

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



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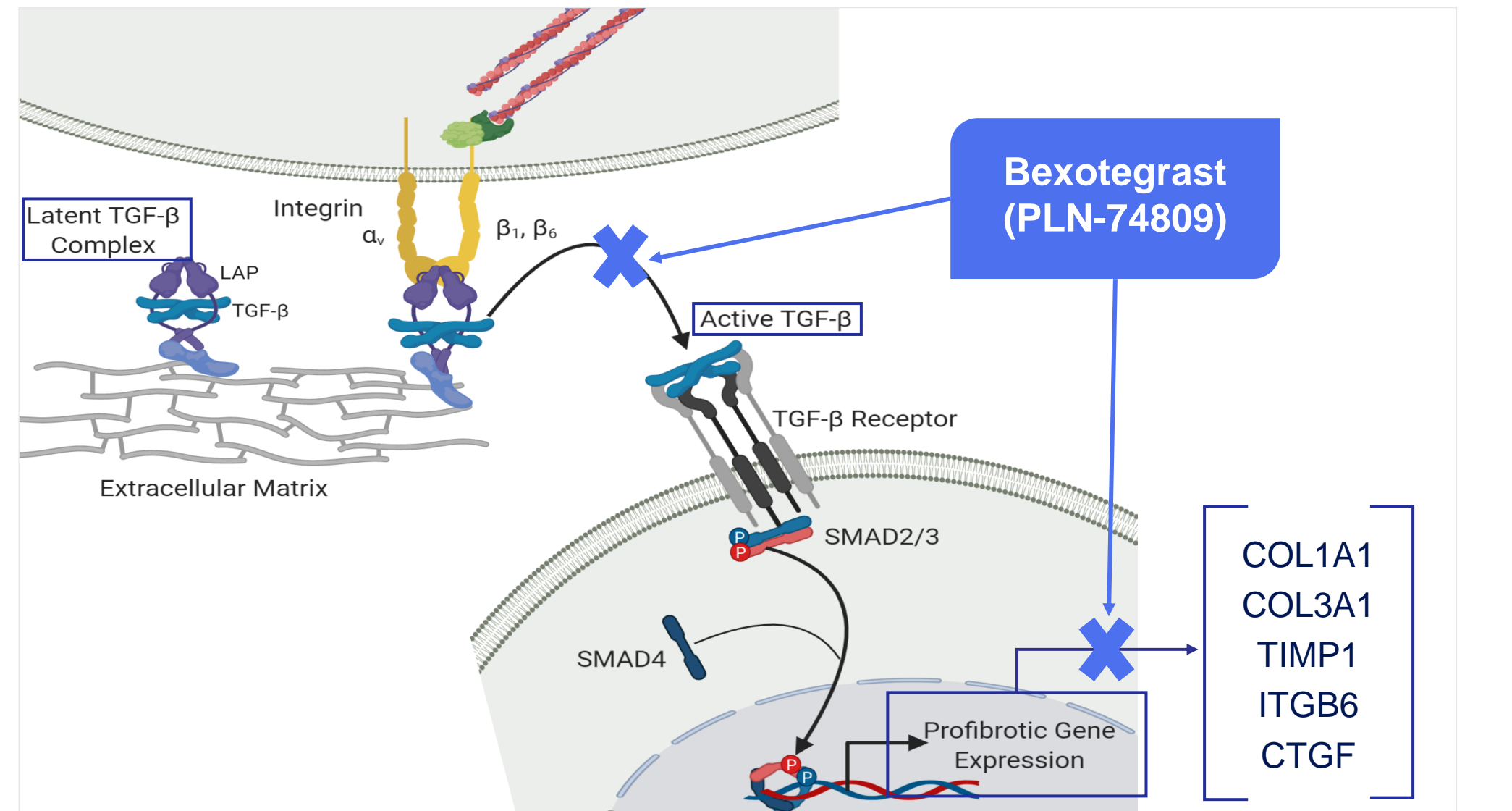
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BACKGROUND

