



CLINICAL STUDY PROTOCOL

PLN-74809-IPF-206

Study Title: A randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of PLN-74809 (bexotegast) for the treatment of idiopathic pulmonary fibrosis (BEACON-IPF)

Study Number: PLN-74809-IPF-206

Study Phase: 2b

Product Name: PLN-74809 (bexotegast)

IND Number: 139,998

Indication: Treatment of idiopathic pulmonary fibrosis (IPF)

Sponsor: Pliant Therapeutics Inc
331 Oyster Point Boulevard, South San Francisco, CA 94080, USA

Sponsor Study Director: [REDACTED]

Original Protocol (Version 1.0)	16 March 2023
Amendment 1 (Version 1.1)	09 January 2024
Amendment 2 (Version 1.2)	04 June 2024

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SYNOPSIS

Study Title: A randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of PLN-74809 (bexotegrast) for the treatment of idiopathic pulmonary fibrosis (BEACON-IPF)	
Study Number: PLN-74809-IPF-206	
Study Phase: 2b	
Product Name: PLN-74809 (bexotegrast)	
Sponsor: Pliant Therapeutics Inc, 331 Oyster Point Boulevard, South San Francisco, CA 94080, USA	
Objectives and Endpoints:	
Objectives	Endpoints
<i>Primary</i>	
To characterize the effect of bexotegrast versus placebo on the change in forced vital capacity (FVC) in participants with idiopathic pulmonary fibrosis (IPF) at Week 52	Change from baseline in absolute FVC (mL) at Week 52
<i>Secondary</i>	
To characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on disease progression	- Time to disease progression, defined as time to first occurrence of $\geq 10\%$ absolute decline from baseline in forced vital capacity percent predicted (FVCpp), adjudicated respiratory-related hospitalization, adjudicated acute IPF exacerbation or all-cause mortality through Week 52 - Time to disease progression, defined as time to first occurrence of adjudicated respiratory-related hospitalization, adjudicated acute IPF exacerbation or all-cause mortality through Week 52 - Proportion of participants with a $\geq 10\%$ absolute decline in FVCpp from baseline or all-cause mortality through Week 52
To characterize the effect of bexotegrast versus placebo on the change in FVC in participants with and without background therapy at baseline with IPF at Week 52	Change from baseline in absolute FVC (mL) at Week 52 - In participants on background therapy at baseline - In participants not on background therapy at baseline

To characterize the effect of bexotegrast versus placebo after 52 weeks of treatment on overall symptom and functional improvement associated with IPF	• Change from baseline in Living with Pulmonary Fibrosis (L-PF) Dyspnoea Domain score at Week 52 • Change from baseline in L-PF Cough Domain score at Week 52 • Change from baseline in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total score at Week 52
To characterize the effect of bexotegrast versus placebo on change in lung fibrosis by high-resolution computed tomography at Week 52	• Absolute change from baseline in quantitative lung fibrosis (QLF) extent (%) at Week 52
To characterize the safety and tolerability of bexotegrast versus placebo in participants with IPF over 52 weeks of treatment	• Proportion of participants with treatment-emergent adverse events and serious adverse events
<i>Exploratory</i>	
To characterize the pharmacokinetics of bexotegrast over 52 weeks	• Bexotegrast concentration
To further characterize the effect of bexotegrast versus placebo after 52 weeks of treatment on measures of disease progression	• Time to a $\geq 10\%$ absolute decline in diffusing capacity for carbon monoxide percent predicted from baseline to Week 52 or all-cause mortality through Week 52
To further characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on symptoms of IPF	• Change from baseline in L-PF total score at Week 52 • Change from baseline in the L-PF Fatigue score at Week 52 • Change from baseline in the L-PF Impacts score at Week 52 • Change from baseline in the K-BILD Breathlessness and Activities score at Week 52 • Change from baseline in the K-BILD Psychological score at Week 52 • Change from baseline in the K-BILD Chest Symptoms score at Week 52 • Change from baseline in EuroQol-5 Dimensions (EQ-5D-5L) index score at Week 52 • Change from baseline in EQ-5D-5L visual analog scale score at Week 52
To further characterize the effect of bexotegrast on pulmonary function versus placebo at Week 52	Absolute change from baseline at Week 52 • Diffusing capacity for carbon monoxide • Diffusing capacity for carbon monoxide percent predicted

To characterize the effect of bexotegrast versus placebo for the proportion of participants with improvement in QLF at Week 52	- Proportion of participants with $\geq 2\%$ reduction in QLF extent at Week 52 - Proportion of participants with $\geq 2\%$ reduction or stable QLF extent at Week 52 - Proportion of participants with $\geq 2\%$ increase QLF extent at Week 52
To characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on pharmacodynamic biomarkers	Absolute change from baseline at Week 52: 

Study Design:

This is a randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of 2 doses of bexotegrast (ie, 160 and 320 mg) taken for 52 weeks by participants with IPF taking and not taking background therapy (ie, nintedanib or pirfenidone).

The study will consist of an up to 35-day Screening Period, a 52-week Treatment Period, and a 14-day Safety Follow-up Period. Eligible participants will be stratified by type of background therapy (pirfenidone, nintedanib, or none) and gender-age-physiology index for IPF stage (I or II/III), and Region (Americas/ Europe/Middle East/Africa, Japan, India, or Asia-Pacific excluding Japan and India) at study entry. Of note, participants who are not taking background therapy at study entry will be allowed to initiate it at any time during the study.

A Data Safety Monitoring Board will assess participant safety at regular intervals during the study, and make recommendations for the continuation, termination, or change in conduct of the study. An adjudication committee will be established to assess acute IPF exacerbations, respiratory hospitalizations, and/or respiratory deaths.

Number of Participants (Planned):

The study will comprise approximately 360 participants randomized 1:1:1 to bexotegrast 160 mg, bexotegrast 320 mg, or placebo.

Study Population:*Inclusion Criteria:*

Each participant must meet the following criteria to be enrolled in this study:

- ≥ 40 years of age prior to screening
- IPF diagnosis ≤ 7 years prior to screening based upon American Thoracic Society / European Respiratory Society / Japanese Respiratory Society / Latin American Thoracic Association 2018 guidelines and confirmed with central review ([Raghu et al 2018](#)). An HRCT scan performed ≤ 2 years prior to screening may be used for eligibility.
- FVC_{pp} $\geq 45\%$ confirmed with central review
- Diffusing capacity for carbon monoxide percent predicted (hemoglobin-adjusted) $\geq 30\%$ and $< 90\%$ confirmed with central review
- Current treatment for IPF with background therapy is allowed, if at a stable dose for ≥ 12 weeks prior to screening

6. If not currently receiving treatment for IPF (either treatment naïve or discontinued prior treatment), participant must not have taken background therapy within 8 weeks prior to Screening
7. [REDACTED]
8. Female participant of nonchildbearing potential must be surgically sterile or postmenopausal
9. Female participant of childbearing potential must use a highly effective contraceptive method with a failure rate of <1% per year during Screening and the Treatment Period and for 4 weeks after the last dose of study drug(s)
10. Male participants with a female partner of childbearing potential must agree to use a highly effective contraceptive method with a failure rate of <1% per year and to use a condom during Screening and the Treatment Period and for at least 12 weeks after the last dose of study drug(s)
11. Agree to abstain from sperm or egg donation for the duration of the study, through 12 weeks or 4 weeks, respectively, after administration of the last dose of study drug(s)
12. Understand the study procedures and agree to participate in the study by giving written informed consent

Exclusion Criteria:

Participants who meet any of the following criteria will be excluded from the study:

1. Receiving pharmacologic therapy for pulmonary hypertension
2. Forced expiratory volume in the first second/FVC ratio < 0.7 at Screening (as confirmed with central review)
3. Clinical evidence of active infection, including, but not limited to bronchitis, pneumonia, or sinusitis that can affect FVC measurement during screening or at randomization
4. Active viral infection with human immunodeficiency virus, hepatitis A, hepatitis B, or hepatitis C
5. Any other condition that prevents the correct assessment of spirometry performance (for example a broken rib or chest pain of other origin that prevents adequate forced breathing)
6. Known acute IPF exacerbation ([Collard et al 2016](#)), or suspicion by the Investigator of such, 6 months prior to screening
7. Extent of emphysema that is greater than the extent of fibrotic changes on the most recent HRCT scan (as determined by central reader); [REDACTED]
8. Self-reported smoking of any kind (not limited to tobacco) ≤12 weeks prior to the screening or unwilling to avoid smoking throughout the study
9. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the Screening Period
10. History of malignancy within the past 5 years or ongoing malignancy other than basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma, or treated cervical carcinoma in situ
11. [REDACTED]
12. [REDACTED]

13. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening, including, but not limited to, the following:
 - a. Unstable angina pectoris or myocardial infarction
 - b. Congestive heart failure requiring hospitalization during the 6 months prior to Screening
 - c. Uncontrolled clinically significant arrhythmias (eg, potentially resulting in health care utilization or hospitalization)
14. Any clinically relevant electrocardiogram abnormalities, including, but not limited to, QT interval corrected for heart rate using Fridericia's formula >450 msec for males or >460 msec for females at Screening (including Day -1) or prior to administration of the initial dose of study drug (as confirmed with central review)
15. [REDACTED]
16. Any of the following at Screening: hemoglobin <10.0 g/dL, neutrophils $<1500/\text{mm}^3$, or platelets $<100,000/\text{mL}$
17. Pregnant or lactating female participant
18. [REDACTED]
19. Medical or surgical condition known to affect drug absorption (eg, major gastric surgery)
20. Surgical procedure(s) planned to occur during the study period
21. Uncontrolled systemic arterial hypertension (Stage II hypertension with clinic blood pressure $\geq 160/100$ mmHg [[NICE guideline 2023](#)])
22. [REDACTED]
23. Hypersensitivity to bexotegast or to any of the excipients or placebo
24. Receiving any unapproved or investigational agent intended for treatment of fibrosis in IPF
25. Prior use of an investigational drug within 5 half-lives or 30 days prior to screening (whichever time is longer), or the use of an investigational device within 30 days prior to Screening
26. Prior administration of bexotegast
27. Likely to have lung transplantation during the study (being on transplantation list is not an exclusion)
28. Any medical condition that, in the opinion of the Investigator, may make candidates not suitable for the study
 - a. Candidates with a positive screening drug test must be evaluated by the Principal Investigator to assess if it is associated with a potential substance and/or alcohol use disorder that may impact study participation, adherence to study drug, study visits and assessments. This assessment must be documented in the eCRF to satisfy eligibility requirements.
29. Combined treatment with both nintedanib and pirfenidone
30. Current participation in an interventional study with an investigational agent

Test Product, Dosage and Mode of Administration:

Bexotegrast will be supplied by Pliant as 160-mg tablets for oral administration. Study drug will be taken once daily at approximately 24-hour intervals.

Reference Therapy, Dosage and Mode of Administration:

Matching placebo will be supplied by Pliant as tablets for oral administration. Study drug will be taken once daily at approximately 24-hour intervals.

Duration of Treatment:

52 weeks

Study Assessments:*Efficacy:*

- Pulmonary function tests: Spirometry and diffusing capacity for carbon monoxide
- HRCT
- L-PF
- K-BILD questionnaire
- EQ-5D-5L

Safety:

- Treatment-emergent adverse events and serious adverse events

Pharmacokinetics:

- Bexotegrast pharmacokinetics

Pharmacodynamics:

- Biomarkers ([REDACTED])

Other:

- Patient Global Impression of Change

Sample Size Justification:

A sample size of N=90 participants in each treatment group will provide at least 80% power to detect at least a 120 mL difference in FVC between at least 1 dose level of bexotegrast and placebo assuming a common standard deviation of 285 mL and a 2-sided alpha of 0.05. To account for a 25% treatment discontinuation rate, the per treatment group sample size is N=120 for a total of approximately 360 participants.

Statistical Methods:

This study is planned to compare the efficacy and safety of bexotegrast (160 and 320 mg) versus placebo, and the statistical hypothesis of the primary endpoint includes a detection of significance in the primary endpoint (FVC) with a 2-sided alpha of 0.05. The null hypothesis for the treatment comparison will be that there is no difference between the mean change from baseline in FVC (mL) at a given dose level of bexotegrast and the mean change from baseline on the placebo treatment at Week 52. The alternative hypothesis will be that there is a difference. The primary endpoint of FVC change from baseline to Week 52 will be analyzed using a mixed model repeat measures (MMRM) analysis.

The secondary efficacy endpoints of time to event endpoints over 52 weeks will be summarized using Kaplan-Meier methodology with treatment differences analyzed using the log-rank test. The hazard ratio (relative risk) and its associated 2-sided 95% confidence interval will be estimated based on a Cox

proportional hazards model with treatment assignment as a factor. Continuous endpoints will be evaluated using MMRM analysis. Proportion endpoints will be summarized using logistic regression. The type I error is 0.05. Statistical evaluation of the primary endpoints will be conducted using a multiplicity algorithm including the primary endpoint (change from baseline in FVC) and the key secondary endpoint (time to disease progression, defined as time to first occurrence of $\geq 10\%$ absolute decline from baseline in FVCpp, adjudicated respiratory-related hospitalization, adjudicated acute IPF exacerbation, or all-cause mortality through Week 52). Endpoints not included in the multiplicity algorithm will be reported at their nominal statistical levels.

Safety data will be listed by participant and summarized by treatment group using the frequency of event or descriptive statistical summaries, as appropriate. All safety data will be presented in listings.

In general, continuous data will be summarized using a descriptive summary, and categorical data will be summarized using the frequency and percentage of participants.

