STATISTICAL ANALYSIS PLAN

Product Name:	Bexotegrast (PLN-74809)
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 Phase:	2b/3
Plan Version	Version 2.0 02 Apr 2025
Protocol Version:	PLN-74809-IPF-206 (Version 1.2: Phase 2b 04 Jun 2024) PLN-74809-IPF-206 (Version 2.22: Phase 2b/3 05 Jun 2024)
Sponsor:	Pliant Therapeutics Inc 331 Oyster Point Boulevard, South San Francisco, CA 94080, USA
Plan History:	Version 1.0 18 Feb 2025
Plan Prepared by:	[redacted]

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STATISTICAL ANALYSIS PLAN

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)

Plan Version: Version 2.0 02 Apr 2025

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HISTORY OF SAP DEVELOPMENT

Version	Date	Author	Sections Changed	Rationale for Change
1.0	18 Feb 2025	[redacted]	NA	original
2.0	14 Mar 2025	[redacted]	Section 1: Added language on trial early discontinuation Section 9.1: Added language that only Phase 2b analyses will be conducted	Early discontinuation of the trial
2.0	14 Mar 2025	[redacted]	Section 4.3: removed Phase 3 sample size and sample size re-estimation procedures Section 5.2: removed Phase 3 (Groups 2 and 3) randomization details Section 6.13: removed subgroups analyses by Race, Ethnicity, Region, Screening GAP stage (I, II, III), smoking history and baseline oxygen use due to small sample sizes within a subgroup Section 9.9: Removed baseline comparability statistical assessment [redacted] Section 10.3.7: Removed summary of the EQ-5D-5L Section 10.4: Removed all supportive analyses	No longer planned analyses due to early discontinuation of the trial

Version	Date	Author	Sections Changed	Rationale for Change
			Section 10.5 Removed all pooled (Phase 2b and Phase 3) analyses Section 10.6: Removed multiplicity algorithm	
2.0	14 Mar 2025	[redacted]	Section 6.3: Reduce categories for Asian Race	Due to reduced sample size given early discontinuation of the trial
2.0	14 Mar 2025	[redacted]	[redacted]	[redacted]
2.0	14 Mar 2025	[redacted]	Section 7.7, Sections 11.4: removed language on impact of pause on study exposure and compliance	Beginning of the pause in study drug was changed to end of treatment due to the early discontinuation of the trial
2.0	14 Mar 2025	[redacted]	Section 8: Amended changes from planned protocol analyses	Updates due to changes in planned analyses due to early

Version	Date	Author	Sections Changed	Rationale for Change
				discontinuation of the trial
2.0	14 Mar 2025	[redacted]	Section 9.6: Added proportion of participants by QLF % quartile and proportion of participants by QGG % quartile	Administrative error in Version 1.0
2.0	14 Mar 2025	[redacted]	Section 10.3.5: added QHC % and mL to be summarized	Administrative error in version 1.0
2.0	14 Mar 2025	[redacted]	Added Appendix on PRO scoring	Administrative error in Version 1.0
2.0	24 Mar 2025	[redacted]	Section 9.5: intentional protocol deviation category added to protocol deviation categories	New category added to cover changes to the protocol mandated by the Sponsor to sites due to the early discontinuation of the trial
2.0	24 Mar 2025	[redacted]	Added Appendix 9: Tables, figures and listing table of contents	Previously was a stand alone document
2.0	24 Mar 2025	[redacted]	Section 6.13: Added additional subgroups: FVCpp by quartile	Provide more sensitivity to baseline FVCpp analyses

Version	Date	Author	Sections Changed	Rationale for Change
2.0	24 Mar 2025	[redacted]	Section 6.12: Added a modified CT population	To account for on treatment CR scans due to the pause and early termination of the trial
2.0	24 Mar 2025	[redacted]	Section 10.2.2: updated logistic model from repeated measures to single time point	Early discontinuation of the trial and reduced number of events per visit
2.0	24 Mar 2025	[redacted]	Updated definition of follow-up period to extend beyond 14 days post dose to the End of study/ early termination visits	Early discontinuation of the trial
2.0	24 Mar 2025	[redacted]	Sections 10.2.1, 10.3.3.1: updated sample SAS code	To align sample code with actual code
2.0	24 Mar 2025	[redacted]	Global: updated pagination, font types and header notes to align with correct SAP version	Administrative error

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADAM	analysis data model
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below level of quantification
BMI	body mass index
BP	blood pressure
CFB	change from baseline
CI	confidence interval
CSR	clinical study report
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
FEV1/FVC	forced expiratory volume in the first second, forced vital capacity ratio
FEV1pp	forced expiratory volume in the first second percent predicted
FVC	forced vital capacity
FVCpp	forced vital capacity percent predicted
GAP	gender-age-physiology
GCP	Good Clinical Practice
HRCT	high-resolution computerized tomography
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio

Abbreviation	Definition
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITGB6	integrin beta-6
ITT	intent-to-treat
K-BILD	King's Brief Interstitial Lung Disease
LLT	lower level term
L-PF	Living with Pulmonary Fibrosis
LOD	limit of detection
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMP-7	matrix metalloproteinase-7
MMRM	mixed model repeated measures
MWV	Mean Worst Value
NC	non-calculable
NQ	non-quantifiable
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PP	per-protocol
PRO-C3	N-terminal type III collagen fragment
PRO-C6	C-terminal type Viα3 collagen fragment
PT	preferred term
QGG	quantitative ground glass
QILD	quantitative interstitial lung disease
QLF	quantitative lung fibrosis
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor-β
ULN	upper limit of normal

Abbreviation	Definition
VAS	visual analog scale
WHODD	World Health Organization Drug dictionary

Abbreviations used only in tables are defined in the respective table footnote and are not included in the List of Abbreviations.