- IPF is primarily a basilar, subpleural disease characterized by excessive deposition of type 1 collagen¹
 - In patients with IPF, $\alpha_1\beta_1$ and $\alpha_1\beta_2$ integrins are overexpressed in the lungs which activates TGF- β and drives collagen synthesis²
- Bexotegrist is an oral, once-daily, selective, dual inhibitor of $\alpha_1\beta_2$ and $\alpha_1\beta_1$ integrins that is under development for IPF
- ⁶⁸Ga-CBP8, a PET probe, measures type 1 collagen and showed increased uptake in the lungs of patients with IPF³

$\alpha_1\beta_2$ and $\alpha_1\beta_1$ Integrins Promote Fibrosis Through Activation of TGF- β

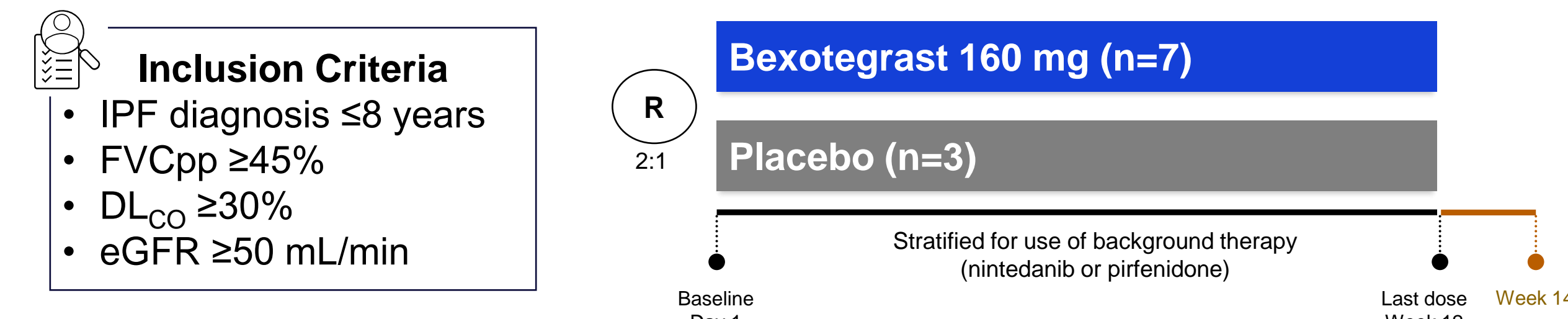


COL1A1, collagen type I alpha 1; COL3A1, collagen type III alpha 1; CTGF, connective tissue growth factor; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; IPF, idiopathic pulmonary fibrosis; ITGB6, integrin beta-6; LAP, latency-associated peptide; PET, positron emission tomography; SMAD,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

