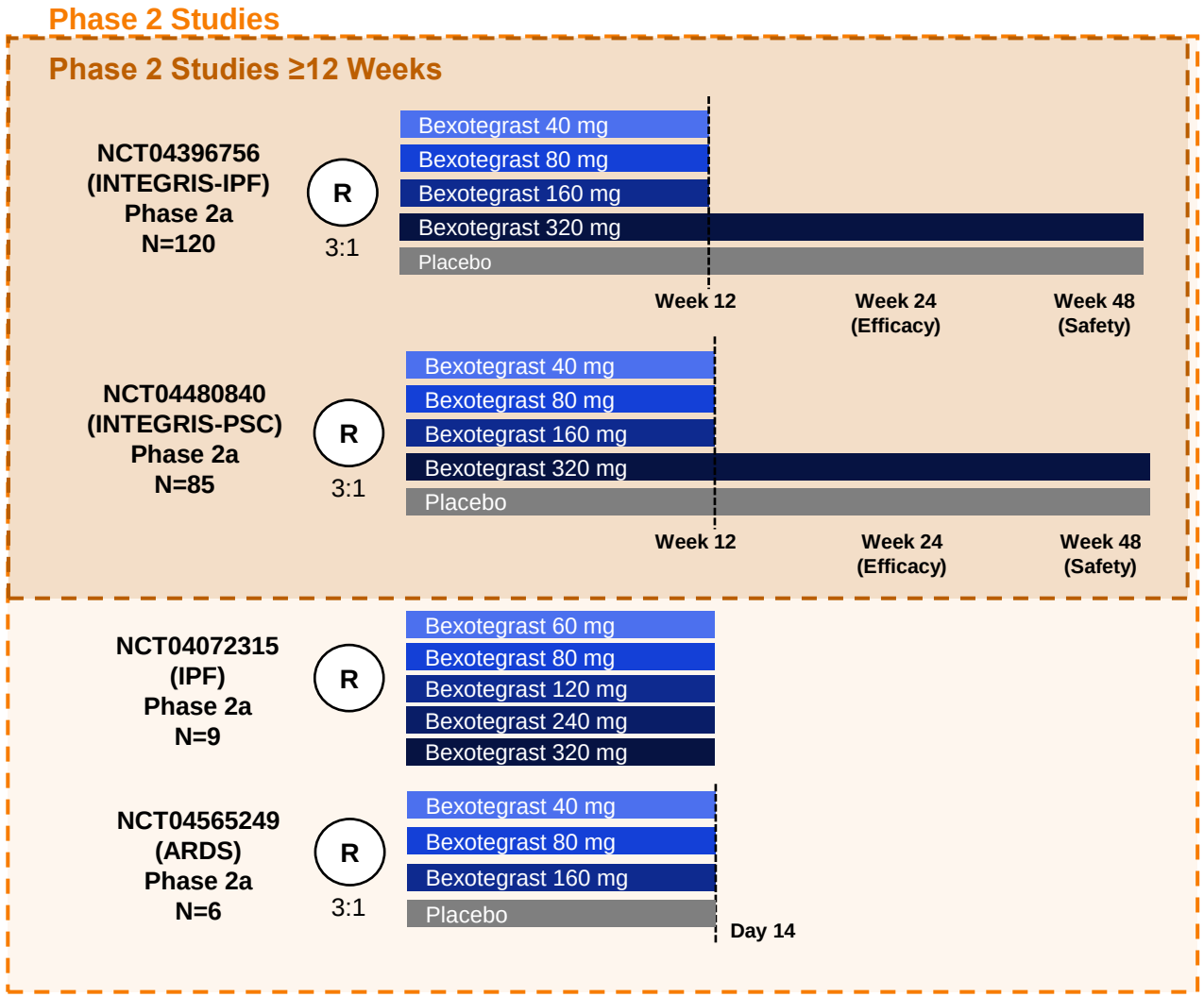
Localized TGF-β inhibition in fibrotic tissue, achieved by targeting $\alpha_v\beta_6$ and $\alpha_v\beta_1$ with bexotegrast, may provide a novel approach to treat IPF and PSC without affecting TGF-β signaling systemically

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' (*Mad*) and the *C elegans* gene *Sma*; TGF-β, transforming growth factor-beta; TIMP1, tissue inhibitor matrix metalloproteinase 1.

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.

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 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



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.

