ORIGINAL ARTICLE

Bexotegrast in Patients with Idiopathic Pulmonary Fibrosis
The INTEGRIS-IPF Clinical Trial

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Abstract

Rationale: Idiopathic pulmonary fibrosis (IPF) is a rare and progressive disease that 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, orally and once daily, bexotegrast at 40 mg, 80 mg, 160 mg, or 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 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. Participants who were treated with bexotegrast experienced a reduction in FVC decline over 12 weeks compared with those who received 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 versus 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.

Clinical trial registered with www.clinicaltrials.gov (NCT04396756).

Keywords: safety; efficacy; IPF; fibrotic disease

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A complete list of PLN-74809-IPF-202 Trial Investigators may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: The currently approved agents for idiopathic pulmonary fibrosis (IPF), pirfenidone and nintedanib, are therapeutic options for patients with IPF; however, neither halt the progression of IPF nor consistently improve quality of life, and both have long-term tolerability issues. Bexotegrast (PLN-74809) is an oral, once-daily investigational drug that blocks the activation of transforming growth factor β (TGF-β) by preventing integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ 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: The results of the INTEGRIS-IPF study suggest that bexotegrast is well tolerated in patients with IPF, and exploratory analyses suggest an antifibrotic effect based on FVC, 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.

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 drug halts the progression of IPF nor consistently improves 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 β (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, 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 (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 of 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 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. The efficacy of bexotegrast in terms of FVC, quantitative lung fibrosis (QLF), and biomarkers of fibrosis was 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 the 2018 guidelines of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax (28); FVC percent predicted ⩾45%; hemoglobin-adjusted D_{LCO} ⩾30%; and a life expectancy of 6 months or longer. Background therapy for IPF with pirfenidone or nintedanib was permitted, provided that these drugs had been administered at a stable dose for 3 months or longer before screening. Key exclusion criteria included receiving any nonapproved agent intended for the treatment of pulmonary fibrosis or IPF and an FEV_1/FVC ratio of $<$0.7. (For additional inclusion and exclusion criteria, *see* the online supplement.)

Study Design

INTEGRIS-IPF (PLN-74809-IPF-202; ClinicalTrials.gov: NCT04396756) was a Phase-2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study that was conducted across 39 sites in North America, Europe, Australia, and New Zealand. This study assessed the effects of treatment with bexotegrast or placebo for at least 12 weeks in patients with IPF (Figure 1). The last study visit took place approximately 14 days after the last dose of the study drug.

Participants were randomized to 80, 160, or placebo in that cohort (40 mg or placebo; 80 mg, 160 mg or placebo; and

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 have been accepted and published by a journal. Before receipt of clinical study data, Pliant and the requesting institution shall enter into an agreement that 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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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article. Please also see the supplement for a plain-language summary infographic that accompanies this article.

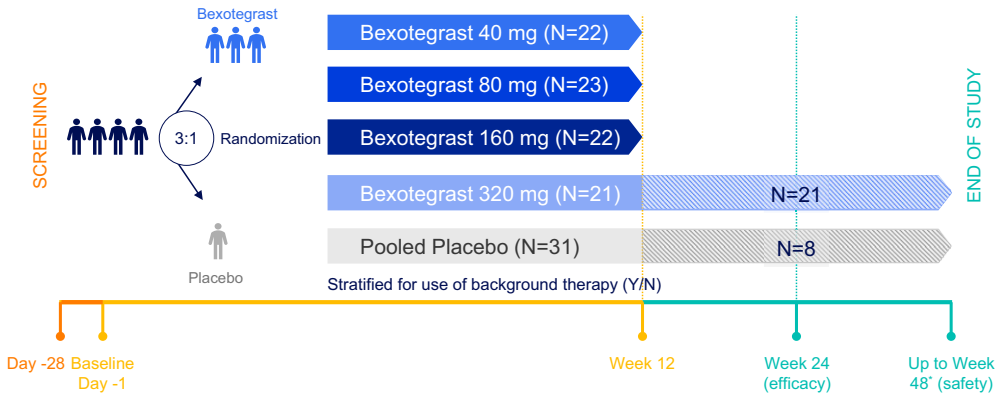

Figure 1. Study design. *One participant, randomized to placebo, received 320 mg bexotegrast for approximately 1 week because of incorrect study-drug dispensation. No adverse events were reported for this participant. They are included in the denominator of the placebo and 320-mg bexotegrast group for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