Date of Synopsis:

04 June 2024

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLCO	diffusing capacity for carbon monoxide
DLCOpp	diffusing capacity for carbon monoxide percent predicted
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQol-5 Dimensions
FEV1	forced expiratory volume in the first second
FVC	forced vital capacity
FVCpp	forced vital capacity percent predicted
GAP	gender-age-physiology
GCP	Good Clinical Practice
HRCT	high-resolution computed tomography
IC ₅₀	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
	
ITT	intent-to-treat
K-BILD	King's Brief Interstitial Lung Disease
L-PF	Living with Pulmonary Fibrosis

Abbreviation	Definition
LS	least squares
██████	████████████████████
MMRM	mixed model repeated measures
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
██████	██
██████	██
PSC	primary sclerosing cholangitis
QGG	quantitative ground glass
QLF	quantitative lung fibrosis
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TGF- β	transforming growth factor- β
ULN	upper limit of normal
VAS	visual analog scale

Abbreviations used only in a table(s) or figure(s) are defined in the footnotes of the respective table(s) and figure(s) and are not included in the List of Abbreviations.

1. INTRODUCTION

Pliant Therapeutics Inc (Pliant) is developing PLN-74809 (bexotegast), a small molecule, selective, dual inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, for the treatment of idiopathic pulmonary fibrosis (IPF) and primary sclerosing cholangitis (PSC).

Please refer to the Investigator's Brochure for detailed information.

1.1. PLN-74809

Bexotegast is a small molecule and a selective dual inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins with antifibrotic activity. Bexotegast prevents $\alpha_v\beta_6$ and $\alpha_v\beta_1$ from binding to the arginine-glycine-aspartate sequence of the latency-associated peptide of the transforming growth factor- β (TGF- β) precursor protein, thereby blocking the release of the activated form of TGF- β and preventing binding to its receptors and activation of pathways relevant to fibrogenesis. Bexotegast was demonstrated to be a potent and selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins in an in vitro ligand-binding assay, exhibiting geometric mean 50% inhibitory concentration (IC₅₀) values of 5.7 and 3.4 nM against the human receptor, respectively. Integrin-ligand binding assays have also demonstrated that bexotegast is highly selective for $\alpha_v\beta_6$ and $\alpha_v\beta_1$ over other integrin receptors, including those leukocyte-expressed integrins where therapeutic inhibition has previously been associated with significant toxicities (eg, vedolizumab [$\alpha_4\beta_7$ inhibitor; increased risk of infections, potential risk of progressive multifocal leukoencephalopathy; [ENTYVIO Prescribing Information 2023](#)] and natalizumab [$\alpha_4\beta_1$ and $\alpha_4\beta_7$ inhibitor; increased risk of progressive multifocal leukoencephalopathy; [TYSABRI Prescribing Information 2023](#)]). In an in vitro coculture assay of TGF- β activation, bexotegast inhibited the release of activated TGF- β mediated by human $\alpha_v\beta_6$ integrin with a geometric mean IC₅₀ of 29.8 nM and by $\alpha_v\beta_1$ integrin with a geometric mean IC₅₀ of 19.2 nM.

The rationale for evaluation of bexotegast as a treatment for IPF comes from its demonstrated effects on mechanisms believed to be important for the pathophysiology of these conditions, specifically TGF- β signaling that drives a fibroproliferative cascade of gene expression with aberrant deposition of collagen and fibrosis. Bexotegast is expected to exert antifibrotic effects, presenting a potential novel therapeutic option for IPF patients. Specific roles proposed for $\alpha_v\beta_6$ in epithelial cells and $\alpha_v\beta_1$ in myofibroblasts for induction of fibrosis are summarized in the Investigator's Brochure for bexotegast.

1.2. Idiopathic Pulmonary Fibrosis

IPF is a rare condition, typically occurring in the sixth and seventh decades of life, characterized by dyspnea and progressive loss of lung function leading to death, with median survival of 3.8 years after diagnosis based on 2014 data in the United States. The appearance of basilar, peripheral predominant reticular changes, traction bronchiectasis, and honeycomb change on high-resolution computed tomography (HRCT) in patients with IPF is the result of extensive fibrosis ([Lederer and Martinez 2018](#)). Although not completely understood, IPF has been proposed to stem from ongoing microinjury to alveolar epithelial cells. Injured epithelium results in upregulation of profibrotic factors, such as TGF- β , which promote fibroblast recruitment, proliferation, and differentiation into fibrogenic myofibroblasts ([Kreuter et al 2015](#); [Wilson and Raghu 2015](#)). As has also been indicated to be the case for other fibrotic interstitial

lung diseases, TGF- β signaling, mediated by α_v integrins, is central to the control of fibrosis in the lungs.

1.3. Summary of Clinical Development

Bexotegast is currently being investigated for the treatment of IPF and PSC. A detailed overview of the bexotegast clinical development program is available in the Investigator's Brochure.

The following information has been collected as of 29 Nov 2023:

- A total of 530 participants enrolled in 11 Phase 1 studies have received bexotegast.
- A total of 98 participants with IPF have received bexotegast, 31 participants have received placebo, and 11 participants have received blinded study drug (bexotegast or placebo) in the following 3 Phase 2a studies:
 - Study PLN-74809-IPF-201, a single center, open-label, single-dose study of bexotegast 60, 80, 120, 240, and 320 mg.
 - Study PLN-74809-IPF-202, a multinational, randomized, double-blind, placebo-controlled study, evaluating bexotegast 40, 80, 160, and 320 mg versus placebo. In parts A, B, and C, participants received bexotegast 40, 80, or 160 mg or placebo once daily for 12 weeks; In part D, participants received bexotegast 320 mg or placebo once daily for at least 24 and up to 48 weeks.
 - Study PLN-74809-IPF-205, an ongoing, single-center, randomized, double-blind, placebo-controlled evaluation of bexotegast on Type 1 collagen deposition using ^{68}Ga -CBP8 positron emission tomography / magnetic resonance imaging in participants with IPF.
- A total of 64 participants with PSC have received bexotegast, 21 participants have received placebo, and 36 participants have received blinded study drug (bexotegast or placebo) in an ongoing, randomized, double-blind, dose-ranging, placebo-controlled study.

Overall, bexotegast has been well tolerated in clinical studies, and safety and tolerability data do not suggest safety concerns. Additional details are provided in the Investigator's Brochure.

1.4. Study Rationale for PLN-74809-IPF-206

Bexotegast prevents $\alpha_v\beta_6$ and $\alpha_v\beta_1$ from binding to the TGF- β precursor protein, thereby blocking the release of the activated form of TGF- β and preventing binding to its receptors and activation of pathways relevant to fibrogenesis. In vivo efficacy studies of bexotegast were performed using the bleomycin mouse model of pulmonary fibrosis, and bexotegast was demonstrated to significantly inhibit collagen deposition and TGF- β signaling in lung tissue.

Safety of bexotegast at doses of 40, 80, 160, and 320 mg once daily have been assessed in participants with IPF in Study PLN-74809-IPF-202 (INTEGRIS-IPF) through 12 weeks of treatment. No dose relationship in the incidence of treatment-emergent adverse events (TEAEs) was observed for bexotegast dose groups. At all bexotegast doses, a numerical treatment effect on forced vital capacity (FVC) was observed in this study population, largely composed of

participants already taking background therapy (approximately 80% of all participants). The bexotegrast 320-mg group demonstrated mean FVC increase of +29.5 mL relative to baseline at 12 weeks, versus a decline of -110.7 mL in the placebo group, resulting in a 140 mL increase compared with placebo. Compared with placebo, reduced FVC decline at Week 12 was observed in the bexotegrast 160-mg group (least squares [LS] mean difference versus placebo: 85.2 mL [$p > 0.05$]).

The main purpose of the current study is to evaluate the efficacy and safety of 2 doses of bexotegrast (ie, 160 and 320 mg) in participants with IPF and to select the dose for Phase 3 evaluation. This study will evaluate approximately 360 participants randomized 1:1:1 to bexotegrast 160 mg, bexotegrast 320 mg, or placebo. The sample size and randomization scheme are adequate to assess differences between the bexotegrast dose groups versus placebo for the primary efficacy endpoint (FVC).

Additional details are provided in the Investigator's Brochure.

1.5. Summary of Benefits and Risks

Benefit Summary

The safety of bexotegrast at doses of 40, 80, 160, and 320 mg once daily has been assessed in participants with IPF in Study PLN-74809-IPF-202 (INTEGRIS-IPF) through 12 weeks of treatment. At all bexotegrast doses, a numerical treatment effect on FVC was observed in this study population, largely composed of participants already taking background therapy (approximately 80% of all participants). The bexotegrast 320-mg group demonstrated mean FVC increase of +29.5 mL relative to baseline at 12 weeks, versus a decline of -110.7 mL in the placebo group, resulting in a 140-mL increase compared with placebo. Compared with placebo, reduced FVC decline at Week 12 was observed in the bexotegrast 160-mg group (LS mean difference versus placebo: 85.2 mL [$p > 0.05$]). Based on the favorable results of reduced FVC decline with bexotegrast treatment in the Phase 2a INTEGRIS-IPF study in combination with approved therapies in the majority of the study population, the Sponsor anticipates efficacy at both the 160-mg and 320-mg doses being evaluated this study. The changes in FVC observed in this study are larger than the changes observed at the corresponding time point (12 weeks) in the pivotal studies for the approved therapies on a 100% treatment naive population, suggesting that bexotegrast may have the potential to provide benefit to a patient population with a progressive disease and a limited life expectancy post diagnosis. Thus, participants who enroll in this study will have the opportunity to access a potential treatment for IPF and could experience a benefit from trial participation.

Risk Summary and Mitigation Strategy

No significant bexotegrast-related risks were identified in nonclinical studies in mouse and monkey at clinically relevant exposures.

In the 39-week monkey study (██████████), the no observed adverse effect level (NOAEL) was considered the highest dose tested at ██████████, correlating to safety margin based on maximum observed unbound plasma concentration at steady state ($C_{max,ss,u}$) and area under the unbound plasma concentration-time curve from time 0 to 24 hours at steady state ($AUC_{0-24,ss,u}$) of ██████ and ██████ fold, respectively, to the highest steady-state clinical dose tested (320 mg once daily).

No cardiovascular abnormalities or notable effects on the electrocardiograms (ECGs) have been observed in clinical studies of ≥ 600 participants exposed to bexotegraft at single doses up to 640 mg and multiple doses up to 320 mg once daily. Routine ECG monitoring of participants in this study will be performed at each visit; guidelines for management of potential ECG-related abnormalities are provided in [Section 9](#).

Integrins are involved in the process of wound healing. However, there is currently no evidence that bexotegraft (or genetic deletion of integrin $\alpha_v\beta_6$) leads to aberrant wound repair in either nonclinical or clinical studies. No TEAEs related to wound healing abnormalities were observed in clinical studies with bexotegraft.

In previous clinical studies of bexotegraft in participants with IPF, the most common TEAEs ($\geq 5\%$) that were reported more frequently in those receiving bexotegraft than placebo included diarrhea and fatigue. Although the incidence of diarrhea was higher in participants receiving bexotegraft than those receiving placebo, all but one of the participants receiving bexotegraft were taking concurrent background therapy (nintedanib or pirfenidone) for which diarrhea is a labeled risk. The remaining bexotegraft-treated participant with a TEAE of diarrhea who was not receiving background therapy had pre-existing ulcerative colitis. The severity of diarrhea TEAEs in all but 1 of 15 bexotegraft-treated participants was mild or moderate. Overall, TEAEs were experienced by a similar percentage of participants in the bexotegraft (any dose) and placebo groups, and most TEAEs were Grade 1 or 2 and not related to study drug. No SAEs occurring in participants with IPF have been assessed as related to bexotegraft. In addition, no notable changes in vital signs and physical examinations were observed in Phase 1 and Phase 2 studies, including those conducted in participants with IPF.

The Sponsor has implemented a rigorous safety monitoring plan to ensure participant safety in the study, including routine monitoring of vital signs, physical examinations, ECGs, lung function tests, hematology, serum chemistry, coagulation parameters, urinalysis, and [REDACTED], and ECG-related abnormalities. In addition, a Data Safety Monitoring Board (DSMB) is in place that assesses unblinded safety data on a regular basis.

This study requires participants to undergo HRCT scans of the chest at Screening/Baseline and at Weeks 24 and 52. Ionizing radiation can cause cancer, which manifests itself after many years or decades. The clinical outlook and prognosis of participants in this study is significantly lowered compared to the general population (the protocol quotes a median survival of 3.8 years after diagnosis). The participant will receive some additional radiation burden, all of which could be above that anticipated in routine clinical care. In practice, the mean survival time of the study cohort is expected to be less than the latent period for induction of any effects relating to the radiation exposures and the extra radiation dose is considered to confer a significantly reduced risk in this group of patients. The research exposure is justified on the basis that HRCT is necessary to confirm a diagnosis of IPF and thereafter for the study endpoints ie, to give an objective assessment of absolute change from Baseline in quantitative lung fibrosis extent at Week 52.

Overall Benefit: Risk Conclusion

IPF is a chronic, progressive, lethal disease with a substantial loss of lung function and symptomatic deterioration, even in those on either of the 2 approved therapies (nintedanib or

pirfenidone), with a median survival of 3.8 years after diagnosis. Given the progressive nature of the disease, it is anticipated that patients, including those who volunteer to participate in clinical studies, will experience progressive symptoms and loss of lung function. Therefore, there is an important unmet medical need for more efficacious therapies.