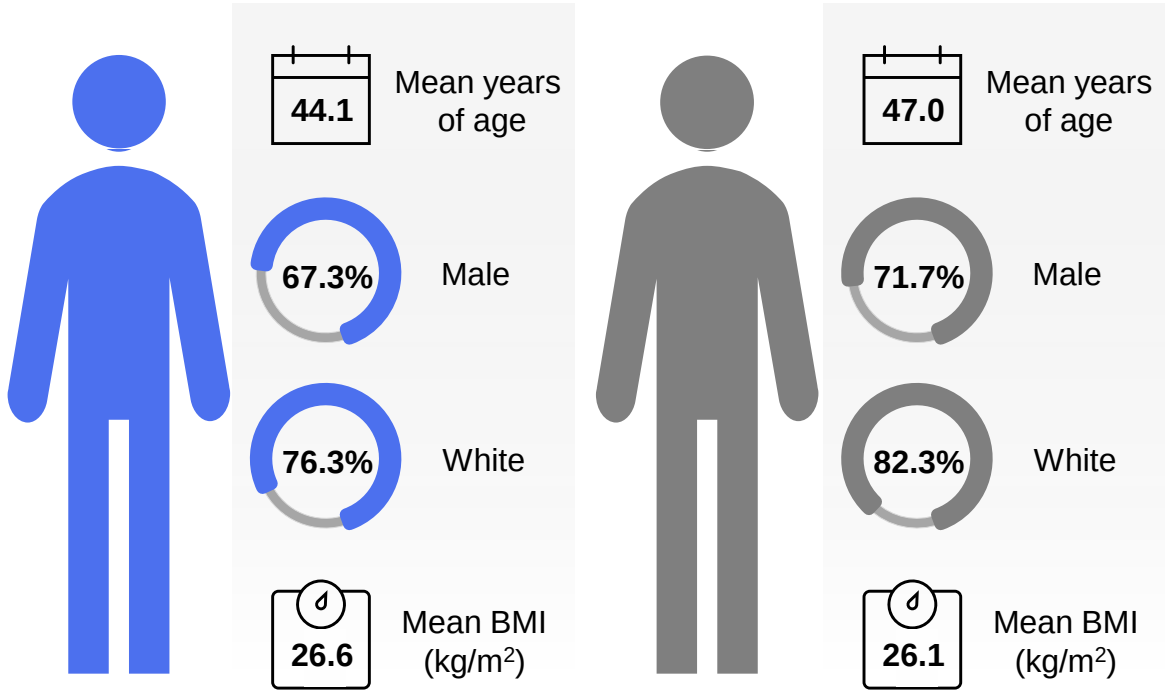
Aims and Objectives

To provide a comprehensive safety analysis of bexotegrast across Phase 1 and Phase 2 clinical studies in IPF and PSC

IPF, idiopathic pulmonary fibrosis; PSC, primary sclerosing cholangitis.