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 or not receiving 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 respective 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, adverse events and concomitant medications, pharmacokinetic sampling, FVC (milliliters and percent predicted), FEV_1, QLF extent, and the 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 and area under the concentration time curve from Time 0 to 24 hours postdose 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 (%) was assessed by high-resolution computed tomography (29), with central quality control, prebaseline and at Week 12. We also conducted analyses of changes from baseline to Week 12 in fibrosis-related biomarkers, serum type III collagen synthesis neoepitope (PRO-C3), and plasma integrin β6 (ITGB6).

Statistical Analysis

A sample size of approximately 21 participants per treatment group was expected to provide a meaningful evaluation of safety, tolerability, and pharmacokinetics of bexotegrast in patients with IPF (for additional details, *see* the online supplement). 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 that occurred during treatment through a 2-week follow-up period. The intent-to-treat (ITT) population included all randomized participants and the modified ITT 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 × Visit interaction as terms in the model with an unstructured covariance structure: Preplanned separate subgroup analyses were performed both for participants who received a background therapy and for those who did not. 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 MMRM analyses of FVC and biomarkers under the assumption that they were missing at random. As this was an exploratory study, no adjustment for multiplicity was planned.

For the quantitative imaging, the per–computed tomography protocol population included the subset of the ITT population with scans at baseline and Week 12 that met technical evaluability criteria per the high-resolution computed tomography imaging protocol (e.g., participants with paired examinations that met technical specifications for quantitative assessment). QLF extent is reported using observed means, SEs, and proportions.

Results

Study Participants

In total, 119 participants met the eligibility criteria and were randomized between September 2020 and June 2022 to receive, orally and once daily, bexotegrast at 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 because of incorrect study-drug dispensation. This participant was included in the denominator of both treatment groups for baseline demographics and

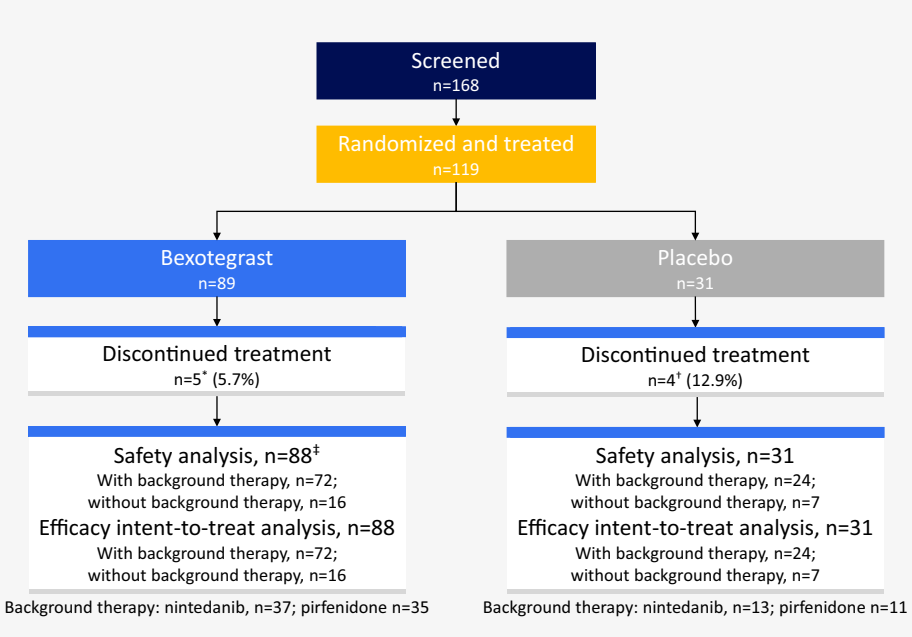

Figure 2. Participant disposition. *Adverse event ($n = 3$), withdrawal of consent ($n = 1$), physician decision ($n = 1$). †Adverse event ($n = 1$), withdrawal of consent ($n = 2$), physician decision ($n = 1$). ‡Eighty-eight participants were randomized to receive bexotegrast; however, one participant,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