STUDY DESIGN AND PARTICIPANT DEMOGRAPHICS



Primary Endpoint

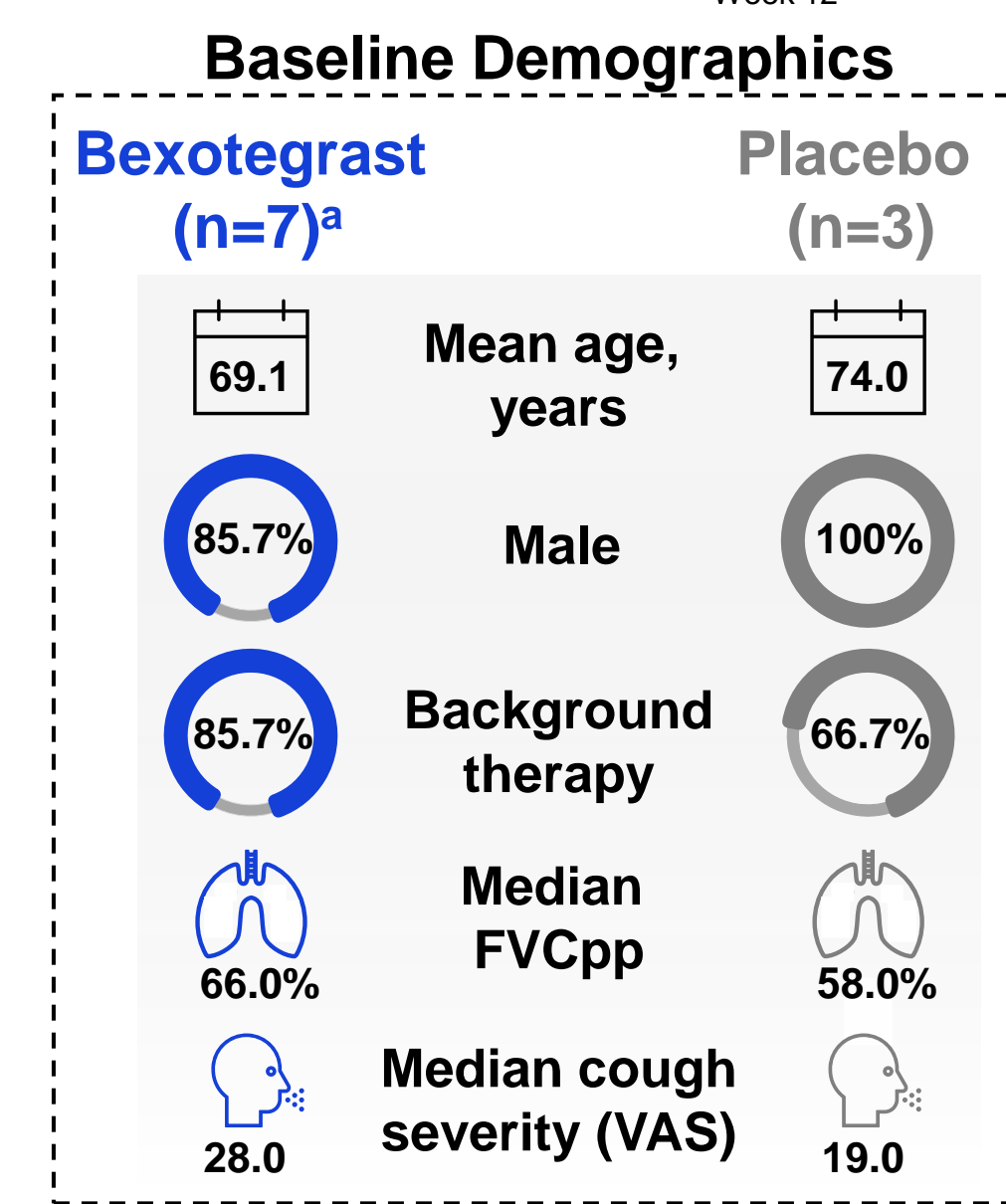
Quantification of type 1 collagen in the lung as assessed by changes from baseline in ⁶⁸Ga-CBP8 PET SUV using top quartile summary metric