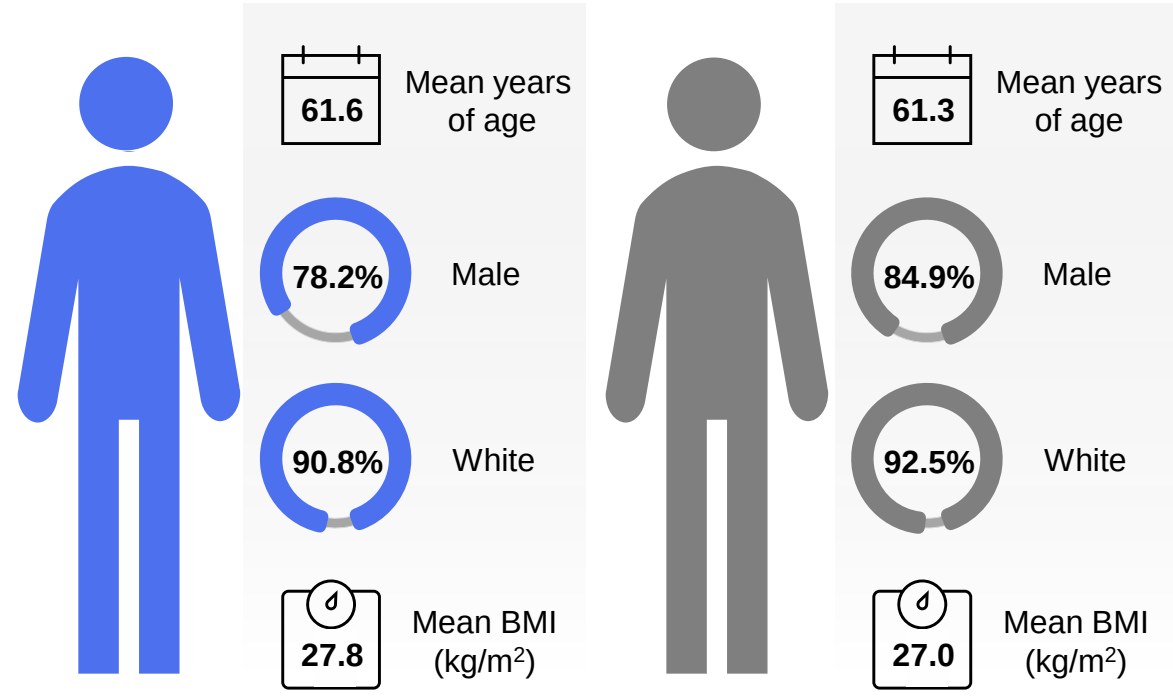
Baseline Demographics

All Completed Studies (N=743)



Bexotegrast (n=630) **Placebo (n=113)**

All Phase 2 Studies (N=227)

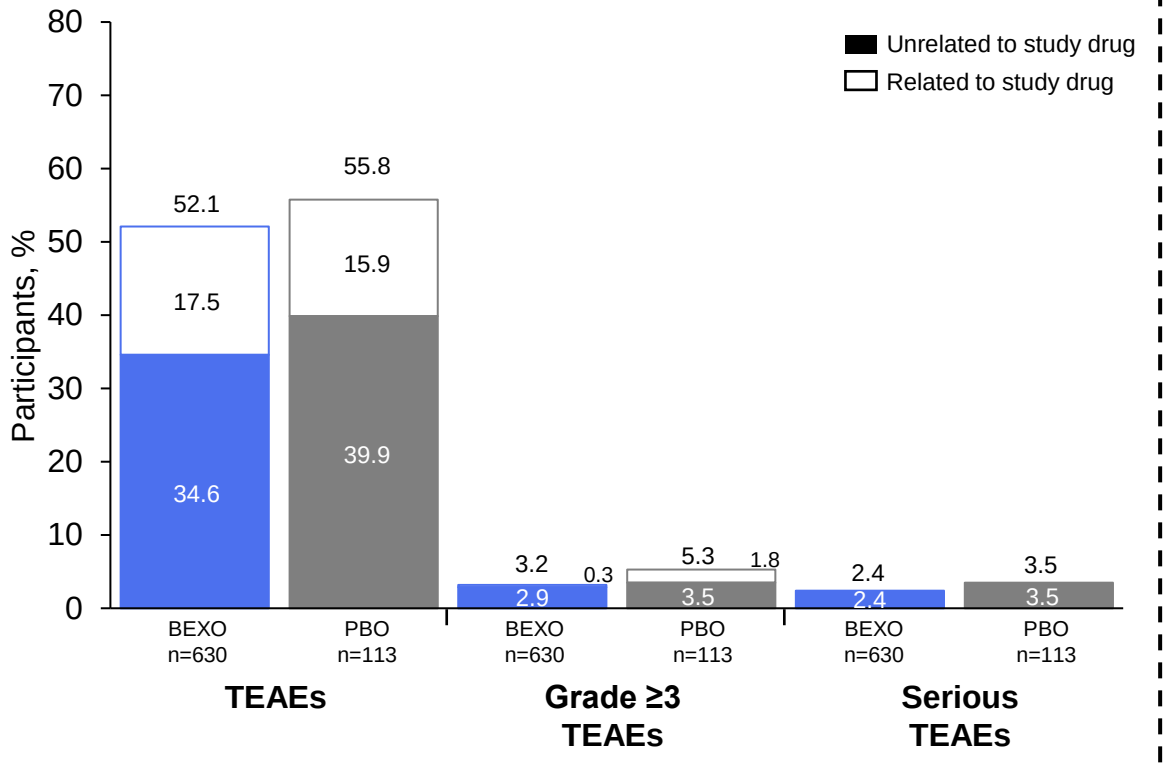


Bexotegrast (n=174) **Placebo (n=53)**

BMI, body mass index.

