Bexotegrast in Patients with Idiopathic Pulmonary Fibrosis: The INTEGRIS-IPF Study

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All authors contributed to, reviewed, and approved the final draft of the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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At a Glance Commentary

Current Scientific Knowledge on the Subject: The currently approved agents for IPF, pirfenidone and nintedanib, are therapeutic options for patients with IPF; however, neither halt the progression of IPF or consistently improve quality of life, and both have long-term tolerability issues. Bexotegrast (PLN-74809) is an oral, once-daily investigational drug that blocks activation of TGF-β by preventing integrins αvβ6 and αvβ1 from binding to the arginine-glycine-aspartate sequence of latent TGF-β, thereby preventing TGF-β from binding to its receptors and activating profibrogenic signaling pathways.

What This Study Adds to the Field: TGF-β from binding to its receptors and activating profibrogenic signaling pathways. The results of the INTEGRIS-IPF study suggests bexotegrast is well tolerated in patients with IPF, and exploratory analyses suggest an antifibrotic effect based on forced vital capacity, quantitative lung fibrosis imaging, and circulating levels of ITGB6 and PRO-C3, indicating the need for further studies of bexotegrast for the treatment of IPF.

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Abstract

Rationale: Idiopathic pulmonary fibrosis (IPF) is a rare and progressive disease, which causes progressive cough, exertional dyspnea, impaired quality of life and death.

Objectives: Bexotegrast (PLN-74809) is an oral, once-daily, investigational drug in development for the treatment of IPF.

Methods: This Phase 2a, multicenter, clinical trial, randomized participants with IPF to receive oral, once daily bexotegrast 40 mg, 80 mg, 160 mg, 320 mg, or placebo, with or without background IPF therapy (pirfenidone or nintedanib), in an approximately 3:1 ratio in each bexotegrast dose cohort, for at least 12 weeks. The primary endpoint was incidence of treatment-emergent adverse events (TEAEs). Exploratory efficacy endpoints included change from baseline in forced vital capacity (FVC); quantitative lung fibrosis (QLF) extent (%) and changes from baseline in fibrosis-related biomarkers.

Measurements and Main Results: Bexotegrast was well tolerated with similar rates of TEAEs in the pooled bexotegrast and placebo groups (62/89 [69.7%] and 21/31 [67.7%], respectively). Diarrhea was the most common TEAE; most participants with diarrhea also received nintedanib. Bexotegrast-treated participants experienced a reduction in FVC decline over 12 weeks vs. placebo, with or without background therapy. A dose-dependent antifibrotic effect of bexotegrast was observed with QLF imaging and a decrease in fibrosis-associated biomarkers was observed with bexotegrast vs. placebo.

Conclusions: Bexotegrast demonstrated a favorable safety and tolerability profile, up to 12 weeks for the doses studied. Exploratory analyses suggest an antifibrotic effect according to FVC, QLF imaging, and circulating levels of fibrosis biomarkers.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare and progressive disease characterized by altered lung structure and function due to excessive extracellular matrix deposition with resulting symptoms of progressive cough, exertional dyspnea, and impaired quality of life.(1-7) Median life expectancy for untreated patients with IPF is approximately 3–4 years.(2, 8, 9)

The currently approved agents for IPF, pirfenidone and nintedanib,(6) represent an important therapeutic option for patients with IPF, reducing the decline of lung function, and potentially reducing the time to acute exacerbations and improving survival if durable therapy is maintained.(10-17) However, neither halt the progression of IPF nor consistently improve quality of life.(10, 12, 13, 18) Both drugs have long-term tolerability issues; pirfenidone is associated with nausea and photosensitivity(12, 14, 19, 20) and nintedanib is associated with diarrhea.(10, 21) Consequently, there remains an unmet need for more effective and better tolerated treatments for patients with IPF.

Transforming growth factor-beta (TGF-β) activation by $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins is a key driver of fibrosis in the lungs.(1, 22, 23) $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins, expressed by lung epithelial cells and fibroblasts/myofibroblasts, respectively, are both upregulated in patients with IPF.(1, 23) Elevated circulating levels of integrin $\alpha_v\beta_6$ are associated with decreased survival in patients with interstitial lung disease (ILD)(24) and specifically IPF.(25)

Bexotegrast (PLN-74809) is an oral, once-daily investigational drug in development for the treatment of IPF. Bexotegrast blocks the activation TGF-β by preventing $\alpha_v\beta_6$ and $\alpha_v\beta_1$ binding to the arginine-glycine-aspartate sequence of latent TGF-β, thereby

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preventing TGF-β from binding to its receptors and activating profibrogenic signaling pathways.(1)

INTEGRIS-IPF was a Phase 2a, multicenter, clinical trial evaluating the safety, tolerability and pharmacokinetics of once-daily oral bexotegrast with or without background therapy (pirfenidone or nintedanib) in patients with IPF. Efficacy of bexotegrast in terms of forced vital capacity (FVC), quantitative lung fibrosis (QLF), and biomarkers of fibrosis were also explored. Some of the results of these studies have been previously reported in the form of abstracts.(26, 27)

METHODS

Study population

The study enrolled participants with a diagnosis of IPF according to ATS/ERS/JRS/ALAT 2018 guidelines,(28) FVC percent predicted ≥45%, diffusing capacity for carbon monoxide (DLco) hemoglobin-adjusted ≥30%, and life expectancy of ≥6 months. Background therapy for IPF with pirfenidone or nintedanib was permitted, provided these drugs had been given at a stable dose for ≥3 months prior to screening. Key exclusion criteria included receiving any non-approved agent intended for the treatment of pulmonary fibrosis or IPF and a forced expiratory volume during the first second (FEV_1)/FVC ratio <0.7. Additional inclusion and exclusion criteria are provided in the supplementary materials.

Study design

INTEGRIS-IPF (PLN-74809-IPF-202; NCT04396756) was a Phase 2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study, conducted across 39 sites in North America, Europe, Australia and New Zealand, which assessed the effects of treatment with bexotegrast or placebo for at least 12 weeks in patients with

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IPF (**Figure 1**). The last study visit took place approximately 14 days after the last dose of the study drug.

Participants were randomized to receive oral bexotegrast 40 mg, 80 mg, 160 mg, 320 mg, or placebo in an approximately 3:1 ratio in each bexotegrast dose cohort (40 mg or placebo; 80 mg, 160 mg, or placebo; and 320 mg or placebo) (**Figure 1**). Randomization was conducted using an interactive voice-response system and participants were stratified according to whether they were receiving/not receiving a background therapy (pirfenidone or nintedanib). Participants, investigators and those involved in the trial conduct were blinded to the trial treatment assignments.

The study was conducted in accordance with the Declaration of Helsinki, the study protocol, and International Council on Harmonisation Good Clinical Practice regulations. The study was approved by the Institutional Review Board, Independent Ethics Committee or Research Ethics Board. All participants provided written informed consent.

Study assessments

Study assessments included safety laboratory assessments, vital signs, electrocardiography (ECG), adverse events and concomitant medications, pharmacokinetic sampling, FVC (mL and percent of predicted), FEV_1, QLF extent, assessment of fibrosis-related biomarkers and patient-reported cough severity.

The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs). Pharmacokinetic endpoints included predicted total and unbound plasma bexotegrast maximum concentration (C_{max}) and area under the concentration time curve from time 0 to 24 hours post-dose (AUC_{0-24}) on Days 1, 28, and 84.

Exploratory efficacy endpoints included absolute change from baseline to 12 weeks in FVC and were assessed using spirometry with central quality control. QLF extent

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(%) was assessed by high-resolution computed tomography (HRCT),(29) with central quality control, pre-baseline and at Week 12. Analyses of changes from baseline to Week 12 in fibrosis-related biomarkers, serum type III collagen synthesis neoepitope (PRO-C3) and plasma integrin beta 6 (ITGB6) were also conducted.

Statistical analysis

A sample size of ~21 participants per treatment group was expected to provide a meaningful evaluation of safety, tolerability, and pharmacokinetics of bexotegrast in patients with IPF (additional detail are in the supplementary materials). No power calculations were conducted as the efficacy and biomarker assessments were exploratory in nature.

All participants who received bexotegrast or placebo were included in the safety analyses. Safety data, which were based on TEAEs, are presented by treatment group, pooled across bexotegrast doses and included events occurring during treatment through a 2-week follow-up period. The intent-to-treat (ITT) population included all randomized participants and the modified ITT (mITT) population excluded one participant who met post hoc statistical outlier criteria, using Grubb's outlier test coupled with the clinical implausibility of the value being representative of the participant's true clinical status. FVC change from baseline was evaluated using a mixed model for repeated measures (MMRM) analysis with treatment group, visit, baseline FVC value, background therapy use (yes/no), and treatment-by-visit interaction as terms in the model with an unstructured covariance structure: pre-planned separate subgroup analyses were performed in participants taking a background therapy and those not taking a background therapy. Change from baseline in biomarkers was analyzed using a similar MMRM analysis without adjustment for background therapy use. Missing data were not imputed for the

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MMRM analyses of FVC and biomarkers, under the assumption that they are missing at random. As this was an exploratory study, no adjustment for multiplicity was planned.

For the quantitative imaging, the per CT protocol population included the subset of the ITT population with scans at baseline and Week 12 that met technical evaluability criteria per the HRCT imaging protocol, e.g., participants with paired examinations that met technical specifications for quantitative assessment. QLF extent is reported using observed means, standard errors, and proportions.

RESULTS

Study participants

In total, 119 participants met the eligibility criteria and were randomized between September 2020 and June 2022 to receive once-daily, oral bexotegrast 40 mg (n=22), 80 mg (n=23), 160 mg (n=22), or 320 mg (n=21), or placebo (n=31) (**Figure 2**). One participant, randomized to placebo, received 320 mg bexotegrast for approximately 1 week due to incorrect study-drug dispensation. This participant was included in the denominator of both treatment groups for baseline demographics and safety analyses; however, this participant was only included in the placebo group for the efficacy analysis. The baseline demographics and disease characteristics are summarized in **Table 1**. The majority of participants were male and the mean (standard deviation) age of bexotegrast-treated participants was 71.4 (6.61) years and 72.1 (6.20) years for placebo-treated participants. Approximately 80% of participants were receiving background therapy. Baseline FVC volume and percent of predicted were comparable between treatment groups. Overall, 92% of participants completed the 12-week treatment period. A total of 9 participants

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prematurely discontinued treatment; 5 (5.7%) in the pooled bexotegrast group and 4 (12.9%) in the placebo group, primarily due to adverse events and withdrawal of consent.

