BEXOTEGRAST REDUCES TYPE 1 COLLAGEN DEPOSITION IN PARTICIPANTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF) AFTER 12 WEEKS OF THERAPY

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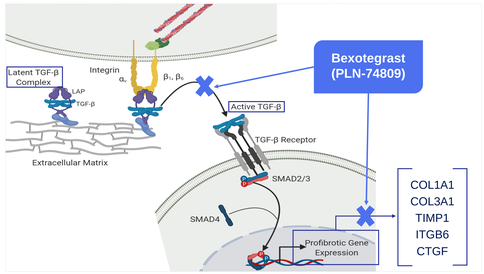
BACKGROUND

- IPF is primarily a basilar, subpleural disease characterized by excessive deposition of type 1 collagen[1]
  - In patients with IPF, $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins are overexpressed in the lungs which activates TGF-β and drives collagen synthesis[2]
- Bexotegrast is an oral, once-daily, selective, dual inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins that is under development for IPF
- ^{68}Ga-CBP8, a PET probe, measures type 1 collagen and showed increased uptake in the lungs of patients with IPF[3]

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



COL1A1, collagen type I alpha 1; COL3A1, collagen type III alpha 1; CTGF, connective tissue growth factor; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; IPF, idiopathic pulmonary fibrosis; ITGB6, integrin beta-6; LAP, latency-associated peptide; PET, positron emission tomography; 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

- We report results from the first interventional Phase 2, single-centre, randomised, double-blind, placebo-controlled study (NCT05621252) evaluating type 1 collagen deposition by PET and architectural changes by DCE-MRI in the lungs of participants with IPF following 12 weeks of treatment with bexotegrast

STUDY DESIGN AND PARTICIPANT DEMOGRAPHICS

Inclusion Criteria
- IPF diagnosis ≤8 years
- FVCpp ≥45%
- DL_{CO} ≥30%
- eGFR ≥50 mL/min

R 2:1

- Bexotegrast 160 mg (n=7)
- Placebo (n=3)

Stratified for use of background therapy (nintedanib or pirfenidone)

Baseline Day 1 — Last dose Week 12 — Week 14

Primary Endpoint

Quantification of type 1 collagen in the lung as assessed by changes from baseline in ^{68}Ga-CBP8 PET SUV using top quartile summary metric

Secondary Endpoint

Safety and tolerability of bexotegrast

Key Exploratory Endpoints

Change from baseline in DCE-MRI contrast peak enhancement and washout rates, absolute and FVCpp, cough severity, and biomarkers

Baseline Demographics

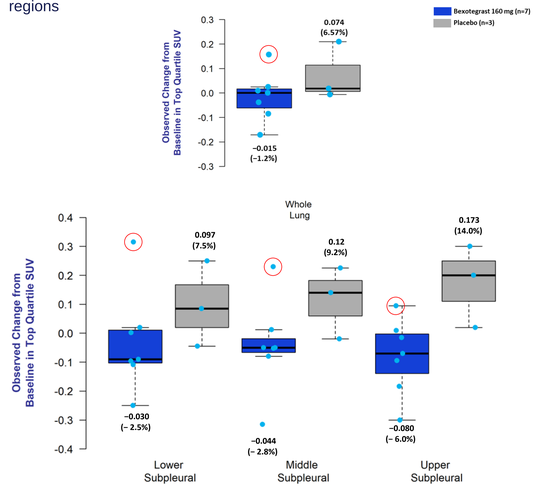
	Bexotegrast (n=7)[a]	Placebo (n=3)
Mean age, years	69.1	74.0
Male	85.7%	100%
Background therapy	85.7%	66.7%
Median FVCpp	66.0%	58.0%
Median cough severity (VAS)	28.0	19.0

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DL_{CO}, diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; FVCpp, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis; MRI, magnetic resonance imaging; PET, positron emission tomography; R, randomisation; SUV, standardized uptake value; VAS, visual analog scale.
[a]One participant in the bexotegrast group was non-adherent to the study drug (65%) and contracted COVID-19 during the first month on study.