Treatment with bexotegast has the potential to provide benefit to patients with IPF by slowing the progressive decline of lung function and improving symptoms and quality of life with or without use of a background therapy. The available data from the Phase 1 in healthy participants and the Phase 2 studies in IPF and PSC in more than 600 participants exposed to bexotegast demonstrate a favorable safety profile for participants taking up to 320 mg once daily for up to 40 weeks. The favorable safety profile and supportive evidence for a treatment effect of bexotegast suggests the benefit:risk assessment for bexotegast is acceptable and supportive of continued evaluation and late-stage development.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To characterize the effect of bexotegast versus placebo on the change in forced vital capacity (FVC) in participants with idiopathic pulmonary fibrosis (IPF) at Week 52	Change from baseline in absolute FVC (mL) at Week 52
Secondary	
To characterize the effect of bexotegast versus placebo over 52 weeks of treatment on disease progression	- Time to disease progression, defined as time to first occurrence of $\geq 10\%$ absolute decline from baseline in forced vital capacity percent predicted (FVC_{pp}), adjudicated respiratory-related hospitalization, adjudicated acute IPF exacerbation, or all-cause mortality through Week 52 - Time to disease progression, defined as time to first occurrence of adjudicated respiratory-related hospitalization, adjudicated acute IPF exacerbation or all-cause mortality through Week 52 - Proportion of participants with a $\geq 10\%$ absolute decline from baseline in FVC_{pp} or all-cause mortality through Week 52
To characterize the effect of bexotegast versus placebo on the change in FVC in participants with and without background therapy at baseline with IPF at Week 52	Change from baseline in absolute FVC (mL) at Week 52 - In participants on background therapy at baseline - In participants not on background therapy at baseline
To characterize the effect of bexotegast versus placebo after 52 weeks of treatment on overall symptom and functional improvement associated with IPF	- Change from baseline in Living with Pulmonary Fibrosis (L-PF) Dyspnoea Domain score at Week 52 - Change from baseline in L-PF Cough Domain score at Week 52 - Change from baseline in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total score at Week 52
To characterize the effect of bexotegast versus placebo on change in lung fibrosis by high-resolution computed tomography at Week 52	Absolute change from baseline in quantitative lung fibrosis (QLF) extent (%) at Week 52
To characterize the safety and tolerability of bexotegast versus placebo in participants with IPF over 52 weeks of treatment	Proportion of participants with TEAEs and serious adverse events

Objectives	Endpoints
Exploratory	
To characterize the pharmacokinetics of bexotegrast over 52 weeks	Bexotegrast concentration
To further characterize the effect of bexotegrast versus placebo after 52 weeks of treatment on measures of disease progression	Time to a $\geq 10\%$ absolute decline in diffusing capacity for carbon monoxide percent predicted from baseline to Week 52 or all-cause mortality through Week 52
To further characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on symptoms of IPF	- Change from baseline in L-PF total score at Week 52 - Change from baseline in the L-PF Fatigue score at Week 52 - Change from baseline in the L-PF Impacts score at Week 52 - Change from baseline in the K-BILD Breathlessness and Activities score at Week 52 - Change from baseline in the K-BILD Psychological score at Week 52 - Change from baseline in the K-BILD Chest Symptoms score at Week 52 - Change from baseline in EQ-5D-5L index score at Week 52 - Change from baseline in EQ-5D-5L visual analog scale score at Week 52
To further characterize the effect of bexotegrast on pulmonary function versus placebo at Week 52	Absolute change from baseline at Week 52 - Diffusing capacity for carbon monoxide - Diffusing capacity for carbon monoxide percent predicted
To characterize the effect of bexotegrast versus placebo for the proportion of participants with improvement in QLF at Week 52	- Proportion of participants with $\geq 2\%$ reduction in QLF extent at Week 52 - Proportion of participants with $\geq 2\%$ reduction or stable QLF extent at Week 52 - Proportion of participants with $\geq 2\%$ increase QLF extent at Week 52
To characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on pharmacodynamic biomarkers	Absolute change from baseline at Week 52: 

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

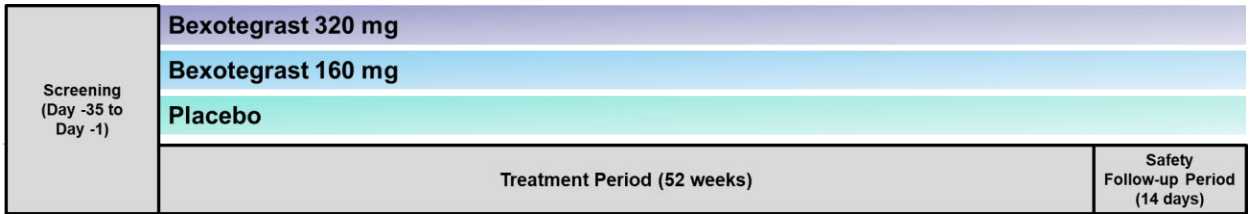
This is a randomized, double-blind, dose-ranging, placebo-controlled study to select a bexotegast dose for evaluation in a future Phase 3 study in participants with IPF. The dose selection of bexotegast in the current study will be based on the efficacy and safety evaluation of 2 doses of bexotegast (ie, 160 and 320 mg) taken for 52 weeks by participants with IPF.

Eligible participants will be stratified by type of background therapy (pirfenidone, nintedanib or none), gender-age-physiology (GAP) index for IPF stage (I or II/III), and Region (Americas/Europe/Middle East/Africa, Japan, India, or Asia-Pacific excluding Japan and India) at study entry.

Of the 360 participants to be enrolled (randomized 1:1:1 to bexotegast 160 mg, bexotegast 320 mg, or placebo), approximately 30% (108 participants) will not be taking background therapy at study entry. Of note, participants who are not taking background therapy at study entry will be allowed to initiate either at any time during the study. Thus, the study is designed to evaluate the efficacy and safety of bexotegast 160 and 320 mg in participants taking or not taking background therapy.

The study will consist of an up to 35-day Screening Period, a 52-week Treatment Period, and a 14-day Safety Follow-up Period. Participants will undergo an end-of-study (EOS) visit at the end of the Safety Follow-up Period. A study schematic is presented in [Figure 1](#).

Figure 1: Study Schematic



Efficacy will be assessed via change in FVC, time to disease progression ($\geq 10\%$ absolute decline in forced vital capacity percent predicted [FVCpp], all-cause mortality, adjudicated IPF acute exacerbations, or adjudicated respiratory -related hospitalization through Week 52), and proportion of participants with a $\geq 10\%$ absolute decline in FVCpp or all-cause mortality through Week 52, diffusing capacity for carbon monoxide percent predicted (DLCOpp), Living with Pulmonary Fibrosis (L-PF), King’s Brief Interstitial Lung Disease (K-BILD), EuroQol-5 Dimensions (EQ-5D-5L), and quantitative lung fibrosis (QLF) extent (%). Safety and tolerability will be assessed via TEAEs, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations. Blood samples for pharmacokinetic (PK) analysis will also be taken at regular intervals. Blood samples for pharmacodynamic (PD) biomarker analysis will also be collected.

A DSMB will assess participant safety at regular intervals during the study and make recommendations for the continuation, termination, or change in conduct of the study.

Details of the DSMB procedures are provided in [Section 12.13](#).

See the Schedule of Events ([Appendix 1](#)) for assessment details.

3.2. Rationale for Study Design

This study will characterize the efficacy, safety, and tolerability of bexotegast taken for 52 weeks by participants with IPF with or without coadministration of background therapy. The proposed randomized, double-blind study design allows a reduction in bias in the assessment of drug safety and tolerability as well as efficacy. Stratification for background treatment, GAP index, and Region will ensure a similar proportion of participants in each treatment group. The proposed sample size is expected to provide at least 80% power to differentiate between either of the bexotegast dose groups versus placebo for the primary efficacy endpoint (FVC). Based on the 12-week efficacy data from Phase 2a Study PLN-74809-IPF-202, the current study has a treatment duration of 52 weeks to evaluate the sustained efficacy of once-daily treatment with bexotegast 160 or 320 mg in participants with IPF.

3.2.1. Selection of Doses in the Study

The bexotegast 160- and 320-mg doses in this study are supported by the available safety, PK, PD, and efficacy data evaluated to date.

In an $\alpha_v\beta_6$ positron emission tomography study in participants with IPF, following single dose administration of bexotegast, estimated target engagement increased with dose between 60 and 320 mg, with peak effect greater than 90% following 320 mg administration. In addition, unbound steady-state PK data indicate that the 160- and 320-mg once-daily doses of bexotegast, on average, achieve IC_{50} for 24 hours, with greater time above 80% inhibitory concentration (21 hours versus 9 hours, respectively) and 90% inhibitory concentration (11 hours versus 3 hours, respectively) for the 320-mg dose compared with the 160-mg dose.

A multinational, randomized, double-blind Phase 2a study has evaluated placebo or bexotegast at doses of 40, 80, 160, and 320 mg once daily in 119 participants with IPF. The study included a 12-week Treatment Period for the 40-, 80-, and 160-mg dose groups and a placebo group and at least a 24-week Treatment Period for the 320-mg dose group and a placebo group. In all parts of the study, randomization was stratified by background therapy use. Approximately 80% of all randomized participants were taking 1 of these agents (ie, nintedanib or pirfenidone). The primary endpoint was safety and tolerability of bexotegast compared with placebo. Exploratory endpoints included changes in FVC, QLF extent, and profibrotic biomarkers. A planned interim analysis of 12-week data for all dose groups was conducted. Bexotegast was well tolerated at all dose levels over 12 weeks of treatment.

Bexotegast has been well tolerated following 160- and 320-mg daily dosing over 12 weeks in IPF participants. Bexotegast 320 mg demonstrated a statistically significant mean increase in FVC, and the highest treatment effect compared with lower dose cohorts. A dose-response relationship was also observed in the percentage of participants who had a $\geq 10\%$ decline in FVCpp (absolute and relative) and for profibrotic biomarker N-terminal type III collagen fragment (PRO-C3) and PD biomarker integrin beta-6 (ITGB6). Given the dose-response relationship observed for these endpoints in the Phase 2a study in IPF, a treatment effect is also anticipated at the 160-mg dose. Inclusion of the 160- and 320-mg doses allows further evaluation of dose response to support dose selection for future IPF studies.

3.3. Study Duration

The duration of the study for each participant will be up to approximately 59 weeks and will include the following:

- Screening Period: 5 weeks (Day -35 to Day -1).
- Treatment Period: 52 weeks
- Safety Follow-up Period: 2 weeks (14 days)

4. STUDY POPULATION SELECTION

This study will enroll participants with IPF who may or may not be receiving background therapy and who otherwise do not present with major health conditions that could affect the study drug or confound the study outcomes.

4.1. Inclusion Criteria

Each participant must meet the following criteria to be enrolled in this study:

1. ≥ 40 years of age prior to screening
2. IPF diagnosis ≤ 7 years prior to screening based upon American Thoracic Society / European Respiratory Society / Japanese Respiratory Society / Latin American Thoracic Association 2018 guidelines and confirmed with central review ([Raghu et al 2018](#)). An HRCT scan performed ≤ 2 years prior to screening may be used for eligibility.
3. FVCpp $\geq 45\%$ confirmed with central review
4. DLCOpp (hemoglobin-adjusted) $\geq 30\%$ and $< 90\%$ confirmed with central review
5. Current treatment for IPF with background therapy is allowed, if at a stable dose for ≥ 12 weeks prior to screening
6. If not currently receiving treatment for IPF (either treatment naïve or discontinued prior treatment), participant must not have taken background therapy within 8 weeks prior to Screening
7. [REDACTED]
8. Female participant of nonchildbearing potential must be surgically sterile or postmenopausal (refer to [Section 5.7.4](#))
9. Female participant of childbearing potential must use a highly effective contraceptive method with a failure rate of $< 1\%$ per year during Screening and the Treatment Period and for 4 weeks after the last dose of study drug(s) (refer to [Section 5.7.4](#))
10. Male participants with a female partner of childbearing potential must agree to use highly effective contraceptive method with a failure rate of $< 1\%$ per year and to use a condom during Screening and the Treatment Period and for at least 12 weeks after the last dose of study drug(s) (refer to [Section 5.7.4](#))
11. Agree to abstain from sperm or egg donation for the duration of the study, through 12 weeks or 4 weeks, respectively, after administration of the last dose of study drug(s)
12. Understand the study procedures and agree to participate in the study by giving written informed consent

4.2. Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study:

1. Receiving pharmacologic therapy for pulmonary hypertension
2. Forced expiratory volume in the first second (FEV1)/FVC ratio <0.7 at Screening (as confirmed with central review)
3. Clinical evidence of active infection, including, but not limited to bronchitis, pneumonia, or sinusitis that can affect FVC measurement during screening or at randomization
4. Active viral infection with human immunodeficiency virus, hepatitis A, hepatitis B, or hepatitis C
5. Any other condition that prevents the correct assessment of spirometry performance (for example a broken rib or chest pain of other origin that prevents adequate forced breathing)
6. Known acute IPF exacerbation (Collard et al 2016), or suspicion by the Investigator of such, 6 months prior to screening
7. Extent of emphysema that is greater than the extent of fibrotic changes on the most recent HRCT scan (as determined by central reader); [REDACTED]
8. Self-reported smoking of any kind (not limited to tobacco) ≤12 weeks prior to screening or unwilling to avoid smoking throughout the study
9. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the Screening Period
10. History of malignancy within the past 5 years or ongoing malignancy other than basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma, or treated cervical carcinoma in situ
11. [REDACTED]
12. [REDACTED]
13. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening, including, but not limited to, the following:
 - a. Unstable angina pectoris or myocardial infarction
 - b. Congestive heart failure requiring hospitalization during the 6 months prior to Screening
 - c. Uncontrolled clinically significant arrhythmias (eg, potentially resulting in health care utilization or hospitalization)
14. Any clinically relevant ECG abnormalities, including, but not limited to, QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec for males or

>460 msec for females at Screening (including Day -1) or prior to administration of the initial dose of study drug (as confirmed with central review)

15. [REDACTED]
16. Any of the following at Screening: hemoglobin <10.0 g/dL, neutrophils <1500/mm³, or platelets <100,000/mL
17. Pregnant or a lactating female participant
18. [REDACTED]
19. Medical or surgical condition known to affect drug absorption (eg, major gastric surgery)
20. Surgical procedure(s) planned to occur during the study period
21. Uncontrolled systemic arterial hypertension (Stage II hypertension with clinic blood pressure $\geq$ 160/100 mmHg [[NICE guideline 2023](#)])
22. [REDACTED]
23. Hypersensitivity to bexotegast or to any of the excipients or placebo
24. Receiving any unapproved or investigational agent intended for treatment of fibrosis in IPF
25. Prior use of an investigational drug within 5 half-lives or 30 days prior to screening (whichever time is longer), or the use of an investigational device within 30 days prior to Screening
26. Prior administration of bexotegast
27. Likely to have lung transplantation during the study (being on transplantation list is not an exclusion)
28. Any medical condition that, in the opinion of the Investigator, may make candidates not suitable for the study
 - a. Candidates with a positive screening drug test must be evaluated by the Principal Investigator to assess if it is associated with a potential substance and/or alcohol use disorder that may impact study participation, adherence to study drug, study visits and assessments. This assessment must be documented in the eCRF to satisfy eligibility requirements.
29. Combined treatment with both nintedanib and pirfenidone
30. Current participation in any other interventional study with an investigational agent

5. STUDY TREATMENTS

5.1. Treatments Administered

Bexotegast and matching placebo for oral administration will be supplied by Pliant. Study drug will be taken once daily at approximately 24-hour intervals.