Safety and tolerability through Week 12

Overall, bexotegrast demonstrated a favorable safety and tolerability profile over 12 weeks of treatment (**Tables 2** and **3** and **Tables E1** and **E2** in the online data supplement). The majority of TEAEs were mild or moderate in severity. The most common TEAEs are presented in **Table 2**. Diarrhea was the most common TEAE, occurring in 15 participants (16.9%) in the bexotegrast (pooled) group and 3 participants (9.7%) in the placebo group. Of the participants reporting diarrhea, 13/15 (86.7%) bexotegrast participants and 1/3 (33.3%) placebo participants were receiving nintedanib background therapy; one participant (6.7%) with diarrhea in the bexotegrast group was receiving pirfenidone (**Table 3**). The remaining participant with diarrhea who received bexotegrast monotherapy had pre-existing ulcerative colitis. Most events of diarrhea (14/15; 93.3%) were mild to moderate in severity; one participant receiving bexotegrast and pirfenidone had Grade 3 diarrhea. Four participants interrupted bexotegrast treatment due to intercurrent COVID-19 (n=1), diarrhea (n=2), and ileus and acute kidney injury (n=1). Two participants discontinued bexotegrast due to mild diarrhea (n=1 receiving background nintedanib; n=1 no background therapy, pre-existing ulcerative colitis). Dose reduction of bexotegrast was not allowed per protocol. No serious adverse events were assessed as being related to study drug.

TEAEs of IPF/pulmonary fibrosis were reported in 2.3% of bexotegrast and 9.7% of placebo participants. Only one of these events was reported as an acute

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exacerbation of IPF in a participant who had completed 12 weeks of treatment with bexotegrast 160 mg and experienced the event 11 days after last dose. The event was not considered to be drug related and resolved the following day after treatment in hospital with corticosteroids and antibiotics.

One participant with gender-age-physiology (GAP) Stage III IPF and pre-existing coronary artery disease and chronic, refractory atrial fibrillation in the bexotegrast 320 mg group experienced a serious and fatal adverse event of acute respiratory failure following elective atrioventricular node ablation.

There were no notable changes in laboratory parameters, vital signs, physical examination findings, or ECG findings associated with study drug. Overall, bexotegrast was well tolerated when used in combination with IPF background therapy or used as monotherapy (**Tables 3** and **Tables E1** and **E2** in the online data supplement).

Pharmacokinetics

Predicted total and unbound exposures (C_{max} and $AUC_{0\text{-}24}$) of bexotegrast in participants with IPF increased approximately proportionally with dose (**Tables E3** and **E4** in the online data supplement).

Efficacy (exploratory endpoints)

Bexotegrast treatment resulted in reduced FVC decline over 12 weeks compared with placebo. In the mITT population, in which 81% of the participants were receiving background therapy, changes in FVC from baseline to Week 12 (standard error) were -46.1 (39.64) mL, 25.6 (38.57) mL, -25.6 (40.49) mL, and 29.4 (43.35) mL in participants in the bexotegrast 40 mg, 80 mg, 160 mg and 320 mg groups, and -3.6

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(21.97) for the pooled bexotegrast treatment cohort, compared with -110.5 (36.38) mL in the placebo group (**Figure 3** and **Figure E1** in the online data supplement). At Week 12, changes in FVC with bexotegrast were statistically significant vs. placebo in the 80 mg (difference: 136.1 mL; P=0.0094) and 320 mg groups (difference: 139.9 mL; P=0.0124). The treatment effect of bexotegrast was observed in participants receiving or not receiving background therapy for IPF (**Figure E2** in the online data supplement). In the extension study, of patients in the bexotegrast 320 mg group who had an increase in FVC at Week 12 (n=10), 88.9% maintained that increase to Week 24; in the placebo group, no participants maintained their FVC increase observed at Week 12 to Week 24 (**Figure E3** in the online data supplement).

A dose-dependent trend of a reduction in the percentage of participants with relative and absolute decline ≥10% of FVC percent predicted (FVCpp) was observed over the 12-week treatment period (**Figure 4**).

Quantitative assessment of lung imaging demonstrated that mean percent change in QLF extent decreased dose-dependently from baseline to Week 12 with no or limited progression at 160 mg and 320 mg (**Figure 5A**). Circulating biomarker analysis revealed an overall dose-dependent decrease in ITGB6 relative to placebo and reductions that were significant at Week 4 for bexotegrast 80, 160 and 320 mg doses and continued to be significant and decline further at Week 12 (**Figure 5B**). For PRO-C3 there was a significant reduction compared with placebo for the 320 mg dose at Week 4 and a further reduction vs. placebo at Week 12 was observed for the 80 and 160 mg doses compared with Week 4 (**Figure 5C**).

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DISCUSSION

The INTEGRIS-IPF study demonstrated a positive safety and tolerability profile for bexotegrast up to 12 weeks, with no dose relationship for TEAEs across the four doses studied (a plain language infographic is provided in the Online Data Supplement). The most common adverse event reported was diarrhea, primarily observed in those taking background nintedanib. Notably, no relationship between the dose of bexotegrast and incidence of diarrhea was observed. Gastrointestinal AEs, including diarrhea, are common adverse reactions in patients treated with nintedanib or pirfenidone.(10, 12-14, 16) The current study did not identify any safety concerns for bexotegrast and confirms the positive safety profile identified in the 11 completed Phase 1 studies, where the most common TEAEs (occurring in >5% of participants receiving bexotegrast) were headache and constipation (Pliant Data on File).(30) No drug-related serious AEs or deaths were reported in any of these studies.

Previously, treatment with the anti-$\alpha_v\beta_6$ IgG1 monoclonal antibody BG00011 (up to 8 weeks treatment in a Phase 2a study and up to 40 weeks treatment in a Phase 2b study) was shown to be associated with a significant imbalance of IPF acute exacerbations compared with placebo.(31, 32) The reported increase in acute exacerbations of IPF was postulated to be a result of the pro-inflammatory potential of prolonged TGF-β inhibition.(32) However, no increased risk of disease progression, denoted by IPF or pulmonary fibrosis, was identified in the current study of bexotegrast over a 12-week treatment duration. In the extended treatment duration for participants enrolled in the bexotegrast 320-mg cohort(mean exposure 27.2 weeks), the favorable safety profile extended to at least 24 weeks and up to 40

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weeks.(26) Chronic toxicology studies of bexotegrast as well as prior studies with systemic inhibition of TGF-β with neutralizing antibodies or small molecule inhibitor have not suggested a pro-inflammatory effect in the lungs of rodents and non-human primates.(33) In our prior investigation in healthy volunteers exposed to bexotegrast for 7 days (PLN-74809-109),(30) there were no notable differences in the total leukocyte cell count or distribution across bexotegrast treatment groups (40 mg, 80 mg, 160 mg and 320 mg) compared with placebo. Therefore, the increased risk of IPF acute exacerbation noted with BG00011 may be drug-specific and not a result of prolonged TGF-β inhibition. Late-stage evaluation of the efficacy and safety of bexotegrast is underway in the 52-week BEACON-IPF trial (PLN-74809-IPF-206, NCT06097260) which will further characterize its benefit-risk.

Pharmacokinetic data indicated dose-proportional increases in bexotegrast exposure, which were consistent with previous studies.(34)

The exploratory efficacy and biomarker data presented here provide the first evidence of the potential effect of bexotegrast in participants with IPF. Previously, bexotegrast showed sustained reduction of TGF-β signaling in bronchoalveolar lavage cells collected from healthy participants (PLN-74809-109)(35) as well as anti-fibrotic effects in ex vivo human and in vivo murine models of pulmonary fibrosis.(1) In the present study, compared with placebo, bexotegrast was associated with reduced FVC decline and trend towards a reduction in participants with relative and absolute decline in FVCpp ≥10%, which are predictors of increased mortality and disease progression.(36, 37) Statistical significance was identified for the absolute change in FVC (mL) at Week 12 for the 80-mg and 320-mg doses, but not the 160-mg dose which may reflect the inherent variability of FVC measurement, short treatment duration or limitations of smaller samples sizes in the individual

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cohorts. The treatment effect of the 160-mg dose at Week 12 is supported by the totality of the data including FVCpp ≥10% (absolute and relative), mean change in QLF, cough severity as assessed by VAS, and change in the prognostic biomarker ITGB6 and PRO-C3. For these endpoints, a clear dose-relationship was observed, with the 160-mg and 320-mg doses providing the best results. The placebo cohort appeared to have a large decline of –110 mL in FVC over 12 weeks in which approximately 80% of patient were receiving background therapy, consistent with that observed in recent IPF trials.(38) The progressive nature of decline in participants receiving background therapy in recent trials remains unexplained. Direct comparison to prior registrational trials for pirfenidone and nintedanib are limited due to the lack of consistent exposure to therapeutic doses, either because of dose reductions or dose interruptions or the mean dose at baseline for participants being lower than the recommended dosage in recent Phase 3 trials.(38) The data from INTEGRIS-IPF were, however, similar to what was observed in placebo groups for other Phase 2 IPF trials where there was a range in FVC decline from –60 to –101 mL.(16, 39-41) Lastly, a post hoc analysis of placebo groups in pirfenidone clinical trials examined FVC variability at 3-month intervals and found that approximately 50% of all 3-month intervals assessed had an increase or decrease of ≥100 mL, suggesting 12-week intervals can be variable.(42) Other factors can also contribute to shifts in FVC such as the intrinsic variability of the measure itself, patient demographics including being male or white, patient progression being unpredictable, differences in patient background therapy, inclusion and analysis of missing data and patient sample size.(43-45) Additional studies in larger patient populations will confirm the robustness of the treatment effect by bexotegrast.

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The majority of study participants were receiving background therapy for IPF. Results suggest that adding bexotegrast to an approved IPF background therapy over a 12-week period improved prevention of FVC decline compared with pirfenidone or nintedanib plus placebo, without additive toxicity. IPF progression in participants receiving bexotegrast or placebo with background therapy was consistent with recent late-stage studies of IPF combination therapies. (38, 41)

The potential additive benefit associated with bexotegrast on IPF was supported by initial radiographic evidence of reduced increases in QLF extent vs. placebo. The extent of QLF correlates with measures of lung function, such as FVCpp and DLCO in longitudinal evaluations at 6 and 12 months.(46, 47) A minimally important clinical difference of 2% has been validated in natural history cohorts of IPF(48, 49) and larger studies over a longer period of time will be needed to assess the correlation of QLF and FVC with bexotegrast.