Secondary Endpoint

Safety and tolerability of bexotegrist

Key Exploratory Endpoints

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

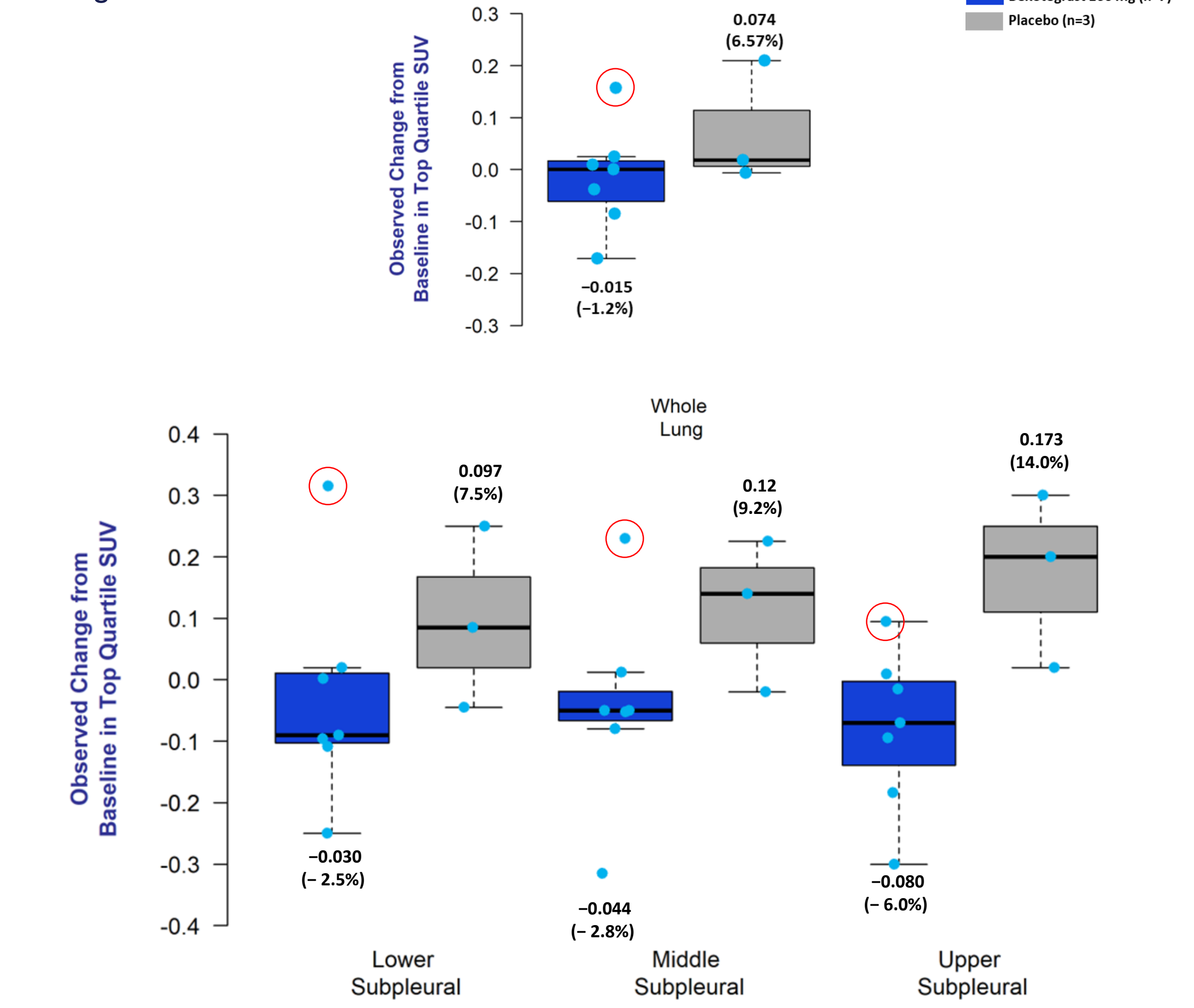


DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DL_{CO}, diffusing capacity for carbon monoxide; eGFR, estimated glomerular filtration rate; FVCpp, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis; MRI, magnetic resonance imaging; PET, positron emission tomography;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