RESULTS

Bexotegrast Reduced Type 1 Collagen in the Lung Using PET Imaging After 12 Weeks

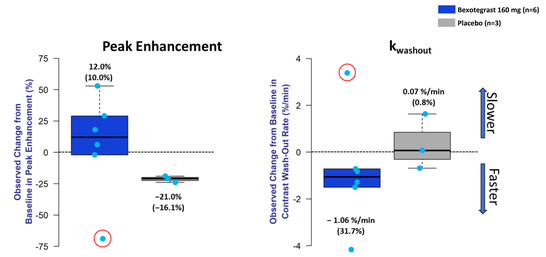
- Bexotegrast 160 mg reduced the ^{68}Ga-CBP8 PET SUVs from baseline, indicating a reduction in total lung collagen
- The SUV changes with bexotegrast at Week 12 were largest in the subpleural lung regions



Individual, mean, and percentage change in top quartile SUV shown. The length of the box represents the interquartile range, and the vertical lines represent the maximum, median, and minimum. Change in central region was of smaller magnitude than changes in subpleural regions. The nonadherent/COVID-19 participant in the bexotegrast group is indicated by red circles.
PET, positron emission tomography; SUV, standardized uptake value.

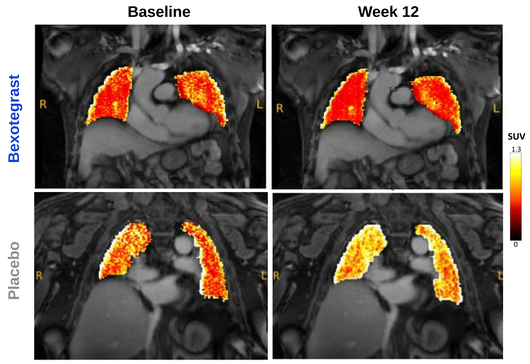
Dynamic Changes in Extracellular Volume Based on DCE-MRI Parameters Observed with Bexotegrast

- Reduced peak enhancement has been associated with increased vascular permeability and/or decreased perfusion[4,5]
- Slower $k_{washout}$ rates may be due to expanded extracellular volume as a result of replacement of cellular components with collagen[3,6]



Contrast agent was gadoterate meglumine. Individual, median, and percentage change shown. The length of the box represents the interquartile range, and the vertical lines represent the maximum, median, and minimum.
DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; $k_{washout}$, washout rate of contrast from the lung.

Bexotegrast Reduced Type 1 Collagen in the Lung After 12 Weeks



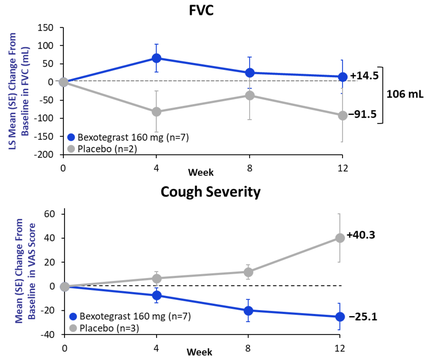
Participant A: bexotegrast 160 mg
- Decrease from baseline to Week 12 in top quartile ^{68}Ga-CBP8 SUV of **−0.17**
- Change in top quartile SUV of **−15.5%**

Participant B: placebo
- Increase from baseline to Week 12 in top quartile ^{68}Ga-CBP8 SUV of **+0.21**
- Change in top quartile SUV of **+18.4%**

Images shown are fused PET and MRI images.
MRI, magnetic resonance imaging; PET, positron emission tomography; SUV, standardized uptake value.