Interestingly, a longitudinal effect of therapy was observed on circulating levels of integrin $\alpha_v\beta_6$ (ITGB6), a biomarker previously associated with disease progression (as defined by death, lung transplant, or ≥10% relative FVC decline) in patients with ILD.(24) There was a significant reduction in ITGB6 levels with bexotegrast compared with placebo, which is consistent with published evidence of the effect of TGF-β on *ITGB6* gene expression.(50) Collagen type III synthesis biomarker (PRO-C3) is also reportedly elevated in patients with IPF and associated with progressive disease.(51) Our analyses revealed circulating levels of PRO-C3 were reduced in a dose-dependent manner in participants receiving bexotegrast 80 mg, 160 mg and 320 mg compared with placebo. Additional, investigation is required to validate biomarkers in IPF.

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Strengths of the current study include its prospective, dose-ranging, randomized design and the inclusion of background therapies for IPF. Although interpretation of safety data is limited by the relatively short treatment period, in terms of efficacy, changes in FVC at 3 months may be a surrogate marker for mortality, disease progression, and change in FVC at 12 months.(37) Another limitation of the current design is that it was not powered to adequately assess efficacy with relatively small patient numbers in each dose group. Given the small number of participants, we should interpret with caution the observed absolute change in FVC (mL) over the 80 to 320 mg dose range. The majority of participants in this study were male and white, consistent with other registrational trials in IPF. Given the recent regulatory guidance to have clinical trials include underrepresented racial and ethnic populations, as well as the high need for effective treatments for all patients, even those with rare diseases such as IPF, future studies should include a broader representation of patients. Longer-term (52 weeks) treatment in the BEACON-IPF trial will assess the durability of the antifibrotic effects and safety profile, as well as the potential to provide meaningful clinical benefits, such as stabilization of the progressive fibrosis and symptomatic deterioration, in patients with IPF.

In summary, the results of the INTEGRIS-IPF study suggest bexotegrast is well tolerated in patients with IPF with no observed dose dependent relationship for AEs, and exploratory analyses suggest an antifibrotic effect according to FVC, QLF imaging, and circulating levels of ITGB6 and PRO-C3. These results support the need for further studies of bexotegrast for the treatment of IPF.

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Data Sharing Statement

Clinical study data access for research use: Pliant Therapeutics, Inc. (“Pliant”) understands and acknowledges the need to share clinical study data with the research community in an open and transparent manner. In furtherance of its research efforts, a member of the scientific community may request aggregated deidentified clinical data collected during a clinical study after its public disclosure by Pliant and filing of any related intellectual property protection. To the extent that Pliant has any additional supporting documentation or summary data, it may, at its discretion, also make such information available. Pliant will take into consideration any reasonable request that it receives pertaining to clinical data that has been accepted and published by a journal. Prior to receipt of clinical study data, Pliant and the requesting institution shall enter into an agreement which takes into consideration applicable data privacy laws and the use of the clinical study data for research purposes only. All requests for access to clinical study data must be submitted in writing to scientificcommunications@pliantrx.com.

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AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

REFERENCES

1. Decaris ML, Schaub JR, Chen C, Cha J, Lee GG, Rexhepaj M, et al. Dual inhibition of αvβ6 and αvβ1 re$_d$uces fibrogenesis in lung tissue explants from patients with IPF. Respir Res. 2021;22(1):265.

2. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018;378(19):1811-23.

3. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. Respir Res. 2021;22(1):197.

4. Booth AJ, Hadley R, Cornett AM, Dreffs AA, Matthes SA, Tsui JL, et al. Acellular normal and fibrotic human lung matrices as a culture system for in vitro investigation. Am J Respir Crit Care Med. 2012;186(9):866–76.

5. Guo H, Sun J, Zhang S, Nie Y, Zhou S, Zeng Y. Progress in understanding and treating idiopathic pulmonary fibrosis: recent insights and emerging therapies. Front Pharmacol. 2023;14:1205948.

6. Mai TH, Han LW, Hsu JC, Kamath N, Pan L. Idiopathic pulmonary fibrosis therapy development: a clinical pharmacology perspective. Ther Adv Respir Dis. 2023;17:17534666231181537.

7. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-e47.

8. Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. Lancet Respir Med. 2014;2(7):566–72.

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

9. Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. Adv Ther. 2018;35(5):724–36.

10. Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respir Res. 2019;6(1):e000397.

11. Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. Lancet Respir Med. 2017;5(1):33–41.

12. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92.

13. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.

14. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9.

15. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of antifibrotic therapy on mortality and acute exacerbation in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Chest. 2021;160(5):1751–63.

16. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365(12):1079-87.

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

17. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS(®) trials. Respir Med. 2016;113:74–9.

18. Fisher M, Nathan SD, Hill C, Marshall J, Dejonckheere F, Thuresson PO, et al. Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. J Manag Care Spec Pharm. 2017;23(3-b Suppl):S17–S24.

19. Costabel U, Albera C, Lancaster LH, Lin CY, Hormel P, Hulter HN, et al. An open-label study of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (RECAP). Respiration. 2017;94(5):408–15.

20. Cottin V, Koschel D, Günther A, Albera C, Azuma A, Sköld CM, et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. ERJ Open Res. 2018;4(4):00084-2018.

21. Crestani B, Huggins JT, Kaye M, Costabel U, Glaspole I, Ogura T, et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. Lancet Respir Med. 2019;7(1):60–8.

22. John AE, Graves RH, Pun KT, Vitulli G, Forty EJ, Mercer PF, et al. Translational pharmacology of an inhaled small molecule αvβ6 integrin inhibitor for idiopathic pulmonary fibrosis. Nat Commun. 2020;11(1):4659.

23. Saini G, Porte J, Weinreb PH, Violette SM, Wallace WA, McKeever TM, et al. αvβ6 integrin may be a potential prognostic biomarker in interstitial lung disease. Eur Respir J. 2015;46(2):486–94.

24. Bowman WS, Newton CA, Linderholm AL, Neely ML, Pugashetti JV, Kaul B, et al. Proteomic biomarkers of progressive fibrosing interstitial lung disease: a multicentre cohort analysis. Lancet Respir Med. 2022;10(6):593–602.

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

25. Oldham J, Huang Y, Ma SF, Lee CT, Kim J, Pugashetti JV, et al. Proteomic determinants of idiopathic pulmonary fibrosis survival. Am J Respir Crit Care Med . 2024;209(9):1111-1120.

26. Wuyts W, Valenzuela C, Jenkins G, Goldin J, Kim G, Jurek M, et al. Late Breaking Abstract - Safety, tolerability and antifibrotic activity of bexotegrast: Phase 2a INTEGRIS-IPF study (NCT04396756). European Respiratory Journal 2023;62(Suppl. 67):OA1423 (abstract).

27. Lancaster L, Cottin V, Ramaswamy M, Goldin J, Kim G, Bellini J, et al. PLN-74809 Shows Favorable Safety and Tolerability and Indicates Antifibrotic Activity in a Phase 2a Study for the Treatment of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2023;207:A2777 (ATS Abstract 023).

28. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–e68.

29. Kim HG, Tashkin DP, Clements PJ, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol. 2010;28(5 Suppl 62):S26–S35.

30. Cosgrove G, Park E, Bellini J, Adegbite E, Cilli F, Jurek M, et al. PLN-74809, a dual-selective inhibitor of αvβ6 and αvβ1, is well tolerated in over 280 healthy participants. Am J Respir Crit Care Med. 2022;205:A2437 (abstract).

31. Raghu G, Mouded M, Chambers DC, Martinez FJ, Richeldi L, Lancaster LH, et al. A phase IIb randomized study of an anti-αvβ6 monoclonal antibody in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2022;206(9):1128–39.

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

32. Raghu G, Mouded M, Prasse A, Stebbins C, Zhao G, Song G, et al. Randomized phase IIa clinical study of an anti-αvβ6 monoclonal antibody in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2022;206(9):1166–8.

33. Mitra MS, Lancaster K, Adedeji AO, Palanisamy GS, Dave RA, Zhong F, et al. A potent pan-TGFβ neutralizing monoclonal antibody elicits cardiovascular toxicity in mice and cynomolgus monkeys. Toxicol Sci. 2020;175(1):24–34.

34. Mooney JJ, Morris K, Jacobs S, Lefebvre E, Cosgrove G, Wong S, et al. PLN-74809, a dual-selective inhibitor of integrins αvβ6 and αvβ1, shows dose-dependent target engagement in the lungs of patients with idiopathic pulmonary fibrosis (IPF). Am J Respir Crit Care Med. 2022;205:A5254 (abstract).

35. Cosgrove G, Decaris M, Park E, Wong S, Park E, Turner S, et al. PLN-74809, an oral, dual-selective αvβ6/αvβ1 inhibitor in phase 2 clinical trials for idiopathic pulmonary fibrosis (IPF), sustainably reduces transforming growth factor-beta (TGF-β) activity in the lungs of healthy participants with once-daily dosing. Am J Respir Crit Care Med. 2022;205:A5251 (abstract).

36. Paterniti MO, Bi Y, Rekic D, Wang Y, Karimi-Shah BA, Chowdhury BA. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2017;14(9):1395–402.

37. Khan FA, Stewart I, Moss S, Fabbri L, Robinson KA, Johnson SR, et al. Three-month FVC change: a trial endpoint for idiopathic pulmonary fibrosis based on individual participant data meta-analysis. Am J Respir Crit Care Med. 2022;205(8):936–48.

38. Maher TM, Ford P, Brown KK, Costabel U, Cottin V, Danoff SK, et al. Ziritaxestat, a Novel Autotaxin Inhibitor, and Lung Function in Idiopathic Pulmonary

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

Fibrosis: The ISABELA 1 and 2 Randomized Clinical Trials. JAMA. 2023;329(18):1567-78.