No dose modifications are allowed.

5.2. Identity of Study Drug

Bexotegast 160-mg tablets and matching placebo are [REDACTED] tablets.

5.2.1. Packaging and Labeling

Study drug will be supplied in [REDACTED]. The clinical study supplies will be labeled with the protocol number, lot number, the storage conditions, the administration directions, and the required label text requirements per country regulations.

5.2.2. Storage and Accountability

Bexotegast and matching placebo tablets should be stored at [REDACTED]

The Investigator (or designee) will maintain accurate records of receipt of all investigational drug supplies, including dates of receipt and the amount of study drug dispensed and used by each participant. Reasons for departure from the expected dispensing regimen must be recorded. Once all study drug is reconciled, it can be destroyed, according to applicable regulations, to satisfy regulatory requirements regarding drug accountability (refer to pharmacy manual for details).

5.3. Method of Assigning Participants to Treatment Groups

Randomization will be performed in a blinded manner using interactive response technology based on a previously generated randomization code. Randomization will occur immediately prior to dosing on the morning of the first dose (Day 1).

5.4. Selection and Timing of Dose for Each Participant

Participants will be encouraged to take the study drug at the same time each day [REDACTED]

If a participant has not taken a dose of study drug at the regular scheduled time and is still within 12 hours of the time it is usually taken, the participant should take a dose of the study drug as soon as possible. The participant may then continue the usual dosing schedule.

A dose will be considered missed if the participant cannot take the dose within 12 hours of their regular dosing time. If the participant has missed a dose of study drug, the participant should not take the missed dose and should resume the usual dosing at the next scheduled time. The participant should not take a double dose to make up for a missed dose.

On study visit days, participants should not take their study drug prior to the study visit as study drug will be taken during the study visit.

5.5. Study Drug Interruptions and Discontinuations

Participants should be instructed to promptly notify the Investigator and/or study personnel if they interrupt or discontinue study drug. The Investigator and/or study personnel will assess and document the reasons for participants interrupting and/or discontinuing study drug and notify the Medical Monitor within 2 business days after being made aware of this information. The Medical Monitor will notify and review the information with the Sponsor's Study Director within 1 business day and subsequently contact the Investigator and/or study personnel, as required.

5.6. Blinding

Matching placebo tablets will resemble the bexotegast tablets in [REDACTED]. This ensures that the participant, Investigator, clinical site staff, and Sponsor are unaware of the treatment allocation during the conduct of the study. Study drug will be provided as blinded kits and will be assigned to participants using a randomization code.

A double dummy design will be utilized to maintain blinding between the 2 dose levels (160 mg and 320 mg) and placebo. Participants randomized to bexotegast 160 mg will receive one 160-mg bexotegast tablet and one matching placebo tablet. Participants randomized to bexotegast 320 mg will receive two 160-mg bexotegast tablets. Participants randomized to placebo will receive two placebo tablets.

The Investigator has the primary right to break the blind of a study participant for emergency treatment. If the safety of the participant is jeopardized, the Investigator (or designee) may break the blind and will contact the Sponsor within 24 hours. Unblinding at the study site for any other reason will be considered a protocol deviation. The Investigator will be supplied with instructions on how to access treatment information.

5.7. Prior and Concomitant Therapy

5.7.1. Prior Medications

Previous and/or current use of background therapy is allowed for participation in this study, provided these drugs have been given at a stable dose for ≥ 12 weeks before Screening.

5.7.2. Allowed Concomitant Medications

During screening, all medications, including overthecounter medications and herbal supplements taken during the 30 days prior to the first dose of study drug(s), will be recorded and reviewed by the Investigator. For other concomitant medications needed during the study conduct, the Investigator should reference [Appendix 2](#) and the Inclusion and Exclusion Criteria for any concerns about the use of concomitant medications, including both prescription and nonprescription drugs, before administration.

The only allowed treatments for IPF are nintedanib or pirfenidone, which must have been taken at a stable dose for ≥ 12 weeks before Screening and are expected to remain unchanged during

the study if initiated prior to first dose of study drug. Participants who are not taking nintedanib or pirfenidone at study entry will be allowed to initiate it at any time during the study. Participants can only be using one background therapy at a time. The time of nintedanib or pirfenidone administration should be recorded on days when blood samples are obtained for assessing bexotegast PK.

Treatments to address IPF disease symptoms (eg, cough, gastroesophageal reflux disease) are allowed.

Acute IPF exacerbations should be treated according to standard clinical practice.

Treatment with short-acting and long-acting bronchodilators is allowed but the bronchodilators need to be withheld prior to clinical visits, including the screening and baseline visits per [Table 1](#) ([Graham et al 2019](#)).

Table 1 Bronchodilator Withholding Times

Bronchodilator Medication	Withholding Time
SABA (eg, albuterol or salbutamol)	4 to 6 hours
SAMA (eg, ipratropium)	12 hours
LABA (formoterol, salmeterol)	24 hours
Ultra-LABA (indacaterol, vilanterol or olodaterol)	36 hours
LAMA (eg, tiotropium, umeclidinium, aclidinium, glycopyrronium, revefenacin)	36 hours

LABA: long-acting β_2 agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting β_2 agonist; SAMA: short-acting muscarinic antagonist



In all cases, medications, including over-the-counter medications and herbal supplements, taken by participants during the study will be recorded using the generic name of the medication.

Acetaminophen/paracetamol, limited to 2 g per 24 hours, may be administered on study without prior Medical Monitor approval for minor ailments.

5.7.3. Disallowed Concomitant Medications

Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever time is longer) before Screening is prohibited.

[REDACTED]

Smoking/vaping of any kind is not permitted ≤ 12 weeks prior to screening and throughout the study.

5.7.4. Contraception

Female Participants of Childbearing Potential

Female participants of childbearing potential must agree to use a highly effective contraceptive method with a failure rate of $<1\%$ per year, as defined below, during Screening and the Treatment Period and for 4 weeks after the last dose of study drug.

A female participant is not considered to be of childbearing potential if:

- She has reached a postmenopausal state, defined as ≥ 12 continuous months of amenorrhea without an alternative medical cause
- She has undergone surgical sterilization, defined as hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy

Male Participants

Male participants with a female partner of childbearing potential must agree to use a highly effective contraceptive method with a failure rate of $<1\%$ per year, as defined below, and also use a condom during Screening and the Treatment Period and for at least 12 weeks after the last dose of study drug.

Highly Effective Methods of Birth Control

Highly effective methods of birth control are defined as those with a failure rate of $<1\%$ per year (adapted from [Trussell 2004](#); [CTFG 2020](#)). Examples of contraceptive methods with a failure rate of $<1\%$ per year include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal or transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Male sterilization or vasectomized male partner
- Complete sexual abstinence (refraining from heterosexual intercourse during the entire period of risk associated with the study treatment); only if this is the preferred and usual lifestyle of the participant
 - The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
 - Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Participants will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign an informed consent form (ICF) that they understand the requirements for avoidance of pregnancy during the course of the study. The Investigator is responsible for ensuring that participants understand how to properly use these methods of contraception and the duration of use that is required.

5.8. Treatment Compliance

Study drug will be administered in the presence of site staff every time the participant is on site on dosing days. Participants should return all used and unused study drug to the site at each site visit.

Treatment compliance will be calculated comparing the amount of study drug dispensed and study drug returned.

6. STUDY PROCEDURES

The Schedule of Events with study activities is provided in [Appendix 1](#).

Clinic visits should be scheduled at approximately the same time for each visit (eg, consistent morning visits or consistent afternoon visits).

When several assessments are required at the same time point, evaluations should be completed so that the PK sample is collected at the required time. It is understood that other assessments such as ECGs (± 10 min) and vital signs (± 5 min) will be performed as close to the time point as possible.

Repeat assessments (clinical laboratory tests, spirometry, diffusing capacity for carbon monoxide [DLCO], HRCT, or ECG) are allowable if approved by the Medical Monitor or Sponsor's Study Director and if a result is believed to be technically flawed or spurious in nature.

6.1. Informed Consent

Written and dated informed consent, describing the study and anticipated risks of participation must be obtained from each study participant prior to any study-related procedures being performed.

6.2. Rescreening Procedures

Rescreening prior participants who did not fulfill inclusion or exclusion criteria is allowed. Approval should be obtained from the Medical Monitor or Sponsor's Study Director, who will also determine which tests specified in the protocol must be repeated.

6.3. Medical History

The medical and medication history of the previous 5 years will be reviewed and recorded at the Screening Visit. It should also include any relevant information or condition relevant to the purposes of this study, regardless of the timeframe.

6.4. Demographic Information

Demographic information, including year of birth, sex at birth, race, and ethnicity, will be recorded at the Screening Visit.

6.5. Eligibility Criteria

Eligibility criteria will be reviewed at Screening and Baseline (Day 1). Potential participants must meet all of the inclusion criteria ([Section 4.1](#)) and none of the exclusion criteria ([Section 4.2](#)) to be enrolled in the study.

6.6. Physical Examination

Complete and targeted physical examinations will be performed at the time points specified in the Schedule of Events ([Appendix 1](#)).

Complete physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological (including mental status

[awake and alert], pupils [size, light reflex], and gait/ambulation), extremities, back, neck, musculoskeletal, and lymph nodes. Weight will be recorded in kilograms and height in centimeters.

Targeted physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, and extremities, as well as any pertinent system based on any previous findings.

Physical examinations may be performed at various unscheduled time points if deemed necessary by an Investigator.

6.7. Vital Signs

Vitals signs, defined as pulse rate, temperature, respiration rate, peripheral arterial oxygen saturation (SpO₂) and blood pressure, will be recorded at the time points specified in the Schedule of Events ([Appendix 1](#)). Supplemental oxygen usage at the time of vital sign assessment can affect the outcome of the readings. In order to accurately monitor the safety of study participants, the level of supplemental oxygen usage and oxygen saturation must be recorded during every vital sign assessment. Participants will rest for at least 3 minutes in a supine position prior to vital signs assessment. Vital signs on Day 1 will be performed twice: as part of Baseline assessment and postdose. Postdose vital signs will be assessed 2 hours postdose and around the time of the ECG (see [Table 3](#) for the PK sample collection schedule).

6.8. Electrocardiography

Triplicate 12-lead ECGs will be obtained at visits indicated in the Schedule of Events ([Appendix 1](#)) using standardized equipment provided by the selected vendor, must be electronically transmitted, and centrally read. The triplicate 12-lead ECGs obtained at Screening must be centrally reviewed and must meet eligibility criteria prior to randomization. The ECGs on Day 1 will be performed twice: as part of Baseline assessment and postdose. Postdose ECGs will be collected within 15 minutes of a time-matched PK sample (approximately 2 hours postdose). At Week 52, triplicate ECG will be collected within 15-minutes of final PK sample. Additional 12-lead ECGs may be obtained at other times if clinically indicated, during unscheduled visits. All ECGs should be obtained after the participant has rested quietly in the supine position for at least 10 minutes. If PK samples are collected before ECG, then it should be within 15 minutes from the beginning of the first ECG. If PK samples are collected after ECG, then it should be within 15 minutes from the end of the third ECG. The triplicate ECGs will be averaged and the mean values per time point (average of the 3 assessments) used to interpret the ECG tracings.

The Investigator (or designee) will evaluate the ECG tracings and will record 1 of the following interpretations on the electronic case report form (eCRF): normal; abnormal, not clinically significant; or abnormal, clinically significant. Clinically significant changes from baseline in ECG findings will be recorded as AEs.

6.9. Clinical Laboratory Tests

Laboratory assessments will be conducted by central laboratory as detailed in the Schedule of Events ([Appendix 1](#)), including at the end of treatment (EOT) or at early termination. Urine

pregnancy assessments will be completed locally with supplies provided by the central laboratory. The required clinical laboratory tests are listed in [Table 2](#).

If local laboratory assessments are conducted by local laboratory, the Investigator should consult with the Medical Monitor or Sponsor's Study Direction, and results will be recorded in the eCRF.

Clinical laboratory tests will include hematology, serum chemistry, urinalysis, coagulation, and serology, together with pregnancy testing in females. Safety laboratory tests (hematology, serum chemistry, and coagulation) will be collected from fasting (at least 8 hours) participants during the Screening Visit. Fasting is not required for safety laboratory assessments conducted after the Screening Visit.