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 ages were 71.4 years (SD = 6.61) for bexotegrast-treated participants and 72.1 years (SD = 6.20) for placebo-treated participants. Approximately 80% of participants were receiving background therapy. Baseline FVC volume and percent predicted were comparable between treatment groups. Overall, 92% of participants completed the 12-week treatment period. A total of 9 participants prematurely discontinued treatment—5 (5.7%) in the pooled bexotegrast group and 4 (12.9%) in the placebo group—primarily because of 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, 3, E1, and E2 in the online 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%) participants in the bexotegrast group and 1/3 (33.3%) participants in the placebo group 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 preexisting 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 because of intercurrent coronavirus disease (COVID-19) ($n = 1$), diarrhea ($n = 2$), and ileus and acute kidney injury ($n = 1$). Two participants discontinued bexotegrast because of mild diarrhea ($n = 1$ receiving background nintedanib; $n = 1$ receiving no background therapy and having preexisting ulcerative colitis). Dose reduction of bexotegrast was not allowed per protocol. No serious adverse events were assessed as being related to the study drug.

TEAEs of IPF/pulmonary fibrosis were reported in 2.3% of participants in the bexotegrast group and 9.7% of participants in the placebo group. Only one of these events was reported as an acute exacerbation of IPF in a participant who had completed 12 weeks of treatment with 160 mg bexotegrast and experienced the event 11 days after the 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 Stage III IPF and preexisting coronary artery disease and chronic refractory atrial fibrillation in the 320-mg bexotegrast group experienced a serious and fatal adverse event of acute respiratory failure after elective atrioventricular node ablation.

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

Pharmacokinetics

Predicted total and unbound exposures (maximum concentration and area under the concentration time curve from Time 0 to 24 hours postdose) of bexotegrast in participants with IPF increased approximately

Table 1. Baseline Demographics and Disease Characteristics

Demographics	Bexotegrast					Placebo
	40 mg (*n* = 22)	80 mg (*n* = 23)	160 mg (*n* = 22)	320 mg (*n* = 22)	Pooled (*n* = 89)	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)
Age, yr, mean (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)
Weight, kg, mean (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)*
BMI, kg/m^2, mean (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)*
Time since IPF diagnosis, mo, mean (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)
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)
Duration of background therapy at randomization, mo, mean (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, ml, mean (SD)	2,930.63 (789.73)	3,155.90 (859.05)	2,847.10 (703.84)	3,192.00 (678.39)	3,032.81 (763.47)	3,083.62 (783.34)
FVC percent 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)
D_{LCO} 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* (%)						
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)

Definition of abbreviations: BMI = body mass index; GAP = gender-age-physiology; IPF = idiopathic pulmonary fibrosis.
*Data available for 29 participants.
†Data available for 21 participants.
‡Data available for 88 participants.