Safety Summary

All Completed Studies (N=743)



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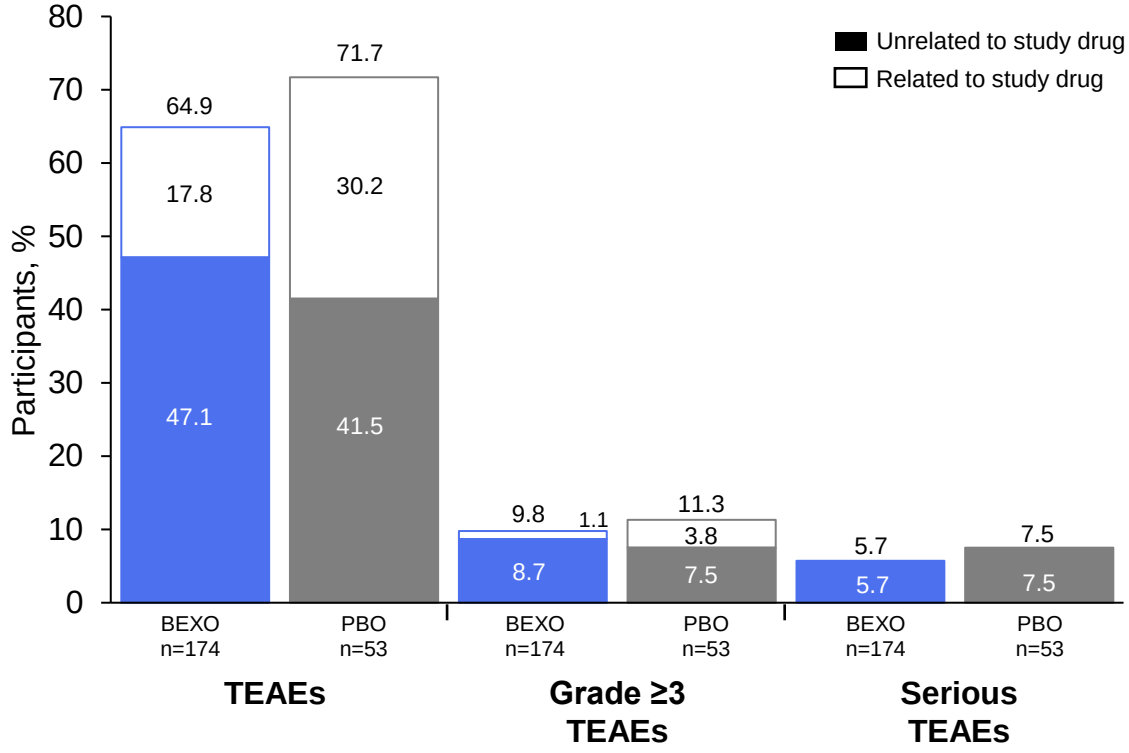
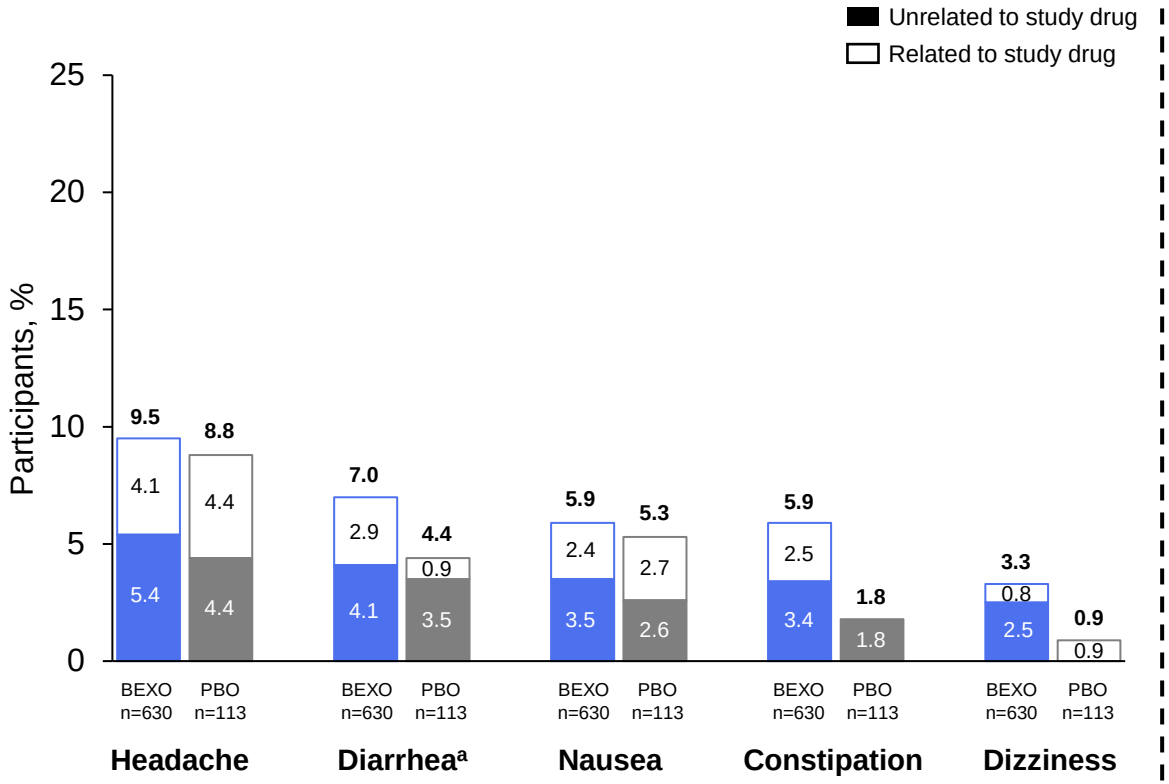