Changes in ^{68}Ga-CBP8 SUV Correlated With Changes in Lung Function and Improved Cough Severity

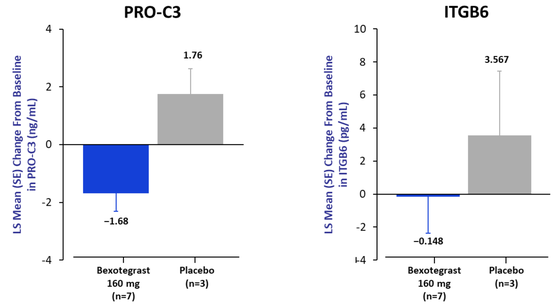
- Treatment with bexotegrast numerically improved FVC over 12 weeks, with the bexotegrast group maintaining a clear separation from placebo at all time points
  - Correlation between change in ^{68}Ga-CBP8 SUV and change in FVC (ρ=−0.57)
- Participants in the bexotegrast group reported decreased cough severity across all on-treatment time points compared with placebo
  - Change in cough severity is predicted by change in FVC (R^2=0.77)



FVC, forced vital capacity; LS, least squares; ρ, correlation; PET, positron emission tomography; SUV, standardized uptake value; VAS, visual analog scale.

Bexotegrast Reduced Prognostic IPF Biomarkers

- Circulating biomarker analysis showed decreases in biomarkers of collagen synthesis (PRO-C3) and interstitial lung disease progression (ITGB6)[7] in the bexotegrast vs placebo group after 12 weeks of treatment



IPF, idiopathic pulmonary fibrosis; ITGB6, integrin beta-6; LS, least squares; PRO-C3, type III collagen synthesis neoepitope.

Bexotegrast Was Well Tolerated Over 12 Weeks

- Overall, bexotegrast demonstrated a favourable safety and tolerability profile over 12 weeks

TEAE, n (%)	Bexotegrast (n=7)	Placebo (n=3)
TEAE	6 (85.7)	1 (33.3)
TEAE related to study drug	5 (71.4)	1 (33.3)
Serious TEAE	0	0
TEAE leading to interruption of study drug	1 (14.3)[a]	0
TEAE leading to withdrawal from study	0	0
TEAE leading to early termination from study	0	0
TEAE leading to death	0	0
Most frequent TEAEs (n>1)		
Cough	4 (57.1)[b]	0
Diarrhea	3 (42.9)[c]	1 (33.3)

TEAE, treatment-emergent adverse event.
[a] Participant with COVID-19.
[b] All cough events occurred post Week 12 (end of treatment) during the 14-day follow-up period.
[c] All events of diarrhea were considered mild. The 3 participants were taking nintedanib, which was listed as an alternative cause.

CONCLUSIONS AND FUTURE RESEARCH

- Changes in type 1 collagen PET imaging with ^{68}Ga-CBP8 and DCE-MRI support antifibrotic effects of bexotegrast, suggesting favourable lung remodelling
- Treatment with bexotegrast numerically improved FVC, cough severity, and prognostic biomarkers, suggesting its potential for disease modification in IPF
- Changes in lung uptake of the PET probe ^{68}Ga-CBP8 directionally correlated with changes in pulmonary function
- Limitations include the small sample size and short duration of treatment
- Late-stage evaluation of bexotegrast will further explore the efficacy and safety in participants with IPF (BEACON-IPF; NCT06097260)

References: 1. Désogère P, *et al. Sci Transl Med.* 2017;9(384):eaaf4696; 2. Decaris ML, *et al. Respir Res.* 2021;22(1):265; 3. Montesi S, *et al. Am J Respir Crit Care Med.* 2019;200(2):258-261; 4. Zhang W-J *et al. Radiology.* 2016;278(3):906-916; 5. Amundson T *et al. J Magn Reson Imaging.* 2000;12(2):224-231; 6. Kehr E, *et al. Int J Cardiovasc Imaging.* 2008;24(1):61-68; 7. Bowman *et al. Lancet Respir Med.* 2022;10(6): 593-602.

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