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

Nature of TEAE	Participants, *n* (%)					
	Bexotegrast					
	40 mg (*n* = 22)	80 mg (*n* = 23)	160 mg (*n* = 22)	320 mg (*n* = 22)	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)
TEAE ⩾Grade 3	2 (9.1)	0 (0.0)	2 (9.1)	2 (9.1)	6 (6.7)	2 (6.5)
TEAE ⩾Grade 3 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)
TEAE leading to early termination from the study	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)‡,§,‖	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)
Skin abrasion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)

Definition of abbreviations: COVID-19 = coronavirus disease; GAP = gender-age-physiology; IPF = idiopathic pulmonary fibrosis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
*Grade 3 event of diarrhea in a participant taking pirfenidone.
†Participant had a TEAE of COVID-19 that led to the interruption of the study drug.
‡Abdominal pain/diarrhea in a participant with preexisting ulcerative colitis.
§Acute respiratory failure in a GAP Stage III participant with preexisting coronary artery disease and atrial fibrillation after elective atrioventricular node ablation.
‖Diarrhea in a participant with concomitant use of nintedanib.

proportionally with dose (*see* Tables E3 and E4).

Efficacy (Exploratory Endpoints)

Bexotegrast treatment resulted in reduced FVC decline over 12 weeks compared with placebo. In the modified ITT population, in which 81% of the participants received background therapy, changes in FVC from baseline to Week 12 were −46.1 ml (SE = 39.64), 25.6 ml (SE = 38.57), −25.6 ml (SE = 40.49), and 29.4 ml (SE = 43.35), respectively, for participants in the groups receiving 40, 80, 160, and 320 mg bexotegrast and −3.6 (SE = 21.97) for the pooled bexotegrast treatment cohort, compared with −110.5 ml (SE = 36.38) for participants in the placebo group (Figures 3 and E1). At Week 12, changes in FVC with bexotegrast were statistically significant compared with placebo in the groups who received 80 mg (difference: 136.1 ml; $P = 0.0094$) and 320 mg bexotegrast (difference: 139.9 ml; $P = 0.0124$). The treatment effect of bexotegrast was observed in participants receiving or not receiving background therapy for IPF (*see* Figure E2). In the extension study, of patients taking 320 mg bexotegrast 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 (*see* Figure E3).

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 doses at 80, 160 and 320 mg and that continued to be significant and declined 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 compared with placebo at Week 12 was observed for the 80- and 160-mg doses compared with Week 4 (Figure 5C).

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 (for a plain-language infographic, *see* the online supplement). The most common

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

Nature of TEAE	Participants, *n* (%)					
	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)
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 (9.1)
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)

Definition of abbreviations: COVID-19 = coronavirus disease; IPF = idiopathic pulmonary fibrosis; TEAE = treatment-emergent adverse event.