39. Maher TM, van der Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. Lancet Respir Med. 2018;6(8):627-35.

40. Strambu IR, Seemayer CA, Fagard LMA, Ford PA, Van der Aa TAK, de Haas-Amatsaleh AA, et al. GLPG1205 for idiopathic pulmonary fibrosis: a phase 2 randomised placebo-controlled trial. Eur Respir J. 2023;61(3).

41. Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, et al. Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis. N Engl J Med. 2022;386(23):2178-87.

42. Nathan SD, Yang M, Morgenthien EA, Stauffer JL. FVC variability in patients with idiopathic pulmonary fibrosis and role of 6-min walk test to predict further change. Eur Respir J. 2020;55(5).

43. Santermans E, Ford P, Kreuter M, Verbruggen N, Meyvisch P, Wuyts WA, et al. Modelling Forced Vital Capacity in Idiopathic Pulmonary Fibrosis: Optimising Trial Design. Adv Ther. 2019;36(11):3059-70.

44. Thabut G, Crestani B, Porcher R, Richeldi L. Missing data in IPF trials: do not let methodological issues undermine a major therapeutic breakthrough. Eur Respir J. 2015;46(3):607-14.

45. Neely ML, Hellkamp AS, Bender S, Todd JL, Liesching T, Luckhardt TR, et al. Lung function trajectories in patients with idiopathic pulmonary fibrosis. Respir Res. 2023;24(1):209.

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

46. Kim HJ, Brown MS, Chong D, Gjertson DW, Lu P, Coy H, et al. Comparison of the quantitative CT imaging biomarkers of idiopathic pulmonary fibrosis at baseline and early change with an interval of 7 months. Acad Radiol. 2015;22(1):70-80.

47. Kafaja S, Clements PJ, Wilhalme H, Tseng CH, Furst DE, Kim GH, et al. Reliability and minimal clinically important differences of forced vital capacity: Results from the Scleroderma Lung Studies (SLS-I and SLS-II). Am J Respir Crit Care Med. 2018;197(5):644-52.

48. Kim GHJ, Goldin JG, Hayes W, Oh A, Soule B, Du S. The value of imaging and clinical outcomes in a phase II clinical trial of a lysophosphatidic acid receptor antagonist in idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2021;15:17534666211004238.

49. Kim GHJ, Weigt SS, Belperio JA, Brown MS, Shi Y, Lai JH, et al. Prediction of idiopathic pulmonary fibrosis progression using early quantitative changes on CT imaging for a short term of clinical 18-24-month follow-ups. Eur Radiol. 2020;30(2):726-34.

50. Sheppard D, Cohen DS, Wang A, Busk M. Transforming growth factor beta differentially regulates expression of integrin subunits in guinea pig airway epithelial cells. J Biol Chem. 1992;267(24):17409–14.

51. Organ LA, Duggan AR, Oballa E, Taggart SC, Simpson JK, Kang'ombe AR, et al. Biomarkers of collagen synthesis predict progression in the PROFILE idiopathic pulmonary fibrosis cohort. Respir Res. 2019;20(1):148.

AJRCCM Articles in Press. Published June 06, 2024 as 10.1164/rccm.202403-0636OC

FIGURE LEGENDS

Figure 1. Study design. *One participant, randomized to placebo, received 320 mg bexotegrast for approximately 1 week due to incorrect study-drug dispensation. No AEs were reported for this participant. They are included in the denominator of the placebo and bexotegrast 320 mg group for the safety analyses. This figure represents the ITT population. AE adverse event, ITT intent-to-treat, QD once daily, Y/N yes/no.

Figure 2. Participant Disposition**.** *AE (n=3), withdrawal of consent (n=1), physician decision (n=1). †AE (n=1); withdrawal of consent (n=2), physician decision (n=1). ‡88 participants were randomized to receive bexotegrast; however, one participant, randomized to placebo, received both placebo and bexotegrast 320 mg for approximately 1 week due to incorrect study-drug dispensation. They are included in the denominator of the placebo and bexotegrast 320 mg group for the safety analyses. AE adverse event.

Figure 3. Change in FVC from Baseline to Week 12 (Efficacy mITT Population). Change in FVC from baseline through Week 12 in all participants receiving (A) 40 mg, (B) 80 mg, (C) 160 mg, and (D) 320 mg bexotegrast compared with placebo. Change from baseline analyzed using an MMRM. *P<0.05 vs. placebo; **P<0.01 vs. placebo. FVC forced vital capacity, LS least squares, mITT modified intent-to-treat, MMRM mixed model for repeated measures; SE standard error.

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Figure 4. Percentage of Participants with FVC (**A**) Relative Decline ≥10% of Predicted and (**B**) Absolute Decline ≥10% of Predicted at Week 12 (Efficacy mITT Population). FVC forced vital capacity, mITT modified intent-to-treat.

Figure 5. Exploratory endpoints: (A) mean change in QLF (%) from Baseline to Week 12, (B) LS mean change from Baseline in plasma ITGB6 relative to placebo at Weeks 4 and 12, and (C) LS mean change from Baseline in serum PRO-C3 relative to placebo at Weeks 4 and 12. The data in panel (A) are from the per CT protocol population (a subset of the ITT population with available HRCT imaging data and HRCT images) who completed the study without any major protocol violations within the prespecified time interval between screening and randomization. The data in panels (B) and (C) are from the PD analysis population. Change from Baseline in biomarker concentration was analyzed using an MMRM.

*P<0.05 vs. placebo; **P<0.01 vs. placebo; ****P<0.0001 vs. placebo.

CT computed tomography, HRCT high-resolution computer tomography, ITGB6 integrin beta-6, ITT intent-to-treat, LS least squares, MMRM mixed model for repeated measures, NPX Normalized Protein eXpression, PRO-C3 type III collagen synthesis neoepitope, PD pharmacodynamic, QLF quantitative lung fibrosis, SE standard error.

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Table 1. Baseline Demographics and Disease Characteristics

Demographics	**Bexotegrast 40 mg (n=22)**	**Bexotegrast 80 mg (n=23)**	**Bexotegrast 160 mg (n=22)**	**Bexotegrast 320 mg (n=22)**	**Bexotegrast pooled (n=89)**	**Placebo pooled (n=31)**
Male sex, n (%)	18 (81.8)	19 (82.6)	16 (72.7)	21 (95.5)	74 (83.1)	27 (87.1)
Female sex, n (%)	4 (18.2)	4 (17.4)	6 (27.3)	1 (4.5)	15 (16.9)	4 (12.9)
Mean age, years (SD)	69.2 (7.11)	74.2 (4.70)	71.5 (6.63)	70.5 (7.14)	71.4 (6.61)	72.1 (6.20)
Race, n (%)						
White	22 (100.0)	21 (91.3)	22 (100.0)	21 (95.5)	86 (96.6)	30 (96.8)
Asian	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.1)	1 (3.2)
Other/unknown/unreported	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.5)	2 (2.2)	0 (0.0)
Mean weight, kg (SD)	86.09 (18.22)	85.89 (14.95)	85.37 (13.51)	88.51 (15.61)	86.46 (15.44)	83.95 (11.41)*
Mean BMI, kg/m^2 (SD)	27.67 (4.21)	28.54 (5.79)	29.28 (4.66)	28.13 (4.08)	28.40 (4.70)	27.33 (2.57)*
Mean time since IPF diagnosis, months (SD)	22.2 (12.44)	28.6 (17.08)	27.8 (12.43)	34.4 (28.97)	28.2 (19.12)	34.0 (21.62)

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Background therapy use, n (%)	17 (77.3)	19 (82.6)	19 (86.4)	18 (81.8)	73 (82.0)	24 (77.4)
None	5 (22.7)	4 (17.4)	3 (13.6)	4 (18.2)	16 (18.0)	7 (22.6)
Nintedanib	12 (54.5)	9 (39.1)	7 (31.8)	10 (45.5)	38 (42.7)	13 (41.9)
Pirfenidone	5 (22.7)	10 (43.5)	12 (54.5)	8 (36.4)	35 (39.3)	11 (35.5)
Mean duration of background therapy at randomization, months (SD)	19.47 (11.53)	20.21 (11.52)	20.07 (11.63)	23.29 (21.76)	20.76 (14.51)	22.55 (17.85)
FVC						
Mean, mL (SD)	2930.63 (789.73)	3155.90 (859.05)	2847.10 (703.84)	3192.00 (678.39)	3032.81 (763.47)	3083.62 (783.34)
Percent of predicted value, mean (SD)	73.47 (14.37)	83.34 (14.61)	78.18 (15.55)	77.48 (15.83)	78.18 (15.26)	78.05 (17.16)
DLco percent predicted, corrected for hemoglobin level, mean (SD)	57.2 (14.74)	51.8 (14.67)	48.6 (15.11)	47.6 (12.97)†	51.3 (14.65)‡	50.1 (15.23)
GAP index stage, n (%)						

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Stage I	11 (50.0)	8 (34.8)	7 (31.8)	7 (31.8)	33 (37.1)	10 (32.3)
Stage II	10 (45.5)	15 (65.2)	13 (59.1)	13 (59.1)	51 (57.3)	18 (58.1)
Stage III	1 (4.5)	0 (0.0)	2 (9.1)	2 (9.1)	5 (5.6)	3 (9.7)

*Data available for 29 participants.

†Data available for 21 participants.

‡Data available for 88 participants.

BMI body mass index, DLco diffusing capacity for carbon monoxide, FVC forced vital capacity, GAP gender-age-physiology, IPF idiopathic pulmonary fibrosis, SD standard deviation.