RESULTS

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

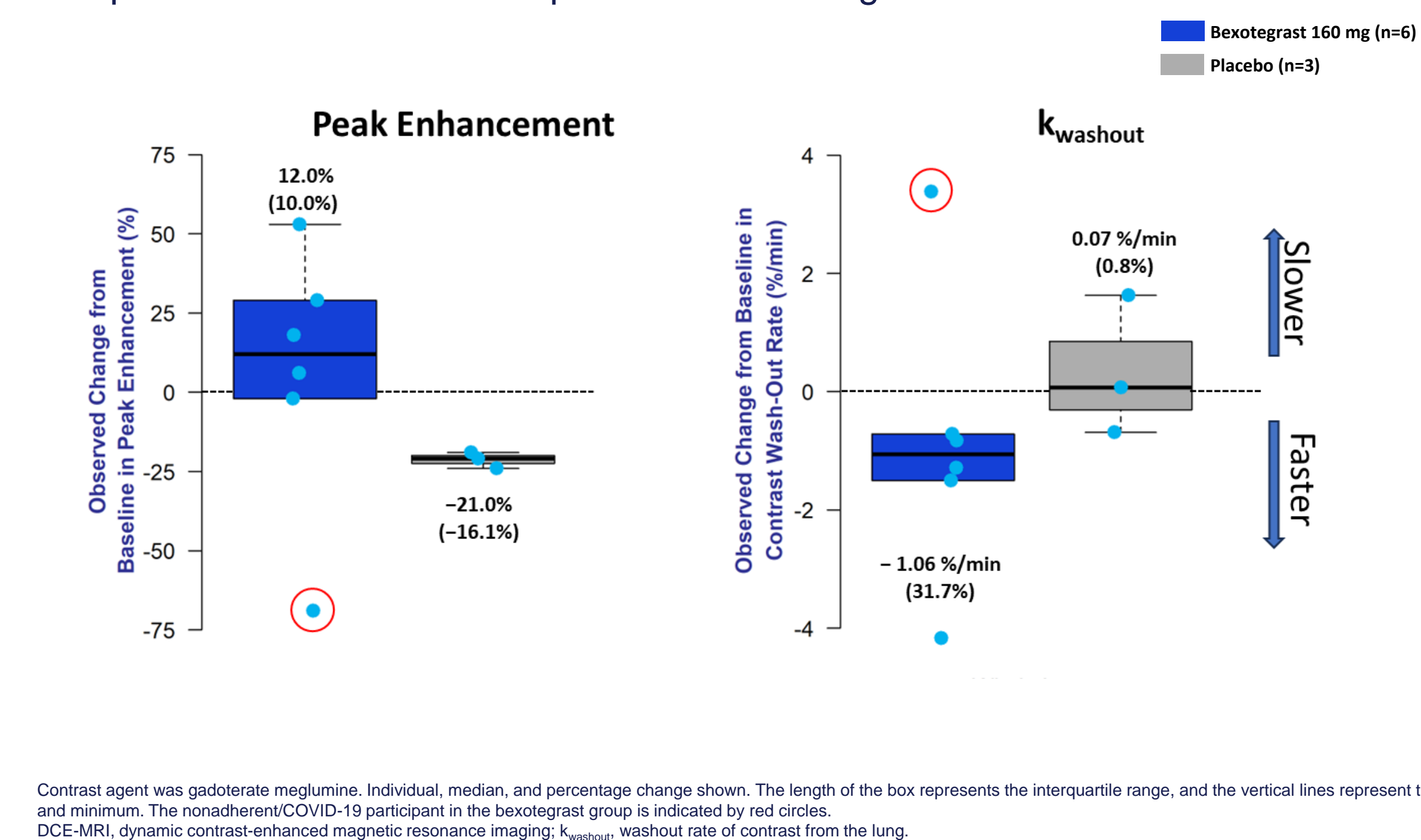
- Bexotegrist 160 mg reduced the ⁶⁸Ga-CBP8 PET SUVs from baseline, indicating a reduction in total lung collagen
- The SUV changes with bexotegrist at Week 12 were largest in the subpleural lung regions



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 bexotegrist group is indicated by red circles. PET, positron emission tomography; SUV, standardized uptake value.