The Investigator will review the results of all laboratory tests as they become available and will ascertain if any laboratory value is abnormal or represents a clinically significant change from baseline for the individual participant. If a laboratory value is determined to be abnormal and to represent a clinically significant change from baseline for the participant, the Investigator will determine if it qualifies as an AE. If "yes," the abnormality will be reported on the AE eCRF. All clinically significant laboratory abnormalities that occur during the study and that were not present at baseline should be followed and evaluated with additional tests, if necessary, until diagnosis of the underlying cause or resolution.

Information on sample collection, processing, storage, and shipping will be provided.

Table 2: List of Laboratory Tests

Hematology^a	Serum Chemistry^a
Hematocrit	Alanine aminotransferase
Hemoglobin	Albumin
Mean corpuscular hemoglobin	Alkaline phosphatase
Mean corpuscular hemoglobin concentration	Alpha-1-acid-glycoprotein ^c
Mean corpuscular volume	Amylase (reflex lipase if amylase $\geq 1.5 \times \text{ULN}$)
Platelet count	Aspartate aminotransferase
Red blood cell count	Bilirubin (total and direct)
White blood cell count with differential	Blood urea nitrogen
Coagulation^a	Calcium
International normalized ratio	Chloride
Prothrombin time	Creatinine
Urinalysis	Creatine kinase
Appearance	Gamma-glutamyl transferase
Bilirubin	Glucose
Color	Lactate dehydrogenase
Glucose	Lipid panel ^d
Ketones	Total cholesterol
Reflex microscopic examination of sediment	High-density lipoprotein cholesterol
Nitrite	Low-density lipoprotein cholesterol
Occult blood	Triglycerides
pH	Phosphorus
Protein	Potassium
Specific gravity	Sodium
Urobilinogen	Total protein
Screening Only	Uric acid
Urine drug screen, including, but not limited to ^b :	Pregnancy Testing
Amphetamines	Serum pregnancy test (for women of childbearing potential) ^c
Barbiturates	Urine pregnancy test (for women of childbearing potential) ^{f g}
Benzodiazepines	Screening Only
Cocaine	Serum follicle-stimulating hormone – to confirm postmenopausal status
Methadone	Hepatitis A IgM antibody (HAV-IgM Ab)
Phencyclidine	Hepatitis B surface antigen (HBsAg)
Opiates	Hepatitis C virus antibody (HCV Ab)
Cotinine	Human immunodeficiency virus (HIV)
Tetrahydrocannabinol	
Alcohol metabolites	

ULN: upper limit of normal

^a Safety laboratory tests (hematology, serum chemistry, and coagulation) will be collected from fasting (at least 8 hours) participants during the Screening Visit; participants are not required to fast for safety laboratory tests at any other visit. Other laboratory tests may be obtained as part of a predetermined panel.

^b Urine drug screens should be utilized in determining the suitability for the study per Exclusion Criteria 28.

^c Only drawn/analyzed at baseline/Day 1 and Early Termination. Alpha-1-acid-glycoprotein is not required to assess Inclusion /Exclusion criteria.

^d Screening only.

^e Screening only unless urine pregnancy test is positive.

^f Performed locally with supplies provided by the central laboratory.

^g Positive tests will be confirmed with a serum test.

6.10. Dispensing Study Drug

Study drug will be prepared by the dispensing pharmacist (refer to pharmacy manual for details).

6.11. Efficacy Assessments

6.11.1. Spirometry

All spirometry assessments should be conducted in a consistent timeframe across study visits. All the results must be electronically transmitted and confirmed by central reading. Spirometry results obtained at Screening must meet eligibility criteria prior to randomization. Post baseline spirometry assessments should be completed around the same time (± 2 hours) of the time of completion of the baseline visit spirometry assessment.

- FVC: Absolute FVC volume and FVC_{pp} will be assessed by spirometry at Screening and at the time points specified in the Schedule of Events ([Appendix 1](#)).
- FEV1 will be assessed by spirometry at Screening.

6.11.2. Quantitative Lung Fibrosis Score

Quantification of lung fibrosis score will be assessed by HRCT at the time points specified in the Schedule of Events ([Appendix 1](#)). HRCT collected for eligibility at Screening can also be used for baseline QLF extent if the HRCT meets quality requirements and is completed within 35 days of the Baseline/Day 1. If the HRCT collected for eligibility was performed > 35 days prior to planned randomization, an additional HRCT for QLF extent needs to be completed for Baseline; this additional HRCT may be completed predose on Baseline/Day 1 but must occur prior to study drug administration.

6.11.3. Diffusing Capacity for Carbon Monoxide

DLCO will be assessed at Screening and at the time points specified in the Schedule of Events ([Appendix 1](#)). All DLCO results must be electronically transmitted and confirmed by central reading. DLCO results obtained at Screening must meet eligibility criteria prior to randomization.

6.11.4. Living With Pulmonary Fibrosis Questionnaire

The L-PF questionnaire will be assessed at the time points specified in the Schedule of Events ([Appendix 1](#)).

The L-PF questionnaire was developed to assess symptoms and health-related quality of life specifically in patients with IPF ([Swigris et al 2021](#)).

The questionnaire consists of 44 items divided into 2 modules: Symptoms (23 items) and Impacts (21 items). The Symptoms module assesses shortness of breath, cough, and fatigue in the past 24 hours. The Impacts module assesses multiple aspects of health-related quality of life

with a recall period of 1 week. Overall scores range from 0 to 100, with higher numbers indicating a greater impairment.

6.11.5. King's Brief Interstitial Lung Disease Questionnaire

The K-BILD questionnaire will be assessed at the time points specified in the Schedule of Events ([Appendix 1](#)).

The K-BILD is a clinically validated health status questionnaire developed for patients with interstitial lung disease ([Patel et al 2012](#)). The K-BILD questionnaire is a brief, self-completed health status measure of interstitial lung disease containing 15 items that measure health status in 3 domains (breathlessness and activities, chest symptoms, and psychological). The K-BILD domain and total score ranges are 0 to 100; 100 represents the best health status ([Sinha et al 2019](#)).

6.11.6. EuroQol-5 Dimension

The EQ-5D-5L will be administered to participants at the time points specified in the Schedule of Events ([Appendix 1](#)).

The EQ-5D-5L is a patient-reported outcome instrument that is used to evaluate quality of life in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression ([Balestroni and Bertolotti 2012](#)).

6.12. Pharmacokinetic Assessments

Total [REDACTED] plasma samples for bexotegast PK analysis will be obtained predose and at postdose at the visits indicated in [Table 3](#) and in the Schedule of Events ([Appendix 1](#)). For each study visit, study drug should not be taken at home and only be taken as instructed during the study visit.

Table 3: Pharmacokinetic Sample Collection Schedule

Study Day/Visit	Collection Time Point
Day 1	Predose 2 hours postdose (± 15 minutes of ECG)
Week 4	At least 2 hours postdose (± 15 minutes of ECG)
Week 12	At least 2 hours postdose (± 15 minutes of ECG) 3 to 4 hours postdose
Week 24	1 hour predose (-1 hour) (± 15 minutes) 1 hour postdose (1 hour) (± 15 minutes) At least 2 hours postdose (± 15 minutes of ECG)
Week 36	At least 2 hours postdose (± 15 minutes of ECG)
Week 52	1.5 hours predose (-1.5 hours) (± 15 minutes) 0 hours predose (1.5 hours after the previously collected PK sample predose) (± 15 minutes of ECG)
Early termination	At visit

ECG: electrocardiogram; PK: pharmacokinetic(s)

Note: If PK sample is collected before ECG, then it should be within 15 minutes from the beginning of the first ECG. If PK sample is collected after ECG, then it should be within 15 minutes from the end of the third ECG.

Note: All Baseline assessments should be done prior to first dose. Vital signs and ECGs on Day 1 will be performed twice: as part of Baseline assessment and postdose.

Dosing date and time will be recorded for the 3 days prior to visits with PK sample collection.

On visits with PK sample collection, the actual collection time of each sample, as well as the dosing time, must be recorded in the source data and on the eCRF. If the participant discontinues the study early, a plasma sample for PK should be taken at the early termination visit if possible.

Aliquots of these PK samples may be used to measure nintedanib or pirfenidone concentrations in those participants who are receiving these treatments.

Information on the collection, processing, storage, and shipping of PK samples will be provided.

6.13. Pharmacodynamic Assessments (Biomarkers in Plasma and Serum)

Plasma and serum samples will be obtained at predetermined times as indicated in the Schedule of Events ([Appendix 1](#)).

Baseline samples will be obtained prior to the first dose, with subsequent samples also collected predose. These samples will be used to measure specific proteins and peptides that may be elevated in participants with inflammatory/fibrotic disease or act as PD markers that may change with inhibition of $\alpha_v\beta_6$ and/or $\alpha_v\beta_1$. The Sponsor may also use these samples to perform exploratory investigations using metabolomic, transcriptomic, or proteomic methods to identify putative biomarkers for use in future studies in participants with fibrotic diseases.

Details of sample collection, storage, and assay will be provided.

Exploratory biomarkers of interest and evidence for their potential prognostic or PD value are presented in [Table 4](#).

Table 4: Exploratory Biomarkers

Biomarker	Evidence of Prognostic or Pharmacodynamic Value
[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]

DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; IPF: interstitial pulmonary fibrosis;

6.14. Pharmacogenomic Assessment (Optional)

Whole blood samples may be collected for evaluation of genetic factors that may affect the PK of bexotegrast at the visit indicated in the Schedule of Events ([Appendix 1](#)).

A whole blood sample for deoxyribonucleic acid (DNA) isolation may be collected from participants in the study before dosing on Day 1. The DNA samples may be analyzed to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in PK of bexotegrast. Exploratory analysis of polymorphisms associated with susceptibility to, or the progression rate of IPF may also be performed.

Only if a separate, optional pharmacogenomic informed consent is given in accordance with local ethical and regulatory requirements, a whole blood sample will be collected. Participants will be informed about the purpose of pharmacogenomic samples and the procedures during the informed consent process. Participation in the pharmacogenomic sub-study part is voluntary and not a prerequisite for participation in the study.

Detailed instructions for the handling and shipping of samples will be provided.

6.15. Concomitant Medication Assessments

All medications and therapies (including over-the-counter or prescription medications, vitamins, and herbal supplements, and supplemental oxygen use) that are used by participants at the Screening Visit through the end of study (EOS) or at early termination will be recorded, along with the indication for use, the dose, the frequency of administration, the route of administration, and the start and end dates. Generic names should be used.

6.16. Adverse Event Assessments

All AEs observed by the Investigator, volunteered by the participant, or elicited through open-ended questioning of the participant from the time the ICF is signed at the Screening Visit through the end-of-study visit are to be recorded. Any SAEs must be reported to the Sponsor within 24 hours of Investigator first awareness of the event. All AEs, including SAEs, must be followed to resolution or until the Investigator determines that there is not an anticipated resolution. Definitions of AEs and the procedures for documenting and reporting AEs and SAEs are described in [Section 7](#).

6.17. Missed Safety Assessments

Missed safety assessments will be reported as such and will not be imputed.

6.18. Additional Assessments

6.18.1. Patient Global Impression of Change

Participants will respond to the Patient Global Impression of Change (PGIC) questionnaire at the time points specified in the Schedule of Events ([Appendix 1](#)).

The PGIC asks respondents to rate their impression of the change in their disease before/after treatment using a bidirectional 11-point scale ranging from much better to much worse ([Kamper et al 2009](#)).

6.19. Appropriateness of Measurements

Collection of AEs, safety laboratory assessments, vital signs, physical examinations, and ECG recordings are standard well-established parameters to assess the safety and tolerability of pharmacological agents.

The PK samples will be analyzed according to predefined validated analytical methods to assess the concentrations of bexotegast in plasma. FVC is a standard measure collected according to current American Thoracic Society guidelines for the measurement of IPF progression.

When available, appropriate standard guidelines will be used.

7. SAFETY ASSESSMENTS

7.1. Timing

In this study, AEs will be collected from the time the participant signs the ICF until the last study visit. AEs prior to first dose will be considered as non-treatment-emergent, and AEs post first dose through EOS Visit will be considered as TEAEs.

7.2. Definition of an Adverse Event

An AE is any event, side effect, or other untoward medical occurrence that occurs in conjunction with the use of a study drug in humans, whether or not considered to have a causal relationship to the treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study drug administration even though they may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication (overdose per se will not be reported as an AE/SAE)

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations in which an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Causality/relationship to study drug(s)
- Action taken regarding study drug(s) and continued participation in the study
- Outcome

7.3. Severity of an Adverse Event

Adverse events will be graded by the Investigator for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 criteria. The following guidance applies to any AE for which the CTCAE does not provide more specific criteria:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE; Grade 5 will only be applied to AEs for which the outcome is death.

7.4. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug(s) will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug(s) should be considered and investigated, if appropriate.

The relationship or association of the AE to study drug should be assessed using clinical judgment and the following considerations:

No (not related):	Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
Yes (related):	A temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the participant's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge.

The relationship to study procedures (such as venipuncture) should be assessed using the following considerations:

- | | |
|----------------------|---|
| No
(not related): | Evidence exists that the AE has an etiology other than the study procedure. |
| Yes
(related): | The AE occurred as a result of protocol-mandated procedures. |

7.5. Outcome

The outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolving
- Fatal
- Unknown

7.6. Pregnancy

A pregnancy is not an AE. If a female participant or the female partner of a male participant becomes pregnant while enrolled in the study following administration of study drug(s) and within 4 weeks or 12 weeks, respectively, after administration of the last dose of study drug(s), the Sponsor must be notified within 24 hours of the Investigator learning of the pregnancy. Administration of study drug(s) will be discontinued immediately, and the female participant or the female partner of a male study participant will be followed through the outcome of the pregnancy. The Investigator is required to provide all relevant information to the Sponsor using the Pregnancy Information Form.

The pregnancy will be followed through delivery. If the pregnancy results in a congenital anomaly/birth defects/miscarriage, this will be considered and reported as an SAE, per definition detailed in [Section 7.9.1](#).