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Table 2. Nature and Frequency of TEAEs Over 12 Weeks of Treatment

	Participants, n (%)					
Participants with any:	**Bexotegrast 40 mg (n=22)**	**Bexotegrast 80 mg (n=23)**	**Bexotegrast 160 mg (n=22)**	**Bexotegrast 320 mg (n=22)**	**Bexotegrast pooled (n=89)**	**Placebo (n=31)**
TEAE	16 (72.7)	15 (65.2)	14 (63.6)	17 (77.3)	62 (69.7)	21 (67.7)
TEAE related to study drug	4 (18.2)	7 (30.4)	4 (18.2)	4 (18.2)	19 (21.3)	10 (32.3)
Grade ≥3 TEAE	2 (9.1)	0 (0.0)	2 (9.1)	2 (9.1)	6 (6.7)	2 (6.5)
Grade ≥3 TEAE related to study drug	0 (0.0)	0 (0.0)	1 (4.5)*	0 (0.0)	1 (1.1)	0 (0.0)
SAE	1 (4.5)	0 (0.0)	2 (9.1)	1 (4.5)	4 (4.5)	3 (9.7)
SAE related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to interruption of study drug	0 (0.0)	0 (0.0)	1 (4.5)†	1 (4.5)‡	2 (2.2)	0 (0.0)
TEAE leading to withdrawal of study drug	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)‡,§,‖	3 (3.4)	3 (9.7)

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TEAE leading to early termination from the study	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)[‡,§,ǁ]	3 (3.4)	2 (6.5)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)[§]	1 (1.1)	0 (0.0)
TEAEs occurring in ≥5% of participants in any group (any causality)						
Diarrhea	2 (9.1)	5 (21.7)	5 (22.7)	3 (13.6)	15 (16.9)	3 (9.7)
Fatigue	2 (9.1)	2 (8.7)	1 (4.5)	2 (9.1)	7 (7.9)	2 (6.5)
Nausea	1 (4.5)	1 (4.3)	2 (9.1)	0 (0.0)	4 (4.5)	2 (6.5)
Dyspnea	0 (0.0)	1 (4.3)	2 (9.1)	1 (4.5)	4 (4.5)	0 (0.0)
Atrioventricular block first degree	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)	2 (2.2)	2 (6.5)
Vomiting	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	2 (2.2)	0 (0.0)
COVID-19	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	2 (2.2)	0 (0.0)
Cough	1 (4.5)	1 (4.3)	1 (4.5)	1 (4.5)	4 (4.5)	2 (6.5)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.1)	2 (6.5)
IPF/Pulmonary fibrosis	1 (4.5)	0 (0.0)	1 (4.5)	0 (0.0)	2 (2.3)	3 (9.7)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)

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Skin abrasion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)

*Grade 3 event of diarrhea in a participant taking pirfenidone.

†Participant had a TEAE of COVID-19 that led to interruption of study drug.

‡Abdominal pain/diarrhea in participant with pre-existing ulcerative colitis.

§Acute respiratory failure in a GAP Stage III participant with pre-existing coronary artery disease and atrial fibrillation following elective atrioventricular node ablation.

‖Diarrhea in participant with concomitant use of nintedanib.

COVID-19 coronavirus disease 2019, GAP gender-age-physiology, SAE serious adverse event, TEAE, treatment-emergent adverse event.

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Table 3. Nature and Frequency of TEAEs With or Without Background Therapy Over 12 Weeks of Treatment

	Participants, n (%)					
Participants with any:	**Pooled bexotegrast, no background therapy (n=16)**	**Pooled bexotegrast + nintedanib (n=38)**	**Pooled bexotegrast + pirfenidone (n=35)**	**Placebo (n=7)**	**Placebo + nintedanib (n=13)**	**Placebo + pirfenidone (n=11)**
TEAE	12 (75.0)	10 (76.9)	20 (57.1)	5 (71.4)	33 (86.8)	6 (54.5)
TEAEs occurring in ≥5% of participants in any overall group (any causality)						
Diarrhea	1 (6.3)	16 (42.1)	2 (5.7)	2 (28.6)	2 (15.4)	0 (0.0)
Fatigue	2 (12.5)	1 (2.6)	4 (11.4)	1 (14.3)	0 (0.0)	1 (9.1)
Nausea	2 (12.5)	1 (2.6)	1 (2.9)	1 (14.3)	1 (7.7)	1 (9.1)
Dyspnea	2 (12.5)	3 (7.9)	3 (8.6)	0 (0.0)	1 (7.7)	0 (0.0)
Atrioventricular block first degree	1 (6.3)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	2 (18.2)
Vomiting	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19	1 (6.3)	2 (5.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)

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Cough	1 (6.3)	3 (7.9)	2 (5.7)	1 (14.3)	1 (7.7)	1 (9.1)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	1 (2.9)
IPF/Pulmonary fibrosis	0 (0.0)	3 (7.9)	3 (8.6)	0 (0.0)	0 (0.0)	1 (9.1)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (7.7)	1 (9.1)
Skin abrasion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (9.1)

COVID-19 coronavirus disease 2019, TEAE, treatment-emergent adverse event.

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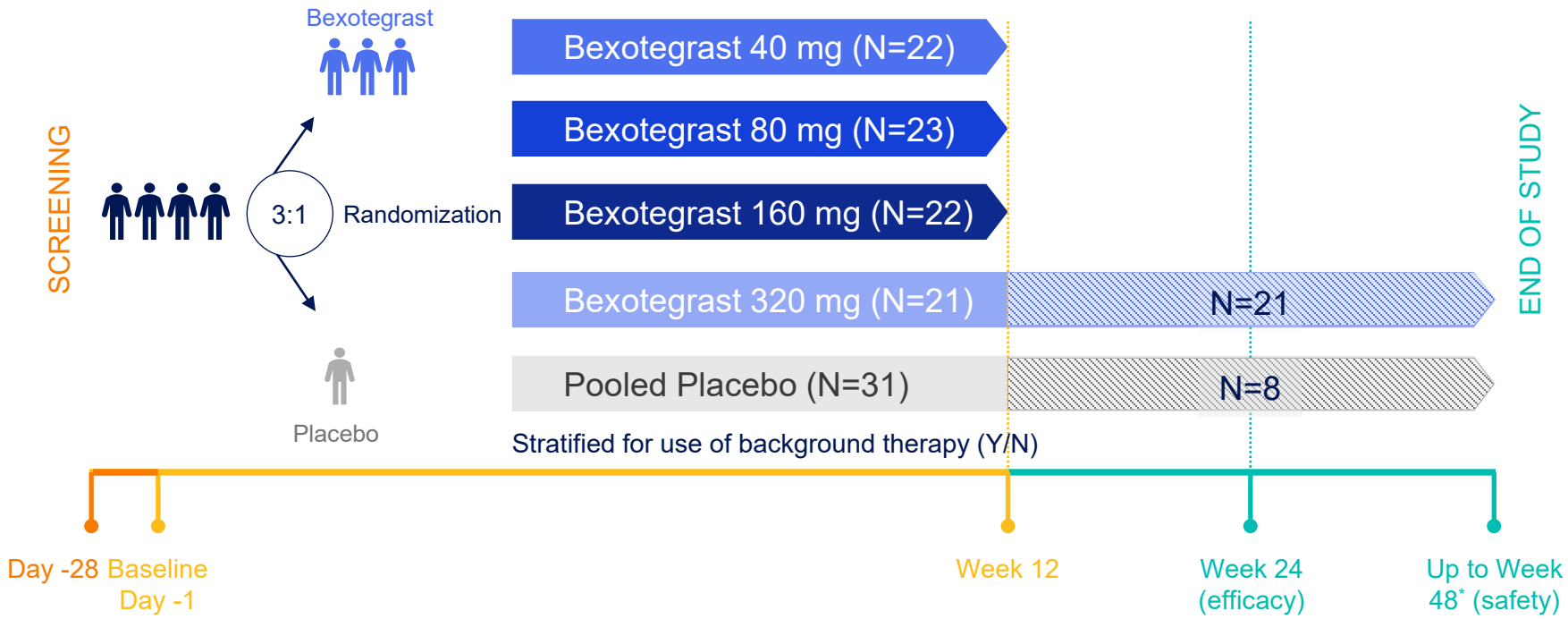

Figure 1

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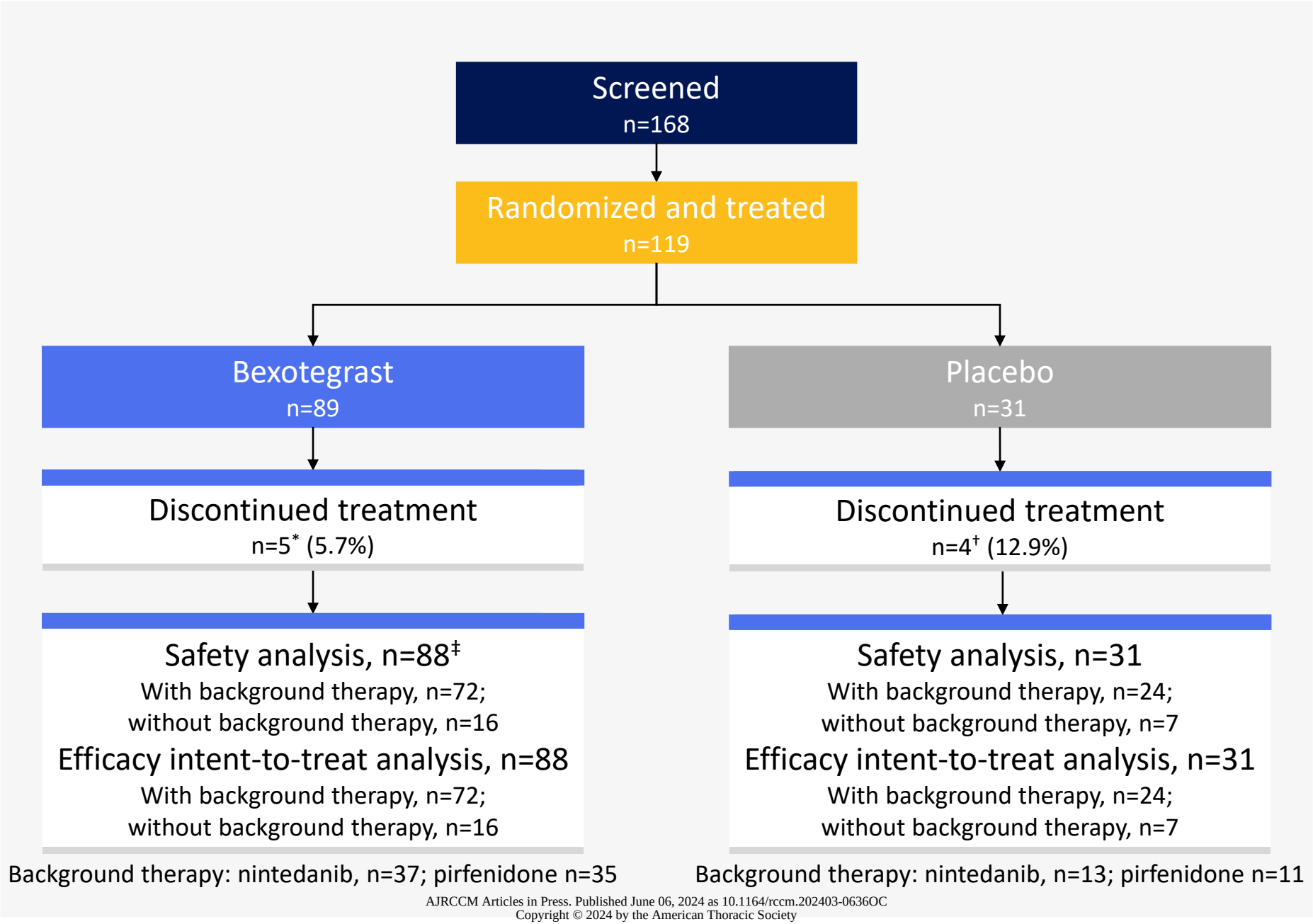