- **Rates of discontinuation were similar between bexotegrast-treated participants in all completed and all Phase 2 studies (2.2% vs 2.9%); 4.4% and 7.5% of PBO-treated participants discontinued from all completed and all Phase 2 studies, respectively**
- **TEAE (overall and by grade category) and serious TEAE rates were higher in the placebo group compared with the bexotegrast group**
- **No SAEs were considered related to the study drug**

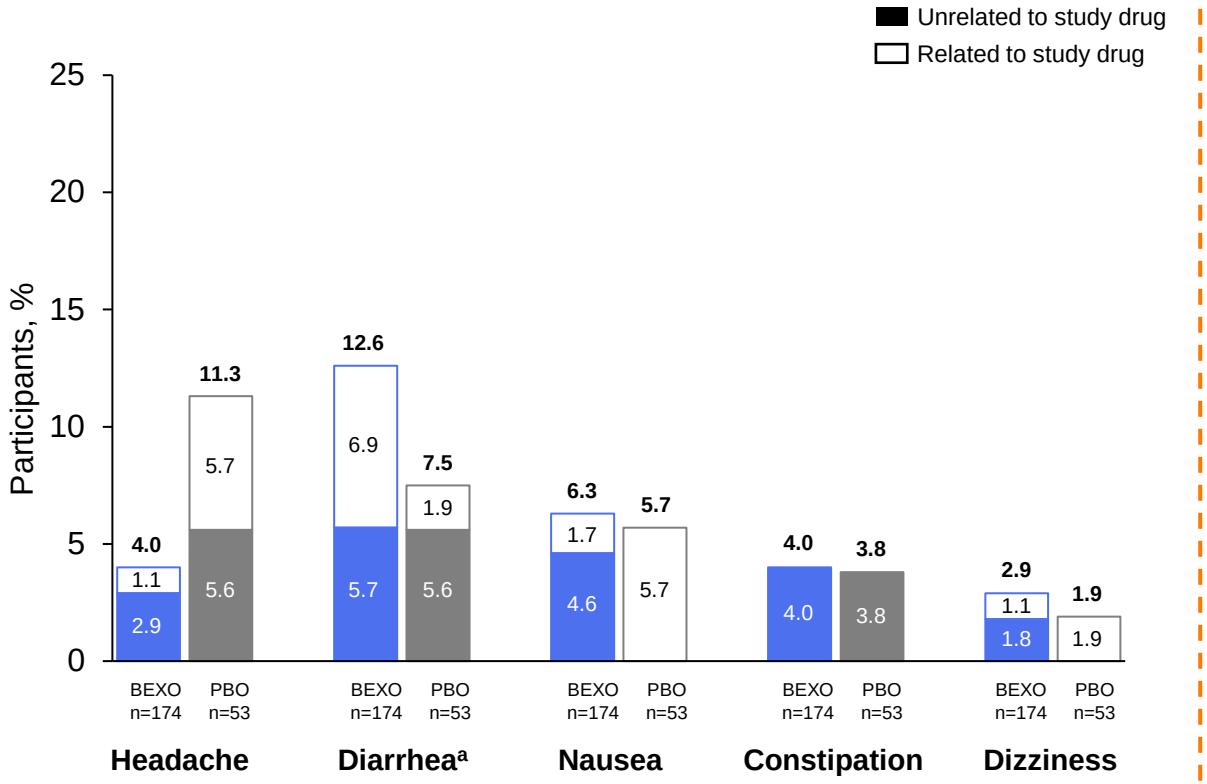
BEXO, bexotegrast; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Most Frequently Reported TEAEs