1. INTRODUCTION

This document outlines the initial plan for the summarization and analysis of clinical data collected in Study 206. Study 206 is an operationally seamless Phase2b/Phase 3 study. In certain countries, Study 206 is being conducted with only the Phase 2b cohort without the Phase 3 cohort (Amendment 1 series) and in other countries with both the Phase 2b and Phase 3 cohorts (Amendment 2 series). The Phase 2b and Phase 3 cohorts' objectives, assessments and conduct are the same. The key difference between the 2 cohorts' statistical analysis is the ordering of hypotheses and corresponding multiplicity algorithm.

A single SAP will cover both the Phase 2b cohort analysis and the Phase 3 cohort analysis. Each cohort will be analyzed independently, with individual type I error spending, using the same objective and endpoints. Pooled analyses, combining both cohorts, will be conducted on select analyses as supportive to the independent cohort analyses.

The compartmental analysis of pharmacokinetics (data derivation and summary of individual PK parameters) is outside the scope of this document and is not addressed here. Concentration-time data will be tabulated by Day/Week and nominal time using descriptive statistics.

Study 206 was discontinued early due to a recommendation of the Study Data Safety Monitoring Board. As such, the SAP has been modified (Version 2.0) to a smaller subset of analyses pertinent to only the Phase 2b cohort. No participants were enrolled in the Phase 3 cohort.

This document describes the priori plan for analysis. Once the analysis is in progress, it may become apparent from the data that the planned analysis should be modified. Any substantive modification to the original analysis plan will be identified in the clinical study report (CSR).

2. STUDY OBJECTIVES AND ENDPOINTS

The following section provides a high-level overview of the objectives, endpoints and analysis methods.

Table 1. Study objectives, endpoints and statistical methods

Type	Objective	Endpoint	Statistical Method
Primary	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	*Separate models with be constructed for absolute change and percent change. The absolute change endpoint is controlled for within the statistical hierarchy.* **Statistical model:** mixed model repeated measures (MMRM) **Model terms**: Baseline FVC, Baseline background therapy use, Screening GAP Stage, Sex, Region, visit, treatment-by-visit interaction and background therapy use-by-treatment-by-time interaction. **Model Assumption**: first order autoregressive (AR[1]) covariance structure **Missing data approach:** Missing at random. Missing data will not be imputed for the analysis of the primary endpoint. **Data summaries:** observed absolute change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% confidence intervals (CI). P-value from the MMRM. Observed percent change and observed difference from placebo; LS mean percent change; LS mean differences and 95% CIs. P-value from the MMRM. **Graphical summaries**: LS mean FVC change over time (Weeks 0- 52), LS Mean Change at Week 52 bar plot, LS mean change cumulative distribution

Type	Objective	Endpoint	Statistical Method
Secondary	To characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on disease progression	Time to disease progression through Week 52, defined as time to first occurrence of: • Adjudicated respiratory-related hospitalization, • Adjudicated acute IPF exacerbation, • All-cause mortality Time to disease progression through Week 52, defined as time to first occurrence of: • ≥10% absolute decline from baseline in forced vital capacity percent predicted (FVCpp), • Adjudicated respiratory-related hospitalization, • Adjudicated acute IPF exacerbation, • All-cause mortality	*Separate models with be constructed for each time to disease progression endpoint.* *The first definition is controlled within the statistical hierarchy only.* **Statistical model:** Cox proportional hazard model. **Model terms:** Baseline background therapy use, Screening GAP Stage, Sex, Region and background therapy use-by-treatment interaction **Model assumption:** proportional hazards **Missing Data approach:** missing data is censored **Data Summaries:** Hazard ratios and 95% CIs. *P*-value from the Cox model. **Graphical summaries:** KM curves

Type	Objective	Endpoint	Statistical Method
		Proportion of participants with a ≥10% absolute decline in FVCpp from baseline or all-cause mortality through Week 52	**Statistical model:** logistic regression (binomial distribution with logit link function) **Model terms:** Baseline background therapy use, Screening GAP Stage, Sex, Region and background therapy use-by-treatment interaction **Model assumption:** autoregressive (1) covariance matrix using a residual option to order the columns of the R-side AR (1) covariance structure by the visit variable. **Missing Data approach:** missing data will be imputed as non-responders **Data Summaries:** observed counts and proportions; least-square proportions and odd ratios; *P*-value from the logistic regression model