Figure 2

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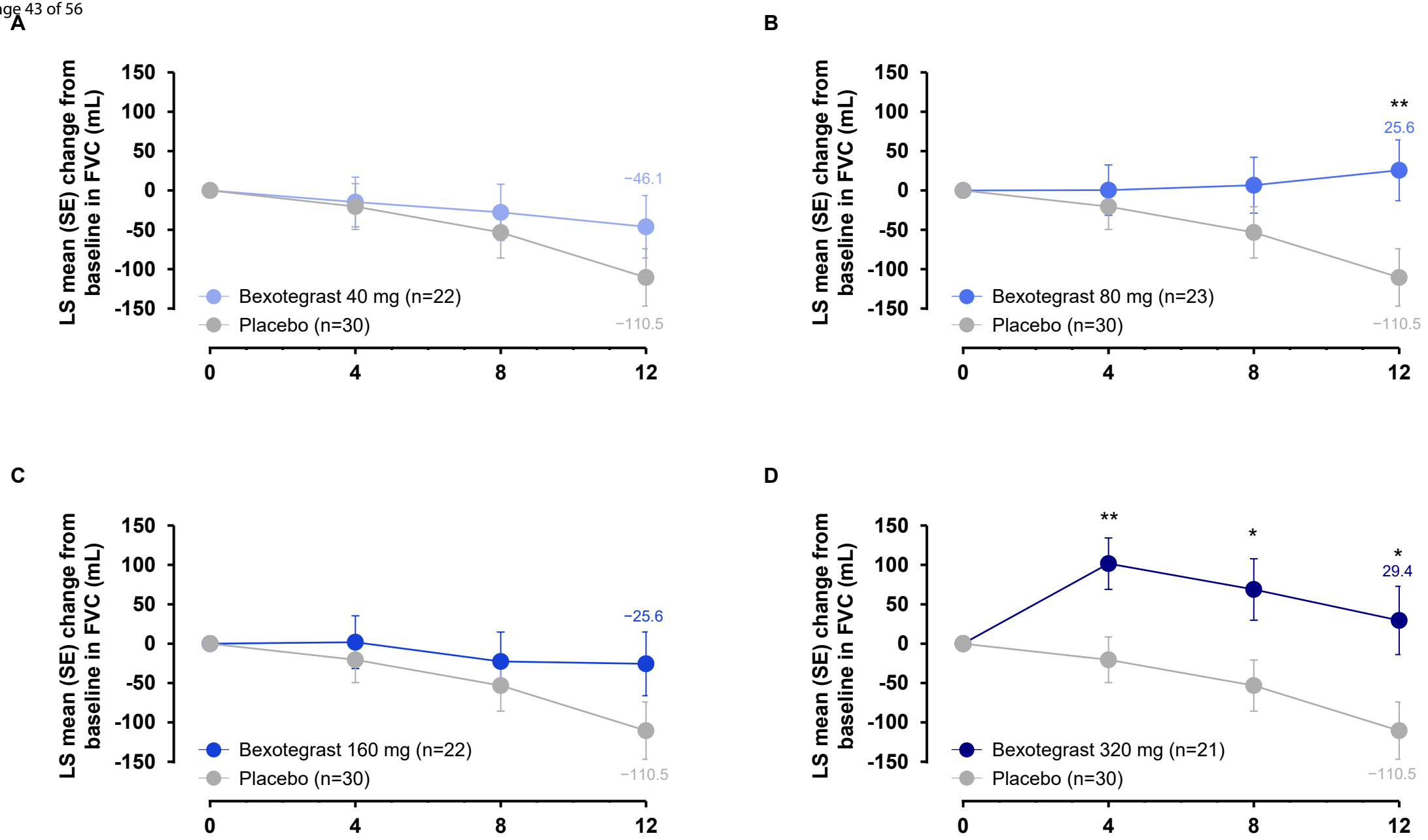

Figure 3

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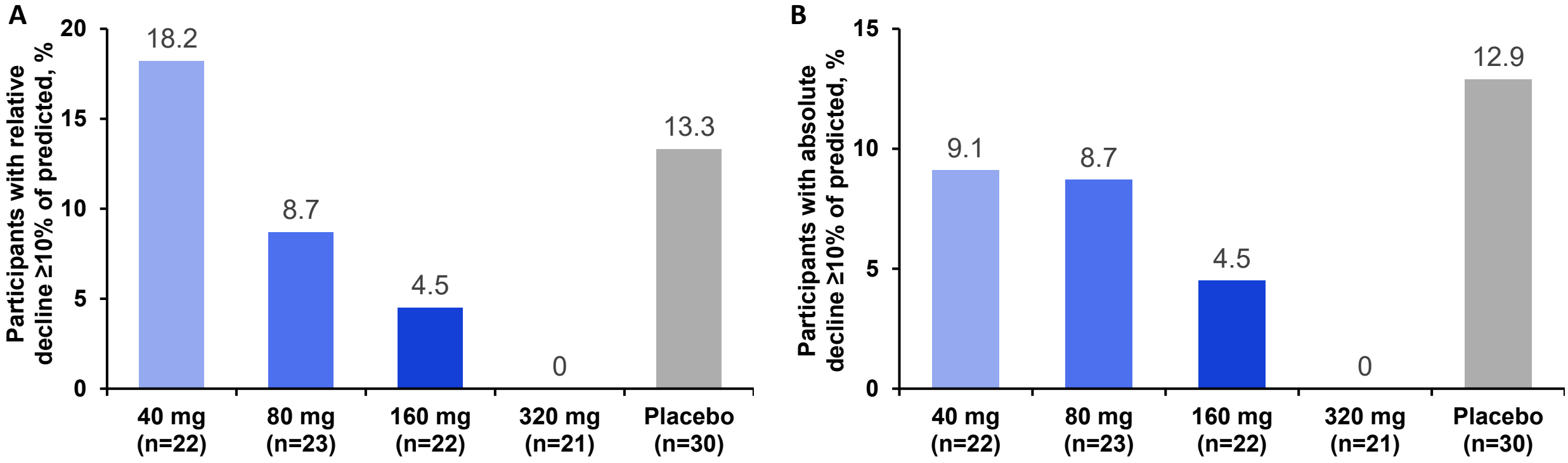

Figure 4

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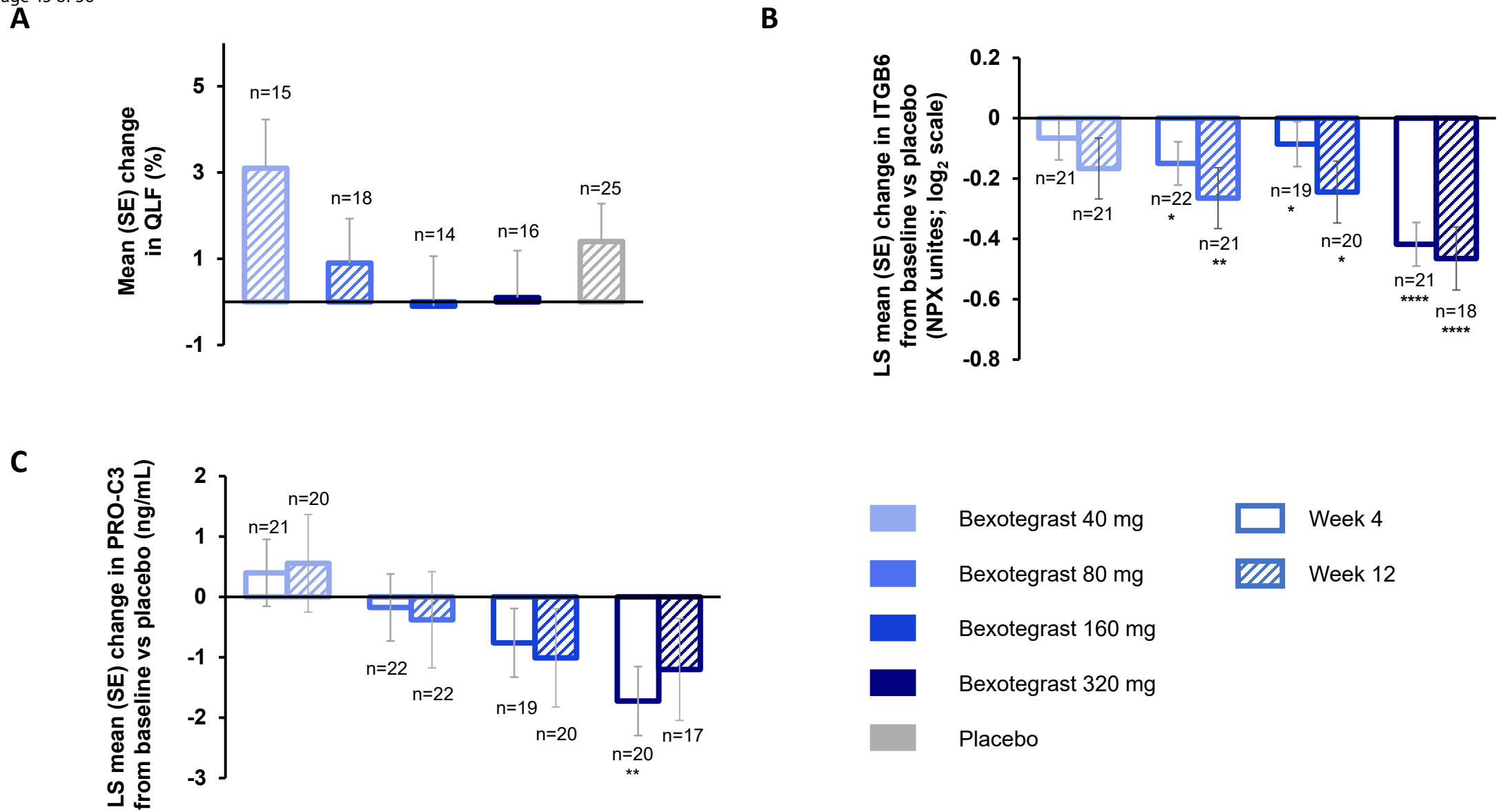

Figure 5

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Bexotegrast in Patients with Idiopathic Pulmonary Fibrosis: The INTEGRIS-IPF Study

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ONLINE DATA SUPPLEMENT

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SAMPLE SIZE

The sample size was chosen on the basis of providing an initial characterization of the safety and tolerability of bexotegrast, qualitatively, across a wide dose range (ie, 40 to 320 mg) while balancing the potential risks associated with blocking the activation of TGF-β in participants with IPF. Approximately 20 participants per bexotegrast dose level would be sufficient to evaluate the incidence of TEAEs across doses and allow for meaningful comparisons with placebo. Given the number of 28 participants per dose cohort and the 3:1 randomization ratio for active:placebo, a sample size of 21 participants receiving bexotegrast was chosen for the study.