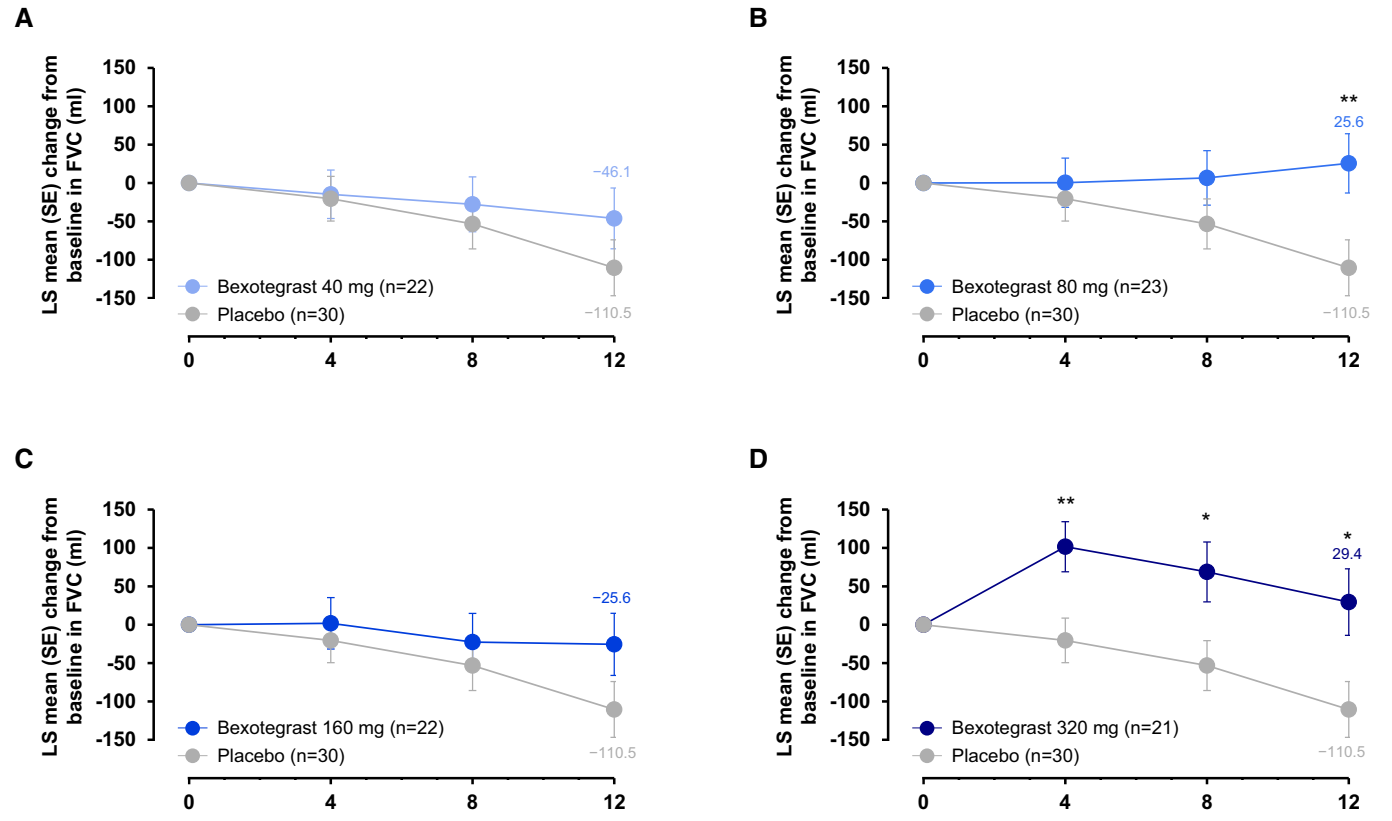

Figure 3. Change in FVC from baseline to Week 12 (efficacy for modified intent-to-treat population). (*A–D*) Change in FVC from baseline through Week 12 in all participants receiving (*A*) 40 mg, (*B*) 80 mg, (*C*) 160 mg, and (*D*) 320 mg bexotegrast compared with placebo. Change from baseline was analyzed using a mixed model for repeated measures. *$P < 0.05$ versus placebo. **$P < 0.01$ versus placebo. LS = least squares.