All Completed Studies (N=743)



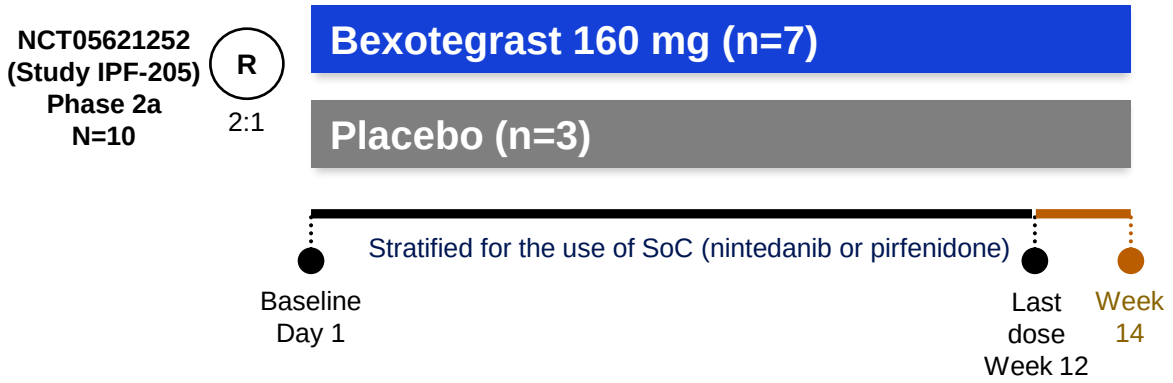
All Phase 2 Studies (N=227)



BEXO, bexotegrast; PBO, placebo; 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.

First Interventional Study to Evaluate Collagen Deposition by PET

Study Design

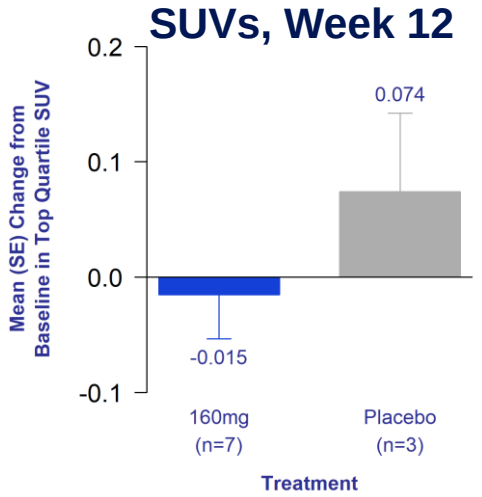


- Participants completed PET scans at Baseline and Week 12 using a ^{68}Ga-CBP8 PET probe that binds type I collagen with high specificity[1,2]
- Safety, spirometry and cough severity also assessed

Safety

- Consistent with data presented for other bexotegrast studies
- No discontinuations of study drug
- No SAEs
- Diarrhea was the only AE reported with bexotegrast in >1 participant during the treatment period (all events occurred with nintedanib co-administration)

Efficacy



- Reduction in SUV post-treatment indicates less total lung collagen
- This suggests potential reversal of fibrosis, supporting bexotegrast's antifibrotic mechanism of action

AE, adverse events; PET, positron emission tomography; R, randomization; SAE, serious adverse events; SoC, standard of care; SUV, standardized uptake values.

1. Désogere P, et al. *Sci Trans Med*. 2017;9(384):eaaf4696. 2. Montesi S, et al. *Am J Respir Crit Care Med*. 2019;200(2):258-261

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

IPF, idiopathic pulmonary fibrosis; PSC, primary sclerosing cholangitis; TEAE, treatment-emergent adverse event.

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