INCLUSION AND EXCLUSION CRITERIA

Additional inclusion criteria were: ≥40 years of age; a diagnosis of IPF for up to 5 years prior to screening according to ATS/ERS/JRS/ALAT 2018 guidelines;(E1) FVC ≥45% of predicted (historical FVC for entry in the study was permitted if within 1 month of screening); diffusing capacity of the lungs for carbon monoxide (DLco) (hemoglobin adjusted) ≥30% (historical DLco was permitted if within 1 month of screening); and estimated glomerular filtration rate ≥50 mL/min according to the Cockcroft-Gault equation.

Additional exclusion criteria included: clinical evidence of infection that could affect FVC measurement at screening or randomization; any condition that could prevent the correct assessment of spirometry performance; known or suspected acute IPF exacerbation within 6 months of screening; emphysema to a greater extent than fibrotic changes on the most recent HRCT scan, as determined by central HRCT review.

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HRCT ASSESSMENTS

Standardized volumetric thin section non-contrast HRCT chest imaging was performed at the trial site with electronic transmission, and central review for eligibility and quantitative analysis of the extent of pulmonary fibrosis, including QLF.(E2) HRCT images for QLF extent were taken at Screening and Week 12. For baseline QLF, a HRCT scan performed within 1 month may be used if meets the central reader specifications.

REFERENCES

E1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–e68.

E2. Kim HG, Tashkin DP, Clements PJ, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol. 2010;28(5 Suppl 62):S26–S35.

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Table E1. Nature and frequency of TEAEs (participants receiving a background therapy**).**

	Participants, n (%)					
Participants with any:	**Bexotegrast 40 mg (n=17)**	**Bexotegrast 80 mg (n=19)**	**Bexotegrast 160 mg (n=19)**	**Bexotegrast 320 mg (n=18)**	**Bexotegrast pooled (n=73)**	**Placebo (n=24)**
TEAE	13 (76.5)	12 (63.2)	12 (63.2)	13 (72.2)	50 (68.5)	16 (66.7)
TEAE related to study drug	4 (23.5)	5 (26.3)	4 (21.1)	3 (16.7)	16 (21.9)	7 (29.2)
Grade ≥3 TEAE	2 (11.8)	0 (0.0)	2 (10.5)	1 (5.6)	5 (6.8)	2 (8.3)
Grade ≥3 TEAE related to study drug	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.4)	0 (0.0)
SAE	1 (5.9)	0 (0.0)	2 (10.5)	0 (0.0)	3 (4.1)	3 (12.5)
SAE related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to interruption of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to withdrawal of study drug	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.4)	2 (8.3)
TEAE leading to early termination from the study	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.4)	1 (4.2)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAE serious adverse event, TEAE treatment-emergent adverse event.

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Table E2. Nature and frequency of TEAEs (no background therapy use).

	Participants, n (%)					
Participants with any:	**Bexotegrast 40 mg (n=5)**	**Bexotegrast 80 mg (n=4)**	**Bexotegrast 160 mg (n=3)**	**Bexotegrast 320 mg (n=4)**	**Bexotegrast pooled (n=16)**	**Placebo (n=7)**
TEAE	3 (60.0)	3 (75.0)	2 (66.7)	4 (100.0)	12 (75.0)	5 (71.4)
TEAE related to study drug	0 (0.0)	2 (50.0)	0 (0.0)	1 (25.0)	3 (18.8)	3 (42.9)
Grade ≥3 TEAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (6.3)	0 (0.0)
Grade ≥3 TEAE related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (6.3)	0 (0.0)
SAE related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to interruption of study drug	0 (0.0)	0 (0.0)	1 (33.3)	1 (25.0)	2 (12.5)	0 (0.0)
TEAE leading to withdrawal of study drug	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (12.5)	1 (14.3)
TEAE leading to early termination from the study	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (12.5)	1 (14.3)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (6.3)	0 (0.0)

SAE serious adverse event, TEAE treatment-emergent adverse event.

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Table E3. Predicted total bexotegrast C_{max} and AUC_{0-24}.

	Day 1 GM (GCV%), n		**Day 28 GM (GCV%), n**		**Day 84 GM (GCV%), n**	
	C_{max}* ng/mL	**$AUC_{0–24}$* ng×hr/mL**	**C_{max}* ng/mL**	**$AUC_{0–24}$* ng×hr/mL**	**C_{max}* ng/mL**	**$AUC_{0–24}$* ng×hr/mL**
Bexotegrast 40 mg	605 (46.6), 22	7810 (48.2), 22	919 (53.6), 22	13800 (62.4), 22	881 (44.1), 17	13000 (50.3), 17
Bexotegrast 80 mg	982 (53.3), 23	13200 (47.9), 23	1550 (50.0), 23	23800 (52.3), 23	1540 (52.8), 22	23300 (55.0), 22
Bexotegrast 160 mg	1720 (36.8), 22	22900 (34.9), 22	2590 (36.4) 21	38700 (41.1), 21	2620 (39.5), 18	39600 (43.0), 18
Bexotegrast 320 mg	2730 (29.4), 21	37500 (28.0), 21	4203.5 (30.0), 21	64500 (38.2), 21	4230 (28.7), 17	66800 (32.2), 17

$AUC_{0–24}$ area under the concentration time curve from time 0 to 24 hours post-dose, C_{max} maximum concentration, GCV% geometric coefficient of variation, GM geometric mean.

*C_{max} and AUC_{0-24} were predicted from a population pharmacokinetic model developed previously using pharmacokinetic data from Phase 1 studies.

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Table E4. Predicted unbound bexotegrast C_{max} and $AUC_{0\text{-}24}$.

	Day 1 GM (GCV%), n		Day 28 GM (GCV%), n		Day 84 GM (GCV%), n	
	C_{max}* ng/mL	**$AUC_{0–24}$* ng×hr/mL**	**C_{max}* ng/mL**	**$AUC_{0–24}$* ng×hr/mL**	**C_{max}* ng/mL**	**$AUC_{0–24}$* ng×hr/mL**
Bexotegrast 40 mg	1.77 (58.6), 22	22 (54.2), 22	2.85 (64.6), 22	40.6 (67.1), 22	2.69 (58.1), 17	38 (60.5), 17
Bexotegrast 80 mg	3.22 (69.5), 23	40.7 (57.0), 23	5.68 (66.3), 23	79.7 (60.7), 23	5.52 (69.1), 22	76.3 (62.4), 22
Bexotegrast 160 mg	6.25 (53.1), 22	74.6 (40.7), 22	12.2 (52.9), 21	153 (47.5), 21	12.4 (61.0), 18	157 (54.5), 18
Bexotegrast 320 mg	16.1 (64.3), 21	176.3 (38.1), 21	42.9 (72.1), 21	435.1 (49.3), 21	42.2 (74.2), 17	445 (45.0), 17

$AUC_{0–24}$ area under the concentration time curve from time 0 to 24 hours post-dose, C_{max} maximum concentration, GCV% geometric coefficient of variation, GM geometric mean.

*C_{max} and $AUC_{0\text{-}24}$ were predicted from a population pharmacokinetic model developed previously using pharmacokinetic data from Phase 1 studies.

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Figure E1. Change in FVC from Baseline to Week 12 (Efficacy mITT Population). Change in FVC from baseline through Week 12 in the pooled bexotegrast population (participants receiving 40 mg, 80 mg, 160 mg, and 320 mg bexotegrast) compared with placebo. Change from baseline analyzed using an MMRM. **P<0.01 vs. placebo. FVC forced vital capacity, LS least squares, mITT modified intent-to-treat, MMRM mixed model for repeated measures; SE standard error.

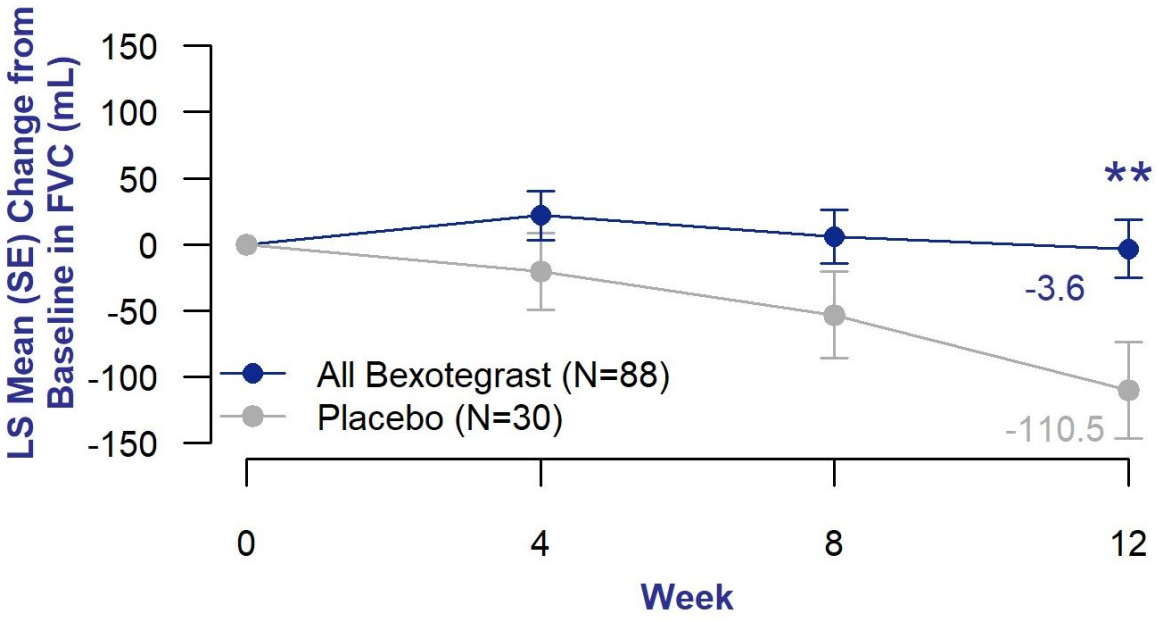

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Figure E2. Change in FVC from Baseline through Week 12 in (A) those receiving background therapy at the time of screening, and (B) those not receiving background therapy at the time of Screening. Change from Baseline analyzed using an MMRM. ***P*<0.01 vs. placebo. FVC forced vital capacity, LS least squares, mITT modified intent-to-treat, MMRM mixed model for repeated measures, SE standard error.