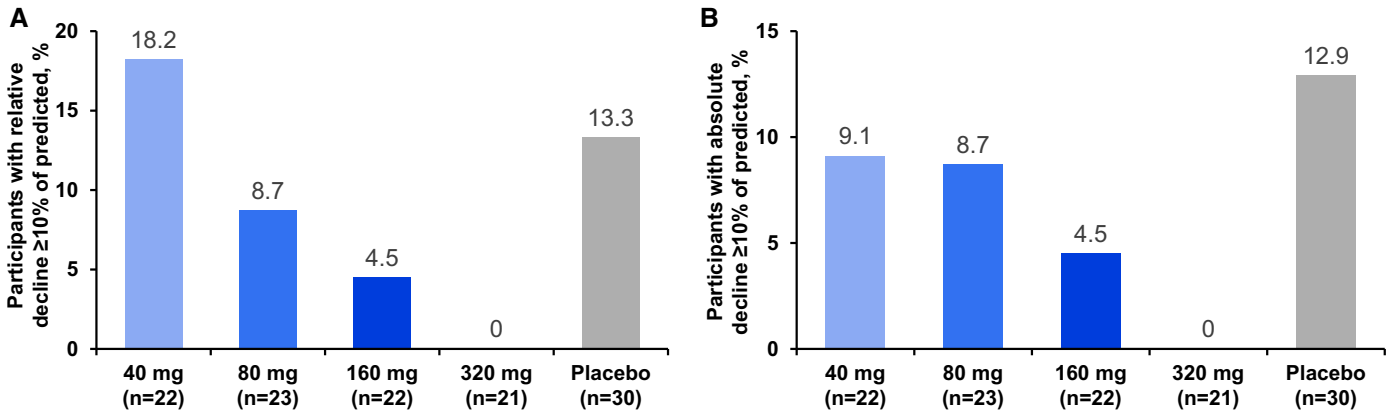

Figure 4. Percentage of participants with FVC (*A*) relative decline ⩾10% of predicted and (*B*) absolute decline ⩾10% of predicted at Week 12 (efficacy for modified intent-to-treat population).

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 adverse events, including diarrhea, are common adverse reactions in patients treated with nintedanib or pirfenidone (10, 12–14, 16). The present study did not identify any safety concerns for bexotegrast and confirms the positive safety profile identified in the 7 completed Phase-1 studies, in which the most common TEAEs (occurring in more than 5% of participants receiving bexotegrast) were