7.7. Clinical Laboratory Adverse Events

Abnormal laboratory findings (eg, clinical chemistry, hematology, urinalysis) or other abnormal assessments (eg, ECG, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or that are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE, as described in [Section 7.2](#) (or recorded as an SAE if they meet the criteria for serious, as described in [Section 7.9.1](#)).

The Investigator should exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize

the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet may be of sufficient magnitude to require glucose administration to prevent such sequelae.

7.8. Recording Adverse Events and Serious Adverse Events

All AEs and SAEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

7.9. Serious Adverse Events

7.9.1. Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Is life-threatening
 - An AE is considered life-threatening if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Results in death
- Requires inpatient hospitalization (ie, admission, overnight stay) or prolongs existing hospitalization
 - An emergency room visit without hospitalization is not considered fulfilling the serious criteria of hospitalization.
 - Planned hospitalization or surgical procedure for an illness or disease which existed before the participant was enrolled in the clinical study is not considered an SAE unless the condition deteriorated in an unexpected manner.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event:
 - For example, an event that does not fulfill any of the serious criteria above but is considered to be clinically significant and may jeopardize the participant, or when medical or surgical intervention may be required to prevent 1 of the outcomes listed above.
 - Examples of such events include, but are not limited to: allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.9.2. Serious Adverse Events Reporting

All SAEs, whether or not considered related to study drug administration, must be reported immediately by the Investigator to the Sponsor, in a timeframe not to exceed 24 hours from the time the Investigator or site personnel first becomes aware of the event. The SAEs should be reported by completing the SAE Report Form and emailing it to:

Initial notification of an SAE provided to the Sponsor by telephone must be confirmed in writing within 24 hours by completing the SAE Report Form. As further information regarding the SAE becomes available, such follow-up information should be documented and sent to

All SAEs must be followed by the Investigator to resolution or medical stabilization.

Discontinuation from the study in the event of an SAE and the therapeutic measures that are taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the eCRF.

7.9.3. Suspected Unexpected Serious Adverse Reaction Reporting Obligations

A suspected unexpected serious adverse reaction (SUSAR) is an SAE for which there is a reasonable possibility of a causal relationship between the study drug and the event, and which is considered unexpected per the Reference Safety Information. For the purposes of expedited reporting, an SAE is considered unexpected if it is not listed in the current Reference Safety Information within the Investigator's Brochure or is not listed at the specificity or severity that has been previously observed.

The Sponsor or its designee will submit all SUSARs to appropriate Regulatory Authorities, IRBs/ECs, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of first knowledge of the event and follow-up information submitted within an additional 8 calendar days. All other SUSARs will be submitted within 15 calendar days of first knowledge of the event.

All SAEs must be reported to the IRB/IEC/REB by the Investigator in accordance with relevant regulations.

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9. MONITORING AND MANAGEMENT OF ELECTROCARDIOGRAM-RELATED ABNORMALITIES

The categories of a cardiac dysrhythmia for ECG QT corrected interval prolonged is presented in [Table 6](#).

Table 6: Grading for Electrocardiogram QT Corrected Interval Prolonged

	Grade 1	Grade 2	Grade 3	Grade 4
Electrocardiogram QT corrected interval prolonged	Average QTc 450 to 480 msec	Average QTc 481 to 500 msec	Average QTc ≥501 msec; or >60 msec change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia

QTc: QT interval corrected

Any participant who experiences a treatment-emergent QT interval corrected (QTc) prolongation of Grade 2 or higher must return to the study site for prompt clinical evaluation after the abnormal ECG results become available and to repeat the safety ECG assessment by the central laboratory. A PK sample must be obtained at the same visit that the repeat ECG assessment is performed, and the date and time of the PK draw and the last dose of study drug (and that of pirfenidone or nintedanib, if applicable) must be recorded in the eCRF.

- Increased >30 to ≤60 msec from baseline value → **The participant must return to the study site within 48 to 72 hours.**
- Grade 2: QTcF interval >480 msec but ≤500 msec → **The participant must return to the study site within 48 to 72 hours.**
- Grade 3: QTcF interval >500 msec; or increased >60 msec from baseline value → **The participant must return to the study site within 24 hours or, if not feasible, to a local clinic or hospital for immediate clinical evaluation.**

Clinical evaluation must include the following:

- Ruling out comorbidities and potential risk factors (eg, congestive heart failure, bradyarrhythmias).
- Evaluation of electrolyte disturbances (eg, potassium, calcium, and magnesium).
- Review of potential concomitant medications known to prolong the QTc interval (eg, serotonin receptor antagonists, antiemetics).

If prompt evaluation is not feasible (as described above and based on severity of abnormality), study drug should be interrupted immediately (date of last study drug dose [and that of pirfenidone or nintedanib, if applicable] must be recorded in the eCRF), and the participant must return to the study site as soon as possible for reevaluation. The Medical Monitor and Sponsor Study Director should be notified within 48 hours of the availability of initial ECG results and/or assessment of clinical symptoms.

Study drug must be permanently discontinued in the event of QTc prolongation meeting the following criteria:

- Confirmed Grade 3 abnormality: QTcF interval >500 msec; or increased >60 msec from baseline value.
- Grade 4 abnormality (does not require confirmation): torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia.

All treatment-emergent QTc abnormalities meeting the criteria for permanent discontinuation (as listed above) must be reported to the Medical Monitor and Sponsor Study Director within 48 hours. The participant must permanently discontinue study drug immediately and continue to be followed for close monitoring and causality and clinical evaluation as follows:

- Repeat central ECG at least once weekly until abnormalities stabilize (ie, QTc interval is comparable to baseline value or baseline grade of abnormality, if applicable) and the participant is asymptomatic.
- Correction of any electrolyte abnormalities, if applicable.
- Obtain a detailed history of symptoms and comorbidities.
- Obtain a history of concomitant drug use (including nonprescription or over-the-counter medications and herbal and dietary supplement preparations).
- Consider a cardiology consultation.

For participants with confirmed QTc prolongation (as described below) warranting temporary interruption of study drug but not meeting permanent drug discontinuation criteria, more frequent central ECG testing and clinical assessments (at least once weekly) must be performed using unscheduled visits, including a thorough causality evaluation and in consultation with the Medical Monitor.

- Confirmed Grade 2 QTcF interval >480 msec but ≤500 msec.
- Confirmed increase >30 to ≤60 msec from baseline value.

Reinitiation of study drug can only be considered if a more likely etiology is identified and if ECG abnormalities have returned to baseline values. **The decision to restart study drug must be discussed and approved in consultation with the Medical Monitor and Sponsor Study Director prior to reinitiation.** More frequent clinical monitoring and central ECG assessments (at least once weekly) after reinitiation of study drug, if applicable, should be performed through use of unscheduled visits. **If the QTc prolongation reoccurs upon rechallenge, study drug must be permanently discontinued.**

Any participant who experiences a QTc prolongation not confirmed upon repeat central ECG assessment may continue or resume administration of study drug and follow the scheduled study visits, if clinically appropriate. More frequent clinical evaluation and central ECG monitoring through use of unscheduled visits is allowed, if clinically warranted.

Participants who permanently discontinue study drug due to potential QTc prolongation must be followed for close monitoring until abnormalities stabilize to baseline levels or baseline grade of

abnormality and the participant is asymptomatic. Participants should be encouraged to remain in the study and complete all scheduled visits and assessments. Long-term follow-up information should be provided for participants who permanently discontinue drug due to confirmed QTc prolongation, including information on corrective therapy and cardiology consultation, if applicable.

10. ACUTE IPF EXACERBATIONS

Investigators will report progression of IPF and acute IPF exacerbations as 2 distinctly different events. IPF progression should be used to represent abnormal assessments or symptoms that are deemed clinically significant and different from prior evaluations and are not consistent with an acute IPF exacerbation.

Acute IPF exacerbation is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new, widespread alveolar abnormality in a participant with IPF. Extra-parenchymal causes (eg, pneumothorax, pleural effusion, pulmonary embolism) should be excluded.

An acute IPF exacerbation ([Collard et al 2016](#)) will be confirmed when all the criteria below are fulfilled.

- Acute worsening or development of dyspnea typically of less than one month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
- Deterioration not fully explained by cardiac failure or fluid overload

Proposed evaluation of acute respiratory deterioration is described in [Appendix 3](#).

11. EARLY DISCONTINUATION OF STUDY OR INDIVIDUAL PARTICIPANTS

In accordance with the Declaration of Helsinki, participants have the right to discontinue from study drug and the study at any time for any reason. Participants that discontinue study drug may still participate in study assessments.

The Investigator or Sponsor may discontinue a participant from study drug for any of the following reasons:

- Noncompliance with protocol procedures, including those relating to administration of study drug
- Occurrence of an SAE or intolerable AE
- A clinically significant change in a laboratory parameter occurs
- Female participants who become pregnant during the study must discontinue study drug immediately

Participants who discontinue study drug early will be encouraged to continue to participate in study assessments and will be analyzed using the ITT principle. If this is not feasible, the participant will be asked to return to the study site for an early termination visit; refer to the Schedule of Events ([Appendix 1](#)).

The study may be terminated at the discretion of the Sponsor. Reasons for termination may include but are not limited to:

- Discovery of an unexpected or unacceptable risk to the participants enrolled in the study
- Sufficient data suggesting lack of efficacy

12. PLANNED STATISTICAL METHODS

12.1. General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS[®] software (SAS Institute, Cary, North Carolina, United States).

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation (SD), median, interquartile range [25% quartile, 75% quartile]), minimum, and maximum value or 7-point descriptive summary (n, mean, SD, coefficient of variation, median, minimum, and maximum), unless otherwise stated.

Categorical data will be summarized using the frequency and percentage of participants.

Any changes to the protocol-specified analyses will be prespecified in the Statistical Analysis Plan (SAP) prior to database lock.

12.2. Sample Size and Power

12.2.1. Power Statement

A sample size of N=90 participants in each treatment group will provide at least 80% power to detect at least a 120 mL difference in FVC between at least 1 dose level of bexotegrast and placebo assuming a common SD of 285 mL and a 2-sided alpha of 0.05. To account for a 25% treatment discontinuation rate, the per treatment group sample size is N=120 for a total of approximately 360 participants.

12.3. Analysis Sets

12.3.1. Analysis Sets

The analysis sets (populations) for this study are:

- **Screened participants:** All participants who sign an ICF.
- **Intent-to-treat (ITT):** All randomized participants, regardless of study drug exposure, will be included in the ITT population. The ITT population will be the primary population for the summarization of efficacy analyses. Participants will be analyzed by randomized treatment.
- **Modified Intent-to-treat:** All participants in the ITT population who receive at least 1 dose of study drug, have at least 1 postdose FVC assessment, and are determined to not have FVC values deemed as outliers per SAP criteria. Participants will be analyzed by randomized treatment.
- **Safety:** All participants in the ITT population who receive at least 1 dose of study drug will be included in the safety population. The Safety population will be the primary population for the summarization of safety analyses. Participants will be analyzed by actual treatment.

- **Per protocol:** All participants in the ITT population who complete the study without any major protocol violations will be included in the per protocol population. Participants will be analyzed by actual treatment.
- **Per computed tomography protocol (CT):** All participants in the ITT population with an HRCT charter evaluable baseline or postbaseline HRCT scans will be included in the CT population. The CT population will be the primary population for the summarization of HRCT analyses. Participants will be analyzed by randomized treatment.
- **Pharmacokinetic:** All participants in the Safety population who have any evaluable PK concentration data will be included in the PK population. The PK population will be the primary population for the summarization of PK analyses. Participants will be analyzed by actual treatment.
- **Pharmacodynamic:** All participants in the safety population who have results from baseline and from at least 1 postbaseline PD assessment will be included in the PD analysis population. The PD population will be the primary population for the summarization of PD analyses. Participants will be analyzed by randomized treatment.

12.3.2. Examination of Subgroups

The following subgroups are predefined for the purposes of analyses. Subgroups will be investigated provided that each subgroup comprises >10% of the ITT population and the distribution of the subgroup is generally balanced across treatment groups.

The primary endpoint analyses and select secondary analyses will also be summarized using the following subgroups:

- Baseline background therapy use: a) yes; b) no
- Baseline GAP stage: a) I; b) II or III; c) II; d) III
- Smoking history: a) smoker (current or former); b) never smoker
- Time since IPF diagnosis: a) <median year; b) ≥median year

Additional subgroups may be defined in the SAP.

12.4. Demographics and Baseline Characteristics

Demographics (including age, sex at birth, race, ethnicity, height, weight, and body mass index) will be summarized for the ITT analysis set.

Baseline characteristics will include summaries for pulmonary function tests, GAP stage, and HRCT parameters. The GAP index and staging system is provided in [Appendix 4](#). Additional baseline summaries may be specified in the SAP.

12.5. Efficacy Analyses

12.5.1. Primary Efficacy Endpoint

The primary estimate of interest, change in absolute FVC (mL) from baseline to Week 52, will be used to evaluate the effectiveness of bexotegrast therapy relative to a placebo comparator in all randomized participants (ITT population). A treatment policy strategy, ignoring the occurrence of intercurrent events, will be used to handle intercurrent events with the exception of death.

The following hypothesis testing schema will be employed to assess the primary endpoint: the null hypothesis for the treatment comparison will be that there is no difference between the mean change in FVC (mL) at a given dose level of bexotegrast and the mean change from baseline on the placebo treatment at Week 52. The alternative hypothesis will be that there is a difference.

Change in FVC from baseline to Week 52 will be analyzed using a mixed model repeated measures (MMRM) analysis. The analysis model will include terms for baseline FVC, stratification factors, visit, and a treatment-by-visit interaction. An unstructured covariance matrix will be used as the within-participant covariance structure. The Kenward-Roger degrees of freedom correction will be used for this analysis. The full analysis model will be detailed in the SAP. Missing data are assumed to be missing at random.