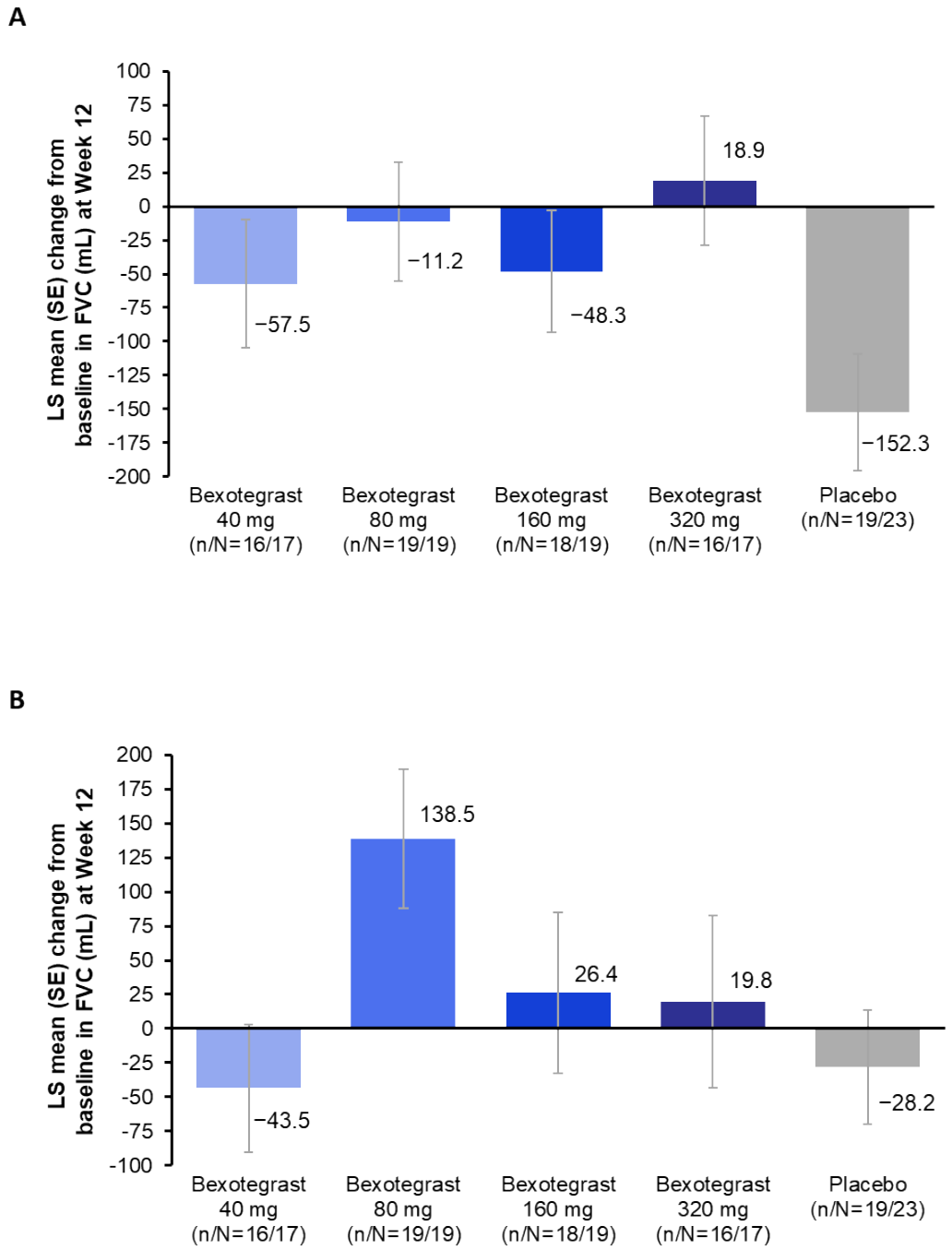

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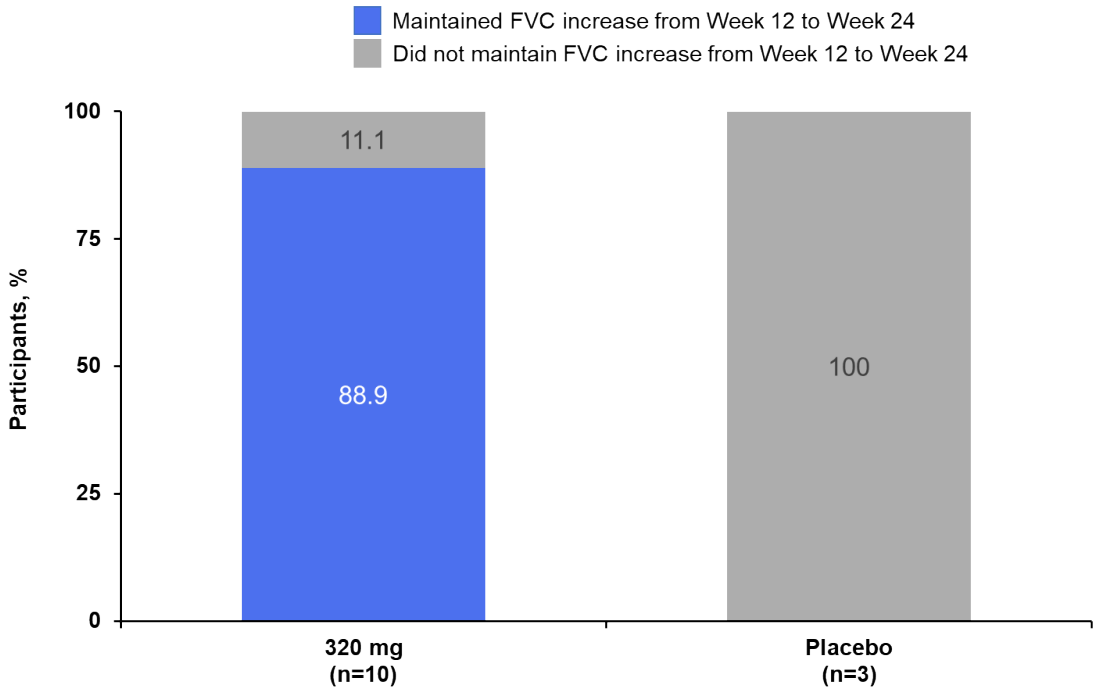
Figure E3. Maintenance of FVC Increase from Week 12 to Week 24 (Efficacy ITT Population). Particiapnts included those in the bexotegrast 320-mg group who had an increase in FVC at Week 12 compared with baseline, and if that increase was maintained to Week 24. FVC forced vital capacity, ITT intent-to-treat.



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INTEGRIS-IPF | A study exploring whether bexotegrast is well tolerated and can improve lung function in adults with idiopathic pulmonary fibrosis

1 WHAT WAS THE STUDY AND WHY WAS IT DONE?

Idiopathic pulmonary fibrosis (IPF) is a rare disease that affects the lungs and worsens over time. The tissue around and between the air sacs in the lungs becomes scarred and thickened, making it increasingly more difficult to breathe.

There are 2 approved medicines for IPF, pirfenidone and nintedanib, but they do not stop IPF from continuing to get worse and do not improve the symptoms of people with this disease.

The phase 2 **INTEGRIS-IPF** study wanted to discover if people with IPF who took

bexotegrast or **placebo**

had side effects and if their lung function related to their IPF improved.

2 WHAT MEDICINES WERE USED IN THIS STUDY?

Bexotegrast is a potential new medicine that is being evaluated in people with IPF. It is not yet approved.

Bexotegrast works to stop two receptors ($\alpha_v\beta_6$ and $\alpha_v\beta_1$) that are found at higher levels in a diseased lung and contribute to IPF progression.

These receptors can release a protein called TGF-β, which promotes thickening and scarring of the lungs.

Bexotegrast is taken by mouth once a day.

Placebo is a treatment which looks like the medicine but has no medical effect.

Placebo is taken by mouth once a day.

3 WHO TOOK PART IN THIS STUDY?

This was a double-blind, randomized study, which means that each person was put into 1 of 2 treatment groups by chance, and neither the people who took the medicine nor the researchers knew which treatment (**bexotegrast** or **placebo**) was being given.

119 adults with IPF were included in this study.

88 were given **bexotegrast** every day for at least 12 weeks.

31 were given **placebo** every day for at least 12 weeks.

39 sites across North America, Europe, Australia, and New Zealand participated in this study.

About **80%** of people were also **taking either pirfenidone or nintedanib**.

4 WHAT WERE THE MAIN FINDINGS OF THIS STUDY?

How many adults had side effects?

70% Bexotegrast — **68%** Placebo

Had side effects during the study for any reason.

21% Bexotegrast — **32%** Placebo

Had side effects that were related to the study medicine.

No one had any serious side effects (death, hospitalization) related to the medicine during the study.

Using **bexotegrast** alone or with pirfenidone or nintedanib was well tolerated.

How well did the treatment work?

People taking **bexotegrast** had a slower decline in lung function compared with people who took **placebo**.

Bexotegrast was well tolerated in patients with IPF and may slow the decline of lung function. Additional studies are evaluating this further.

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