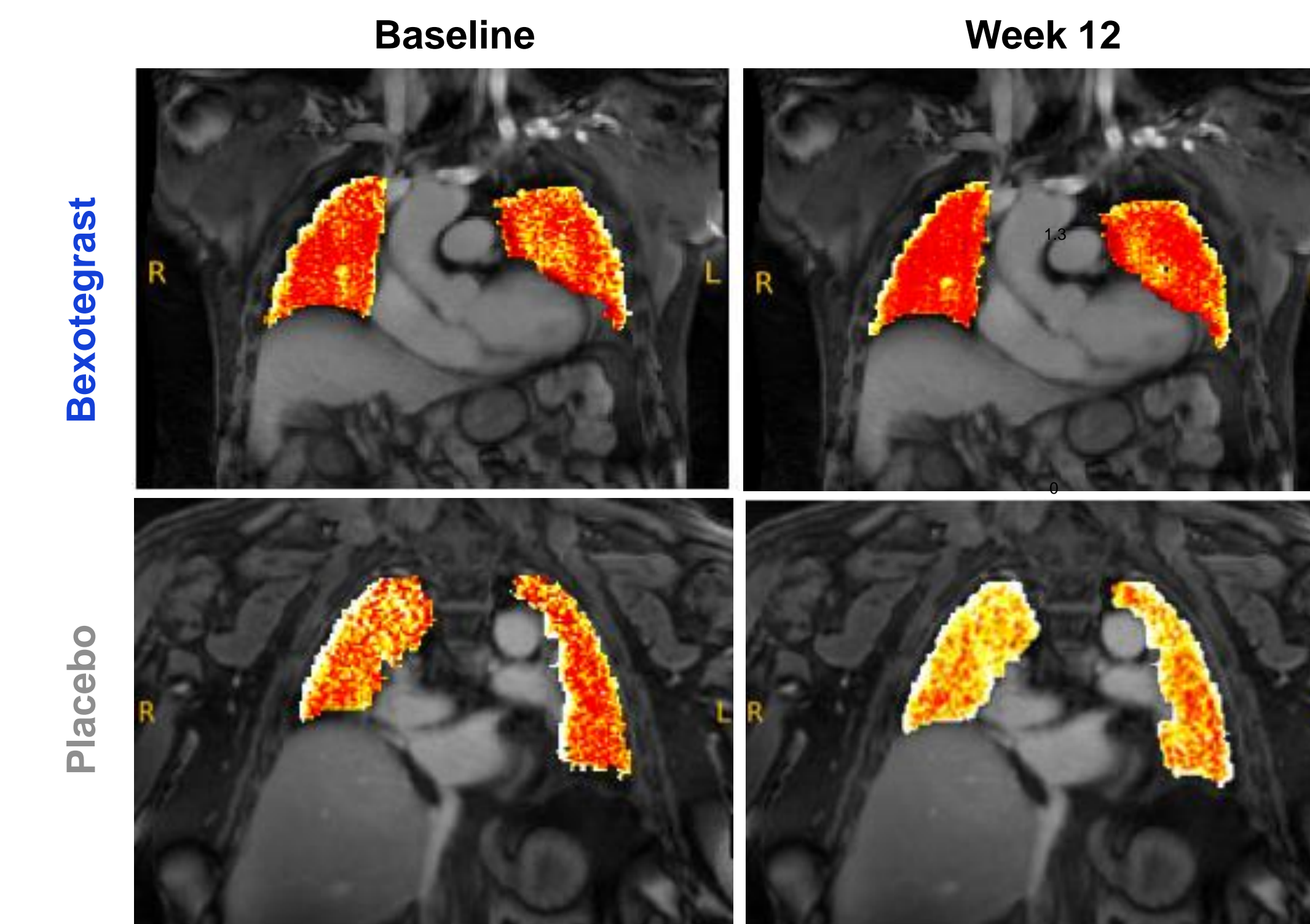
Dynamic Changes in Extracellular Volume Based on DCE-MRI Parameters Observed with Bexotegrist

- 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. The nonadherent/COVID-19 participant in the bexotegrist group is indicated by red circles. DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; $k_{washout}$, washout rate of contrast from the lung.