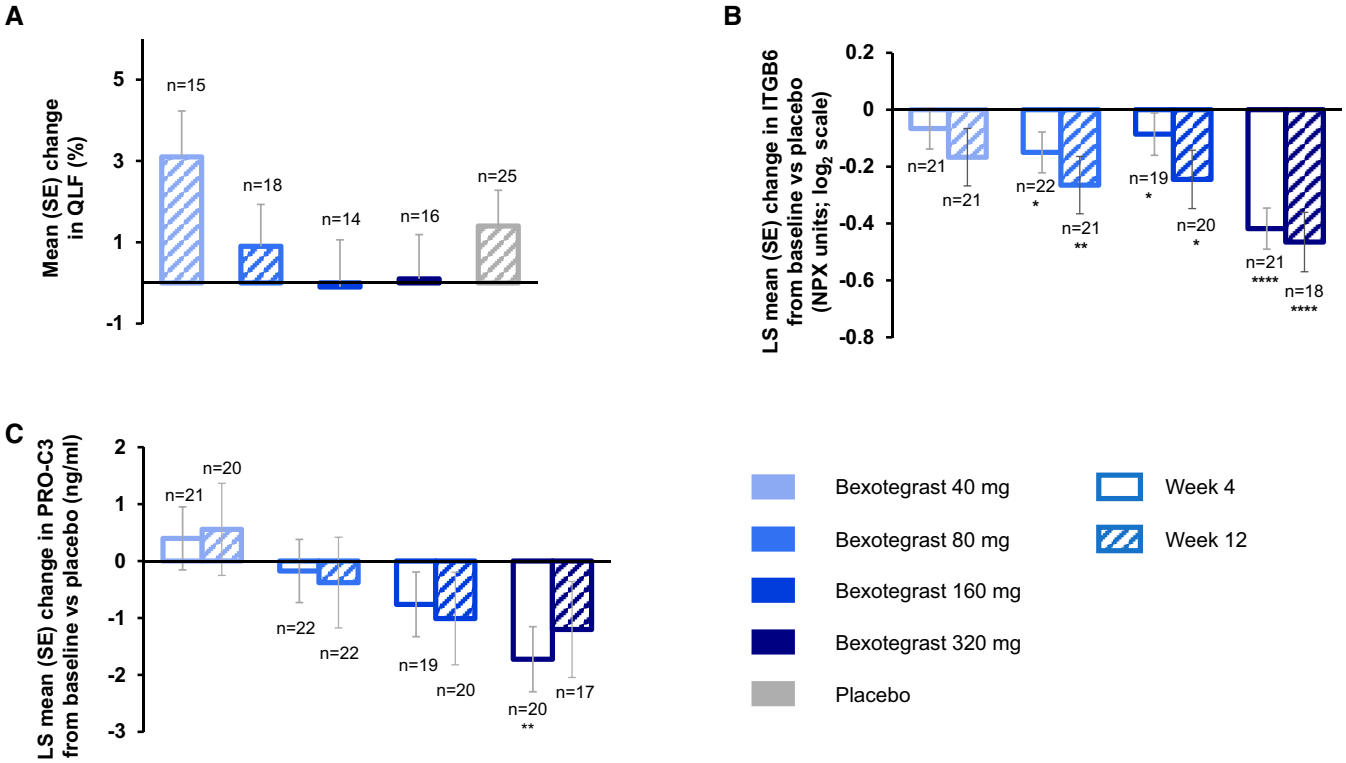

Figure 5. Exploratory endpoints. (*A*) Mean change in QLF (%) from baseline to Week 12. (*B*) Least squares (LS) mean change from baseline in plasma ITGB6 relative to placebo at Weeks 4 and 12. (*C*) LS mean change from baseline in serum PRO-C3 relative to placebo at Weeks 4 and 12. The data in (*A*) are per computed tomography protocol population (a subset of the intent-to-treat population with available high-resolution computer tomography imaging data and images) who completed the study without any major protocol violations within the prespecified time interval between screening and randomization. The data in (*B*) and (*C*) are from the pharmacodynamic analysis population. Change from baseline in biomarker concentration was analyzed using a mixed model for repeated measures. *$P < 0.05$ versus placebo. **$P < 0.01$ versus placebo. ****$P < 0.0001$ versus placebo. ITGB6 = integrin β-6; NPX = Normalized Protein eXpression; PRO-C3 = type III collagen synthesis neoepitope; QLF = quantitative lung fibrosis.

headache and constipation (30). No drug-related serious adverse events 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 wk of treatment in a Phase-2a study and up to 40 wk of 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 proinflammatory potential of prolonged TGF-β inhibition (32). However, no increased risk of disease progression, denoted by IPF or pulmonary fibrosis, was identified in the present study of bexotegrast over a 12-week treatment duration. In the extended treatment duration for participants who were enrolled in the 320-mg bexotegrast cohort (mean exposure, 27.2 wk), the favorable safety profile extended to at least 24 weeks and up to 40 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 proinflammatory effect in the lungs of rodents and nonhuman 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, 80, 160, 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; ClinicalTrials.gov: NCT06097260), which will further characterize its benefit-risk assessment.

Pharmacokinetic data indicated dose-proportional increases in bexotegrast exposure, which were consistent with the findings of 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 BAL cells collected from healthy participants (PLN-74809-109) (35), as well as antifibrotic 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 a trend toward 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 (in milliliters) 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 cohorts. The treatment effect of the 160-mg dose at Week 12 is supported by the totality of the data, including an FVCpp ⩾10% (absolute and relative), mean change in QLF, cough severity as assessed by visual analog scale, and change in the prognostic biomarkers 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 the patients were receiving background therapy, consistent with findings observed in recent IPF trials (38). The progressive nature of decline in participants receiving background therapy in recent trials remains unexplained. Direct comparison with prior registrational trials for pirfenidone and nintedanib are limited because of the lack of consistent exposure to therapeutic doses, either because of dose reductions or dose interruptions or because of 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 in which there was a range in FVC decline from −60 to −101 ml (16, 39–41). Last, 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 that 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.

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 to IPF was supported by initial radiographic evidence of reduced increases in QLF extent versus placebo. The extent of QLF correlates with measures of lung function, such as FVCpp and $D_{L_{CO}}$, 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.

It is interesting that 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 interstitial lung disease (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). PRO-C3 is also reportedly elevated in patients with IPF and associated with progressive disease (51). Our analyses revealed that circulating levels of PRO-C3 were reduced in a dose-dependent manner in participants receiving 80, 160, and 320 mg bexotegrast compared with placebo. Additional investigation is required to validate biomarkers in IPF.

Strengths of the present 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 present 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 (in milliliters) over the dose range of 80 to 320 mg. 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-wk) 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 that 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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