Data summaries will include observed change in both absolute and percent change metrics as well as LS mean absolute change and 95% confidence interval (CI) from the MMRM.

Graphical summaries, including both change over time and cumulative distribution plots, will also be included.

Missing data are assumed to be missing at random for the primary analysis model and will not be imputed with the exception of death. All participants who experience death will have their missing FVC data imputed using a worst-case strategy where the imputed value, through a multiple imputation process, will be imputed to be less than the worst observed change from baseline FVC in the study. More details on missing data sensitivity analyses are included in Section 12.11.

Sensitivity analyses for the primary endpoint that account for missing data assumptions will be specified in the SAP.

12.6. Secondary and Exploratory Efficacy Endpoints

12.6.1. Disease Progression Endpoints

Disease progression in IPF, for the purposes of this study, is defined as: $\geq 10\%$ absolute decline from baseline in FVCpp, adjudicated respiratory-related hospitalization ([Durheim et al 2015](#)), adjudicated acute IPF exacerbation, or all-cause mortality.

The following composite endpoint is a secondary endpoint:

- Time to first occurrence of any of the following events over 52 weeks: $\geq 10\%$ absolute decline in FVCpp from baseline, adjudicated acute IPF exacerbations, adjudicated respiratory-related hospitalization, or all-cause mortality

The individual components to the composite endpoint over 52 weeks will also be reported where the composite events not being summarized are treated as competing risks:

- Time to a $\geq 10\%$ absolute decline in FVC_{pp} from baseline
- Time to first adjudicated acute IPF exacerbation
- Time to first adjudicated respiratory-related hospitalization
- Time to all-cause mortality

The following composite endpoints are secondary endpoints:

- Time to first occurrence of any of the following events over 52 weeks: adjudicated acute IPF exacerbations, adjudicated respiratory-related hospitalization, or all-cause mortality
- Proportion of participants with a $\geq 10\%$ absolute decline in FVC_{pp} from baseline or all-cause mortality at Week 52

Time to event endpoints will be summarized using Kaplan-Meier methodology with treatment differences analyzed using the log-rank test. The hazard ratio (relative risk) and its associated 2-sided 95% CI will be estimated based on a Cox proportional hazards analysis model with treatment assignment and stratification factors as covariates. Additional covariates will be specified in the SAP.

A graphical summary will also be provided.

The proportion of participants with disease progression will be summarized using count and percentages. In addition, proportion endpoints will be summarized using a logistic regression model. The analysis model will include the absence or presence of the event as the dependent variable and treatment and stratification factors as independent variables. The full analysis model will be specified in the SAP.

12.6.2. Pulmonary-based Endpoints

Secondary endpoints will summarize the change in FVC for each of the 2 key subgroups, participants with and without use of background therapy:

- Change in absolute FVC (mL) from baseline to Week 52 for participants with background therapy use
- Change in absolute FVC (mL) from baseline to Week 52 for participants without background therapy use

The same MMRM analysis model as the primary endpoint will be used, adding an interaction term for background therapy use-by-treatment-by-time to construct estimates.

Changes in additional spirometry assessments, FEV₁, forced expiratory volume in the first second percent predicted, and FEV₁/FVC ratio, will also be reported using the same MMRM analysis model as the primary endpoint replacing the independent FVC variables with FEV₁ and the baseline FVC with baseline FEV₁.

Additional exploratory pulmonary function-based endpoints will be analyzed and summarized for the ITT population as well as by background therapy subgroup using a similar manner as the

primary FVC endpoint using the same analysis model replacing the independent variable and baseline values:

- DLCO
- DLCOpp

Data summaries will include observed change in both absolute and percent change metrics as well as LS mean absolute change and 95% CI from the MMRM.

12.6.3. Patient-reported Outcomes

Participants will complete 2 patient-reported IPF symptom assessments, the L-PF questionnaire and the K-BILD questionnaire. The following outcomes will be summarized as secondary endpoints:

- Change from baseline in the L-PF Dyspnea score at Week 52
- Change from baseline in the L-PF Cough score at Week 52
- Change from baseline in the K-BILD Total score at Week 52

In addition, the following components of the L-PF questionnaire, including the total score, will be summarized as exploratory endpoints:

- Change from baseline in the L-PF Total score at Week 52
- Change from baseline in the L-PF Symptoms score at Week 52
- Change from baseline in the L-PF Fatigue score at Week 52
- Change from baseline in the L-PF Impacts score at Week 52

In addition, the following components of the K-BILD questionnaire, including the total score, will be summarized as exploratory:

- Change from baseline in the K-BILD Breathlessness and Activities score at Week 52
- Change from baseline in the K-BILD Psychological score at Week 52
- Change from baseline in the K-BILD Chest Symptoms score at Week 52

Participants will also complete the EQ-5D-5L assessment as exploratory endpoints:

- Change from baseline in the EQ-5D-5L index score at Week 52
- Change from baseline in the EQ-5D-5L VAS score at Week 52

MMRM analysis models will be used to summarize each endpoint. The model will include terms for baseline score, stratification factors, visit, and a treatment-by-visit interaction. The full analysis model will be detailed in the SAP.

Data summaries will include observed value and observed absolute change from baseline metrics as well as LS mean absolute change and 95% CI from the MMRM.

12.6.4. High-resolution Computed Tomography Endpoints

HRCT scan will be conducted. The following HRCT endpoints are exploratory endpoints:

- Change from baseline in QLF extent at Week 52

The following HRCT endpoints are exploratory endpoints:

- Proportion of participants with $\geq 2\%$ reduction in QLF extent at Week 52
- Proportion of participants with $\geq 2\%$ reduction or stable QLF extent at Week 52
- Proportion of participants with $\geq 2\%$ increase QLF extent at Week 52

In addition, the HRCT parameters, QLF (%), quantitative interstitial lung disease (extent and volume), and quantitative ground-glass (extent and volume), will also be summarized. The change from baseline endpoints will be summarized using the same MMRM analysis model as the primary endpoint replacing the independent FVC variables with QLF or QGG (quantitative ground glass) and the baseline FVC with baseline QLF or QGG adding a covariate for baseline total lung capacity.

Data summaries will include observed value and observed absolute change from baseline metrics as well as LS mean absolute change and 95% CI from the statistical model.

The proportion of participants with changes in specific thresholds will be summarized using the count and percentages.

12.6.5. Pharmacodynamic Endpoints

The following are exploratory PD endpoints:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

PD endpoints will be analyzed using a MMRM analysis model. The model will include terms for baseline biomarker, stratification factors, visit, and a treatment-by-visit interaction. The full analysis model will be detailed in the SAP.

Data summaries will include observed change in both absolute and percent change metrics as well as LS mean absolute change and 95% CI from the MMRM.

Graphical summaries, including change over time, will also be included.

Additional biomarkers may be specified in the SAP.

12.7. Safety Analyses

Safety data from all participants who received at least 1 dose of study drug will be incorporated into the final safety analysis. All safety data will be reported in listing format.

The safety population will be used to summarize safety results.

12.7.1. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities. A summary of medical history by treatment group will be provided.

12.7.2. Prior and Concomitant Medications

Prior medications are defined as any medications taken prior to first dose of study drug but stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

Prior and concomitant medications will be coded using the most current World Health Organization Drug Dictionary available. Summaries of concomitant medications by treatment group will be provided. Prior medications will be provided in listing format only.

12.7.3. Study Drug Exposure

Duration of exposure (in days) to study drug will be summarized by treatment group for the Safety Population. All exposure data, including changes in dosing, will be listed.

In addition, a compliance summary will be provided.

12.7.4. Adverse Events

AEs will be collected from the time the participant signs the ICF until the last study visit. TEAEs are defined as AEs that emerged or worsened in severity after the first administration of study drug through the follow-up period. TEAEs will be reported using the Investigator's assessment for safety reporting and may not align with adjudicated assessments used in efficacy reporting.

AEs will be coded using the Medical Dictionary for Regulatory Activities. All AEs will be graded for severity per CTCAE grading scale.

The incidence of TEAEs, the incidence of study drug-related TEAEs, and the severity of TEAEs will be summarized by system organ class, preferred term, and maximum severity by participant. In cases where a participant reports multiple occurrences of the same event (preferred term), the greatest severity will be included in the summary. The numbers and percentages of participants with SAEs and study drug-related SAEs and participants who discontinue study drug or the study due to an AE will be tabulated by treatment group.

In addition, a summary of ECG-related/potentially cardiac-related TEAEs will be provided.

All AE summaries will include summarization by the following groups: a) all participants, b) participants on background therapy, and c) participants not on background therapy.

12.7.5. Physical Examination

A listing of performance of the physical examination will be provided. Clinically significant adverse findings from physical examination will be reported as AEs.

12.7.6. Clinical Laboratory

Clinical laboratory data (serum chemistry, hematology and coagulation, and urinalysis) will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes (shifts) from baseline relative to normal ranges.

Treatment-emergent laboratory abnormalities that are deemed clinically significant must be recorded as AEs if they meet the definition of an AE.

12.7.7. Electrocardiograms

Summaries of ECGs by treatment group and visit will include changes from baseline for each parameter. In addition, summaries of QTcF values meeting specific thresholds in observed value and change from baseline as well as ECG abnormalities will be provided as specified in the SAP.

Clinically significant ECG abnormalities will be reported as AEs.

12.7.8. Vital Signs

Summaries of vital signs, including change from baseline, will be provided by treatment group and visit.

Clinically significant changes in vital signs will be reported as AEs.

12.8. Pharmacokinetic Analyses

For all PK data analyses, the PK population will be used.

Determination of bexotegast concentrations in plasma will be done by a bioanalytical laboratory using validated bioanalytical methods. Details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data for bexotegast will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the preceding bexotegast dosing time. Summary statistics (mean, SD, minimum, maximum, number of participants, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group.

Population PK analysis bexotegast concentrations will be performed using nonlinear mixed effects modeling. The population PK analysis will be conducted and reported separately. Details of the population PK analysis will be described in a separate population PK analysis plan.

Exploratory exposure-response analysis may be conducted using individual predictions of exposure from the population PK analysis in this study. Outcomes from this analysis will be reported separately, if conducted.

12.9. Multiplicity

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

12.10. PLN-74809 Dose Comparisons

The study is statistically powered to detect differences in FVC between a bexotegast dose and placebo. The study is not statistically powered to detect differences in FVC between bexotegast doses.

12.11. Missing Data

Missing data can have an impact on the analysis and interpretation of study data. It is anticipated that the amount of missing data will be minimal in this study. Participants who discontinue study drug early will be encouraged to continue to participate in study assessments and will be analyzed using the ITT principle.

A sensitivity analysis to the primary endpoint incorporating imputation method(s) for missing data will be specified in the SAP.

In addition, a retrieved drop-out approach to missing data may be conducted if an adequate number of participants discontinuing treatment continue with study assessments.

12.12. Interim Analysis

No interim analysis is planned.

12.13. Data Safety and Monitoring Board and Adjudication Committee

No interim analysis is planned, but a DSMB will periodically review the blinded and unblinded safety data from this study until the primary analysis is performed. The DSMB reporting will be detailed in a separate DSMB charter and DSMB SAP. The DSMB will assess the progress of the clinical study based on its safety assessment and recommend to the Sponsor whether to continue, modify, or stop the study. Meetings are planned to occur when approximately 25%, 50%, and 100% of the participants have been enrolled, and approximately quarterly thereafter.

As part of the periodic review of safety, the DSMB will conduct a monthly review of SAEs reported throughout the duration of this study.

The DSMB will maintain written records of all of its meetings.

An independent adjudication committee will assess acute IPF exacerbations, respiratory-related hospitalizations, and respiratory-related deaths.

13. QUALITY CONTROL AND ASSURANCE

During the study, the Sponsor and/or representatives of the Sponsor may visit a site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff are expected to cooperate with the auditors and allow access to all participant records supporting the eCRFs and other study-related documents.

At some point during the development program for the study drug, a regulatory authority may visit the Investigator to conduct an inspection of the study and the site. The Investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study related documents. The Investigator must immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

14. ADMINISTRATIVE CONSIDERATIONS

14.1. Institutional Review Board, Independent Ethics Committee Approval, or Research Ethics Board Approval

The Investigator must inform and obtain approval from the IRB/IEC/REB for the conduct of the study at named sites, for the protocol, for the participant ICF and any other written information that will be provided to the participants, and any advertisements that will be used. Written approval must be obtained prior to recruitment of participants into the study and shipment of study drug.

Proposed amendments to the protocol and aforementioned documents must be submitted to the IRB/IEC/REB for approval and submitted to regulatory authorities as applicable prior to implementation. Amendments may be implemented only after a copy of the local IRB/IEC/REB approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving IRB/IEC/REB approval. However, in this case, approval must be obtained as soon as possible after implementation.

The Investigator will be responsible for reporting protocol deviations to the IRB/IEC/REB as required by local requirements. The Investigator will be responsible for ensuring that an annual update is sent to the IRB/IEC/REB to facilitate continuing review of the study (if needed) and that the IRB/IEC/REB is informed about the end of the study. Copies of the update, subsequent approvals, and final letter must be sent to the Sponsor.

14.2. Ethical Conduct of the Study

The study will be conducted in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans. The study will be conducted in adherence to the study protocol and Good Clinical Practice (GCP), as defined in Title 21 of the United States Code of Federal Regulations Parts 50, 54, 56, 312, and Part 11 and in International Council for Harmonisation (ICH) E6 (R2): Guideline for Good Clinical Practice Consolidated Guidelines, Clinical trials - Regulation EU No 536/2014, and applicable regulatory requirements.

14.3. Participant Information and Consent

It is the Investigator's responsibility to obtain written informed consent from the participant after adequate explanation of the objectives, methods, anticipated benefits, and potential hazards of the study and before any study procedures commence.