Bexotegrist Reduced Type 1 Collagen in the Lung After 12 Weeks



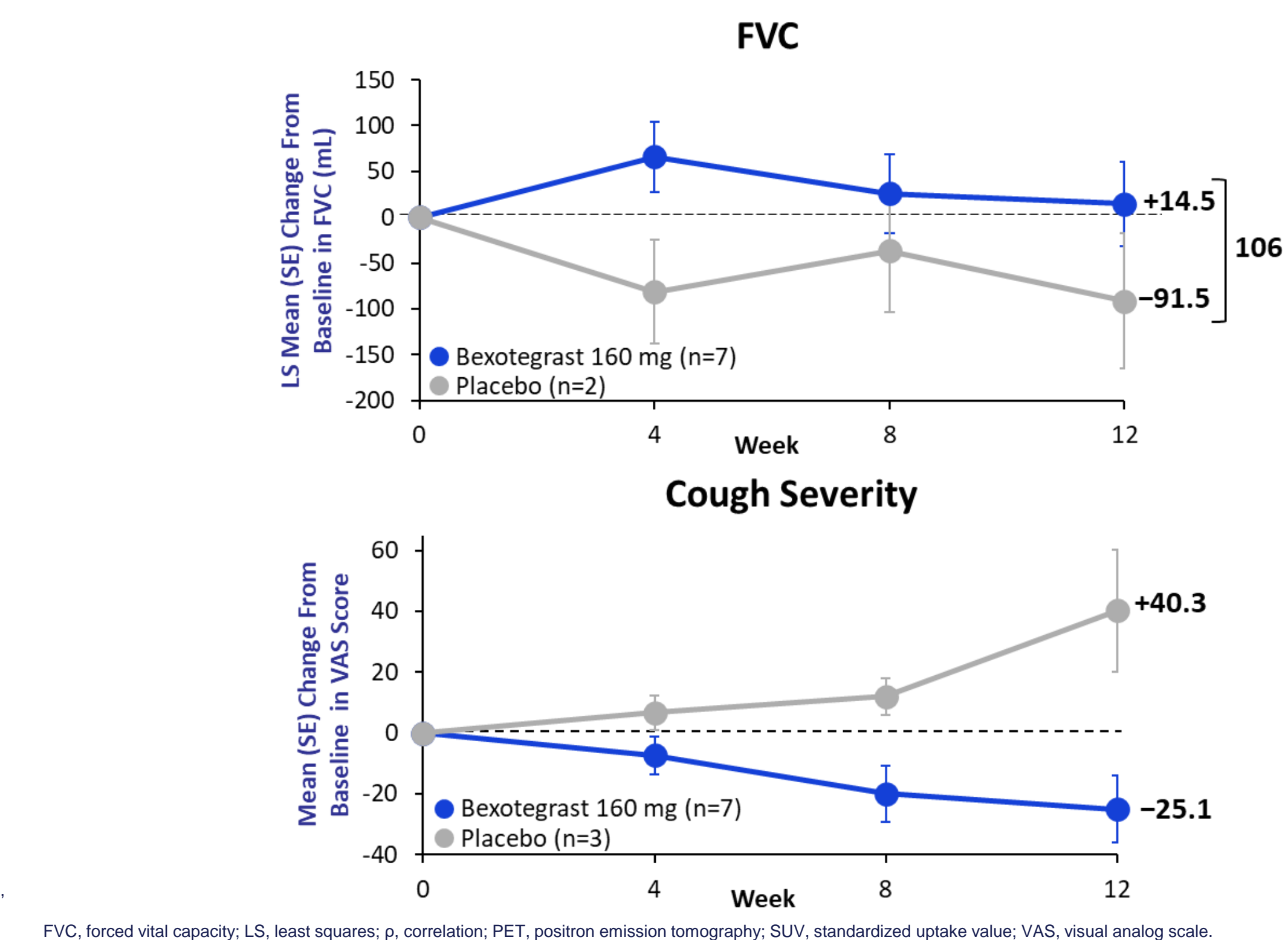
Participant A: bexotegrist 160 mg
 • Decrease from baseline to Week 12 in top quartile ⁶⁸Ga-CBP8 SUV of **-0.17**
 • Change in top quartile SUV of **-15.5%**

Participant B: placebo
 • Increase from baseline to Week 12 in top quartile ⁶⁸Ga-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 ⁶⁸Ga-CBP8 SUV Correlated With Changes in Lung Function and Improved Cough Severity

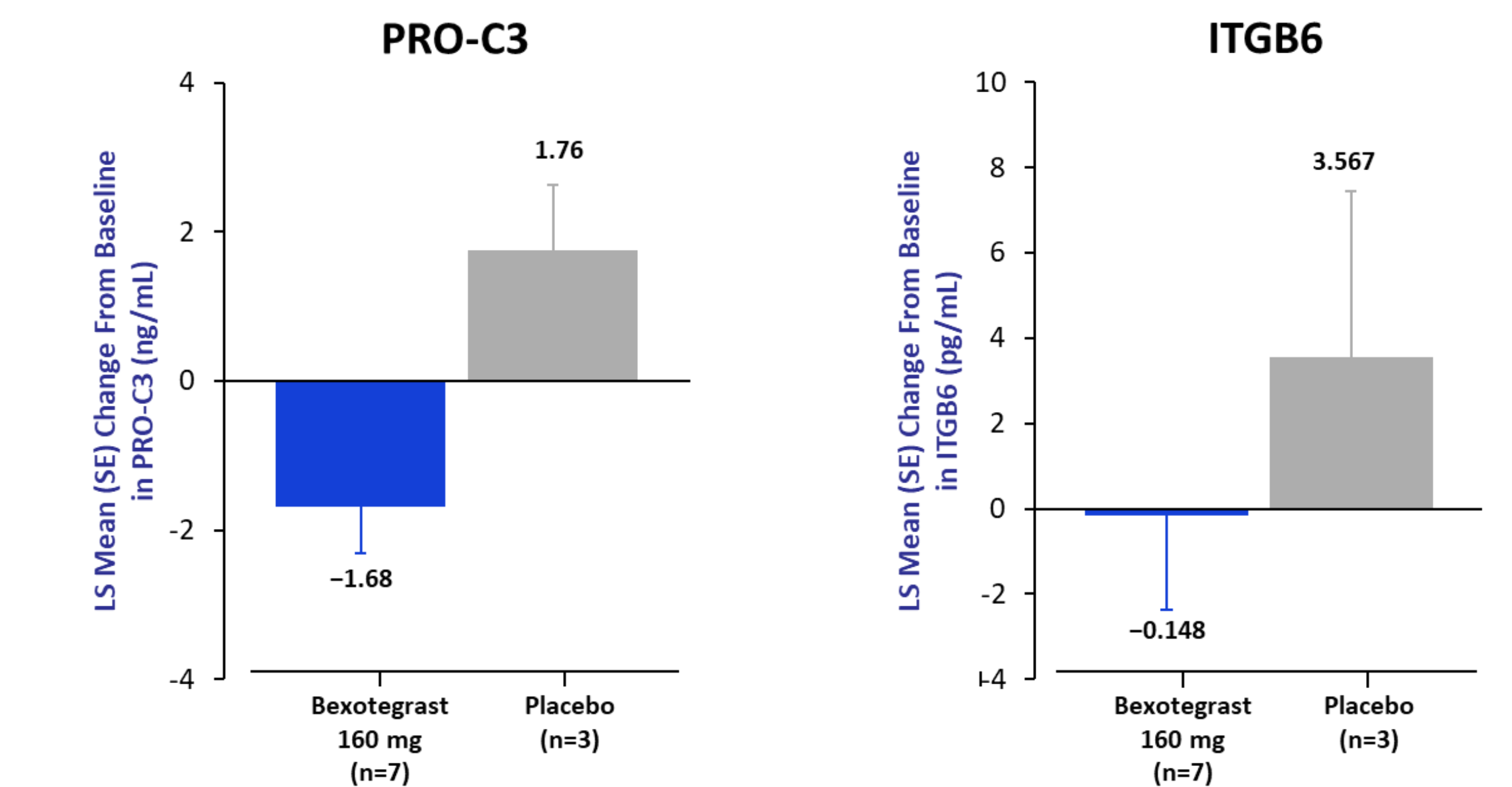
- Treatment with bexotegrist numerically improved FVC over 12 weeks, with the bexotegrist group maintaining a clear separation from placebo at all time points
 - Correlation between change in ⁶⁸Ga-CBP8 SUV and change in FVC ($\rho=-0.57$)
- Participants in the bexotegrist group reported decreased cough 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 analogue scale.

Bexotegrist 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 bexotegrist 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 neopeptide.

Bexotegrist Was Well Tolerated Over 12 Weeks

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

TEAE, n (%)	Bexotegrist (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. ^aParticipant with COVID-19. ^bAll cough events occurred post Week 12 (end of treatment) during the 14-day follow-up period. ^cAll 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 ⁶⁸Ga-CBP8 and DCE-MRI support antifibrotic effects of bexotegrist, suggesting favourable lung remodelling
- Treatment with bexotegrist numerically improved FVC, cough severity, and prognostic biomarkers, suggesting its potential for disease modification in IPF
- Changes in lung uptake of the PET probe ⁶⁸Ga-CBP8 directionally correlated with changes in pulmonary function
- Limitations include the small sample size and short duration of treatment
- Late-stage evaluation of bexotegrist will further explore the efficacy and safety in participants with IPF (BEACON-IPF; NCT06097260)

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