The participant should be given a copy of the IRB/IEC/REB-approved ICF in their preferred language if English is not their native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated ICF must be retained in the institution's records and be available for inspection by representatives of the Sponsor or representatives from regulatory agencies. The participant will be given a copy of the signed ICF.

Participants unable to sign the ICF may participate in the study if a legal representative or witness provides the consent (in accordance with the procedures of ICH-GCP and local regulations) and the participant confirms his/her interest in study participation.

The participant will be informed that he/she can freely withdraw consent and stop participation in the study at any time with no prejudice to further treatment. It is the participant's responsibility to communicate this decision to the Investigator.

14.4. Participant Confidentiality

The Investigator must ensure that the participant's privacy is maintained. On the eCRF and other documents that are submitted to the Sponsor, participants will be identified by a participant study number only. Documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory agencies, and IRBs/IECs/REBs to review the portion of the participant's medical record that is directly related to the study. As part of the required content of informed consent, the participant must be informed that his/her records will be reviewed in this manner.

Applicable data privacy laws and regulations must be adhered to. The Investigator and the Sponsor are responsible for ensuring that personal data is processed in accordance with local data privacy laws (eg, Health Insurance Portability and Accountability Act, Personnel Information Protection and Electronic Documents Act, General Data Protection Regulation). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of personal data must be obtained.

14.5. Study Monitoring

The Investigator must allow the Study Monitors to periodically review, at mutually convenient times, during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records that support the participation of each participant in the study (source data). The eCRFs and other documentation that support the study must be kept up to date by the Investigator and the research staff at the investigative site. These study materials must be available for review by the Study Monitor and/or other qualified representatives of the Sponsor, at each monitoring visit.

It is the Study Monitor's responsibility to inspect the eCRFs at regular intervals throughout the study to verify adherence to the protocol; the completeness, accuracy, and consistency of the data; and adherence to GCP guidelines.

The Investigator agrees to cooperate with the Study Monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

14.6. Case Report Forms and Study Records

The investigative site will use eCRFs to record all the protocol-specified data for each participant who is enrolled in this study. Entries made in the eCRF must be verifiable against source documents. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The Investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each participant's eCRF, verifying that the information is accurate.

14.7. Retention of Data

The Investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and other study documentation are adequately maintained for the longer of (a) 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or (b) if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified; or (c) the record retention period mandated by local regulations.

The Investigator must not destroy any records associated with the study without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The contract research organization will retain the original eCRF data and audit trail.

14.8. Data Protection

The Sponsor has implemented information security policies and procedures designed to not only comply with the General Data Protection Regulation and similar privacy laws, but also to prevent unauthorized persons from gaining access to personal data collected and processed in the context of the study (Clinical Data) and to ensure that persons authorized to access Clinical Data gain access only in accordance with their access rights. The Sponsor also maintains policies and procedures for detecting, monitoring and responding to data security incidents and, as appropriate, for reporting data security incidents to regulators and/or individuals. The Sponsor carries out periodic risk assessments/reviews and, as appropriate, updates its information security policies and procedures accordingly.

14.9. Financial Disclosure

Financial disclosure statements will be handled in a separate agreement apart from the protocol, kept on file, and submitted as applicable with any subsequent license application.

14.10. Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. Any publication of the results of this study must be authorized by the Sponsor. The Sponsor will have the opportunity to review any publications that arise from the Investigators before submission for publication. Any such review and approval of publications related to the study shall be made pursuant to the process agreed between the parties in the site's clinical study agreement with Sponsor. Authorship on any publication of the results from this study will be based on contributions to study design, data acquisition and analysis, and interpretation of results.

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16. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS

Assessment	Screening ^a	Baseline ^b	Treatment Period					ET	EOS (14 days after last dose) (±3 days)
	Day -35 to Day -1	Day 1	Week 4 (±2 days)	Week 12 (±3 days)	Week 24 (±3 days)	Week 36 (±5 days)	Week 52/ EOT (±5 days)		
Informed consent	X								
Medical and medication history	X								
Demographics	X								
Check eligibility criteria	X	X							
Serum pregnancy test (for women of childbearing potential)	X								
Complete physical examination (including height and weight)	X								
Targeted physical examination		X	X	X	X	X	X	X	X
Vital signs ^e	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate) ^d	X	X	X	X	X	X	X	X	X
Randomization		X							
Spirometry (FVC, FEV1) ^e	X	X	X	X	X	X	X	X	
DLCO ^e	X	X	X	X	X	X	X	X	
HRCT for eligibility ^{f,g}	X								
HRCT for QLF extent ^{h,g}	X				X ⁱ		X		

Assessment	Screening ^a	Baseline ^b	Treatment Period					ET	EOS (14 days after last dose) (±3 days)
	Day -35 to Day -1	Day 1	Week 4 (±2 days)	Week 12 (±3 days)	Week 24 (±3 days)	Week 36 (±5 days)	Week 52/ EOT (±5 days)		
K-BILD ^j		X		X	X	X	X		
L-PF		X		X	X	X	X		
EQ-5D-5L		X			X		X		
PGIC					X		X		
Hematology	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X
PK sample (plasma) ^k		X	X	X	X	X	X	X	
Biomarker sample (plasma and serum) ^l		X		X	X		X		
Pharmacogenomic sample (optional)		X							
Pregnancy test (urine) ^{m,g}		X	X	X	X	X	X	X	X
Urinalysis ⁿ	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X
Study drug administration ^o		X	X	X	X	X	X		
Study drug dispensing		X		X	X	X			
Study drug accountability			X	X	X	X	X	X	

DLCO: diffusing capacity for carbon monoxide; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; EQ-5D-5L: Euro Qol-5 Dimensions; ET: early termination; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; HRCT: high-resolution computed tomography; K-BILD:

King's Brief Interstitial Lung Disease; L-PF: Living with Pulmonary Fibrosis; PGIC: Patient Global Impression of Change; PK: pharmacokinetics; QLF: quantitative lung fibrosis

- ^a Safety laboratory tests (hematology, serum chemistry, and coagulation) will be collected from fasting (at least 8 hours) participants during the Screening Visit. Fasting is not required for safety laboratory assessments conducted after the Screening Visit.
- ^b All Baseline assessments should be done prior to first dose. Vital signs and ECGs on Day 1 will be performed twice: as part of Baseline assessment and postdose.
- ^c Participants will rest in a supine position for at least 3 minutes prior to vital signs assessment. Vital signs on Day 1 will be performed twice: as part of Baseline assessment and postdose. Vital signs will be assessed 2 hours postdose and around the time of the ECG.
- ^d Participants will rest in a supine position and in an undisturbed environment at least 10 minutes prior to and during ECG recording with the triplicate ECGs recorded within approximately 5 to 10 minutes. The triplicate 12-lead ECGs obtained at Screening must be confirmed by central reading and must meet eligibility criteria prior to randomization. The ECGs on Day 1 will be performed twice: as part of Baseline assessment and postdose. Postdose ECGs will be collected within 15 minutes of a time-matched PK sample (approximately 2 hours postdose). At Week 52, triplicate ECG will be collected within 15-minutes of final PK sample.
- ^e Order of lung function measurements: 1. Spirometry followed by a rest as needed; 2. DLCO. Each DLCO test should be performed using the same equipment. Measurements should be performed at approximately the same time each visit based on Baseline assessments. All spirometry and DLCO results must be electronically transmitted, confirmed by central reading, and must meet eligibility criteria prior to randomization.
- ^f HRCT scan performed ≤ 2 years prior to the Screening date may be used.
- ^g Women of childbearing potential (WOCBP) will be required to have a negative highly sensitive urine pregnancy test within the 24 hours before the HRCT scan. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required before the HRCT is performed. If the serum pregnancy result at screening is positive, HRCT will not be performed, and the participant will be excluded from the study.
- ^h HRCT collected for eligibility at Screening can also be used for baseline QLF extent if the HRCT meets quality requirements and is completed within 35 days of the Baseline/Day 1. If the HRCT collected for eligibility was performed > 35 days prior to the planned randomization, an additional HRCT for QLF extent needs to be completed for Baseline; this additional HRCT may be completed on Baseline/Day 1 but must occur prior to study drug administration.
- ⁱ HRCT at Week 24 will be performed in accordance with local regulations.
- ^j Questionnaires must always be done by the patients in a quiet place prior to any other visit procedure. Order of questionnaires: 1. K-BILD, 2. L-PF, 3. EQ 5D-5L, PGIC.
- ^k For details of sample collection time at each visit, refer to [Table 3](#).
- ^l Baseline (Day 1) biomarker samples are to be collected prior to first dose of study drug. Post baseline biomarker samples (Week 12, Week 24, Week 52/EOT) should be collected predose.
- ^m Performed locally with supplies provided by central laboratory. Positive tests will be confirmed with a serum test.
- ⁿ Sent to central laboratory for analysis. If abnormal, followed by reflex microscopic examination. Aliquots for drug screening, cotinine, and alcohol are collected at Screening and at Unscheduled visits (as applicable). Candidates with a positive screening drug test must be evaluated by the Principal Investigator to assess if it is associated with a potential substance and/or alcohol use disorder that may impact study participation, adherence to study drug, study visits and assessments. This assessment must be documented in the eCRF to satisfy eligibility requirements.
- ^o Study drug is to be taken on empty stomach: no food from 2 hours predose to 2 hours postdose. Study drug will be administered at the Week 52 visit; at the EOS visit there will be no study drug administration.

APPENDIX 2. DISALLOWED CONCOMITANT MEDICATIONS

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

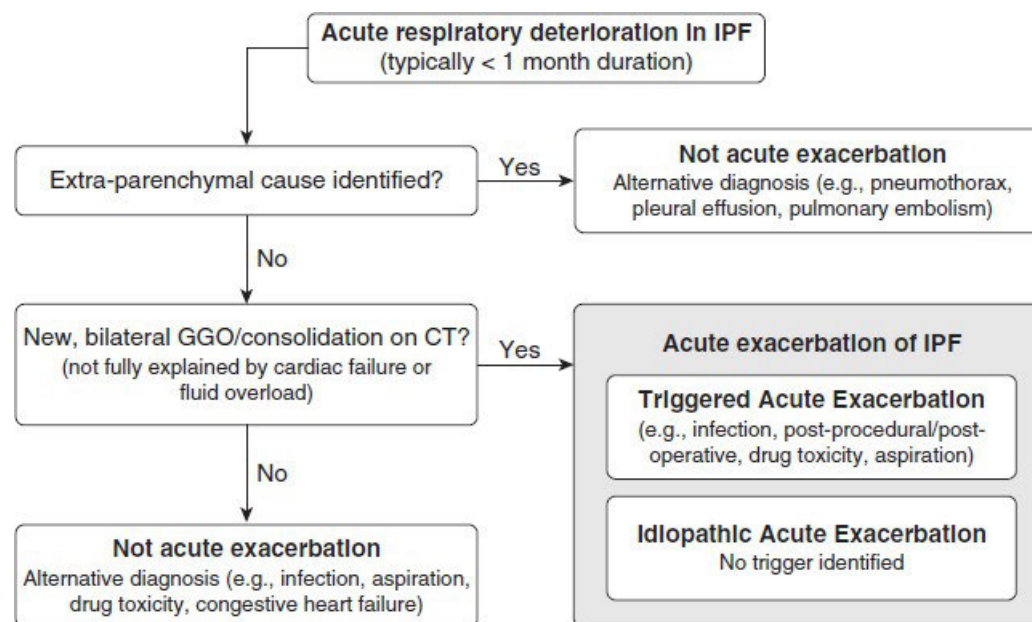
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

APPENDIX 3. Proposed Evaluation of Acute Respiratory Deterioration in IPF



CT: computed tomography; GGO: ground glass opacity; IPF: idiopathic pulmonary fibrosis

Note: Adapted from [Collard et al 2016](#).

APPENDIX 4. GAP Index and Staging System

The GAP index and staging system is a multidimensional, prognostic staging system derived from 4 commonly measured clinical and physiologic variables (gender, age, and 2 lung physiology variables [FVC and DLCO]) (Ley et al 2012). Points are allocated to each clinical or physiological variable and points are summed to provide a total score (from 0 to 8).

GAP Scoring

Predictor	Points Allocated
Gender	Female=0 Male=1
Age	$\leq 60=0$ 61 to 65=1 $> 65=2$
Physiology - FVC, % Predicted	$> 75=0$ 50 to 75=1 $< 50=2$
Physiology - DLCO, % Predicted	$> 55=0$ 36 to 55=1 $\leq 35=2$ Cannot perform ^a =3
Total Point Score	0 to 8

DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; GAP: gender-age-physiology

^a Assigned if symptoms or lung function prohibited performance of the DLCO maneuver. If DLCO is unavailable for a non-respiratory reason (eg, an operational reason), the GAP index and staging system cannot be applied.

The total score is then used to assign a stage (I, II, or III) as follows:

Staging System

Stage	I	II	III
Points	0 to 3	4 to 5	6 to 8

APPENDIX 5. SPONSOR SIGNATURE

Study Title: A randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of PLN-74809 (bexotegast) for the treatment of idiopathic pulmonary fibrosis (BEACON-IPF)

Study Number: PLN-74809-IPF-206

Final Date of Amendment 1 (Version 1.2): 04 June 2024

[REDACTED]

[REDACTED]

APPENDIX 6. INVESTIGATOR'S SIGNATURE

Study Title: A randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy and safety of PLN-74809 (bexotegast) for the treatment of idiopathic pulmonary fibrosis (BEACON-IPF)

Study Number: PLN-74809-IPF-206

Final Date of Amendment 1 (Version 1.2): 04 June 2024

I have read the protocol described above. I agree to comply with all applicable regulations, Good Clinical Practices, and to conduct the study as described in the protocol.

Signed: _____ Date: _____

Name: _____

Affiliation: _____

Site Number: _____