Type	Objective	Endpoint	Statistical Method
	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	*Separate models with be constructed for absolute change and percent change.* *The same model used for the primary analysis will be used for these endpoints* **Statistical model:** mixed model repeated measures (MMRM) **Model terms:** Baseline FVC, Baseline background therapy use, Screening GAP Stage, Sex, Region, visit, treatment-by-visit interaction and background therapy use-by-treatment-by-time interaction. Model Assumption: first order autoregressive (AR[1]) covariance structure **Missing data approach:** Missing at random. **Data summaries:** observed absolute change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% confidence intervals (CI). *P*-value from the MMRM. Observed percent change and observed difference from placebo; LS mean percent change; LS mean differences and 95% CIs. *P*-value from the MMRM. **Graphical summaries**: LS mean FVC change over time (Weeks 0- 52), LS Mean Change at Week 52 bar plot, LS mean change cumulative distribution

Type	Objective	Endpoint	Statistical Method
	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	*Separate models with be constructed for each PRO endpoint* **Statistical model:** mixed model repeated measures (MMRM) **Model terms**: Baseline PRO score, Baseline background therapy use, Screening GAP Stage, Sex, Region, visit, a treatment-by-visit interaction and background therapy use-by-treatment-by-time interaction **Model Assumption**: unstructured (UN) **Missing data approach:** Missing at random. Missing data will not be imputed. **Data summaries:** observed absolute change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% CIs. *P*-value from the MMRM. **Graphical summaries**: LS mean change over time; LS mean change cumulative distribution

Type	Objective	Endpoint	Statistical Method
	To characterize the effect of bexotegrast versus placebo on change in lung fibrosis by high-resolution computerized tomography (HRCT) at Week 52	• Absolute change from baseline in quantitative lung fibrosis (QLF) extent (%) at Week 52	*Separate models with be constructed for absolute change and percent change. The absolute change endpoint is controlled for within the statistical hierarchy.* **Statistical model:** mixed model repeated measures (MMRM) **Model terms**: Baseline QLF %, Baseline background therapy use, Screening GAP Stage, total lung volume, Sex, Region, visit, treatment-by-visit interaction and background therapy use-by-treatment-by-time interaction. **Model Assumption**: unstructured (UN) **Missing data approach:** Missing at random. Missing data will not be imputed. **Data summaries:** observed absolute change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% CIs. *P*-value from the MMRM. observed percent change and observed difference from placebo; LS mean percent change; LS mean difference and 95% CIs. *P*-value from the MMRM. **Graphical summaries**: LS mean FVC change over time, LS Mean Change at Week 52 bar plot, LS Mean cumulative distribution

Type	Objective	Endpoint	Statistical Method
	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 (TEAEs) and serious adverse events (TESAEs)	Summaries will present TEAEs by system organ class (SOC), preferred term (PT), severity, relatedness to study drug and relatedness to background therapy. Participants with multiple TEAE events with the same preferred term will be counted once. The frequency and percentage of participants who experience TEAEs will be summarized overall and by treatment group.
Exploratory	To characterize the pharmacokinetics of bexotegrast over 52 weeks	• Bexotegrast concentration	Individual participant and mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times.
	To further characterize the effect of bexotegrast versus placebo after 52 weeks of treatment on measures of disease progression	• Time to a ≥10% absolute decline in diffusing capacity for carbon monoxide percent predicted from baseline to Week 52 or all-cause mortality through Week 52	**Statistical model:** Cox proportional hazard model. **Model terms:** Baseline background therapy use, Screening GAP Stage, Sex, Region and background therapy use-by-treatment interaction **Model assumption:** proportional hazards **Missing Data approach:** missing data is censored **Data Summaries:** Hazard ratios and 95% CIs. *P*-value from the Cox model. **Graphical summaries:** KM curves with log-rank test *P*-value presented

Type	Objective	Endpoint	Statistical Method
	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 • Patient Global Impression (PGIC) of Change Score at Week 52	*Separate models with be constructed for each exploratory PRO endpoint.* **Statistical model:** mixed model repeated measures (MMRM) **Model terms**: Baseline PRO score, Baseline background therapy use, Screening GAP Stage, Sex, Region, visit, a treatment-by-visit interaction and background therapy use-by-treatment-by-time interaction. **Model Assumption**: unstructured (UN) **Missing data approach:** Missing at random. Missing data will not be imputed. **Data summaries:** observed absolute change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% CIs. *P*-value from the MMRM. Note: PGIC scores will be presented using descriptive statistics only. **Graphical summaries**: LS mean change and percent over time

Type	Objective	Endpoint	Statistical Method
	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 (DLCO) • Diffusing capacity for carbon monoxide percent predicted (DLCOpp)	*Separate models with be constructed for absolute change for each DLCO endpoint.* **Statistical model:** mixed model repeated measures (MMRM) **Model terms**: Baseline FVC, Baseline background therapy use, Screening GAP Stage, Sex, Region, visit, treatment-by-visit interaction and background therapy use-by-treatment-by-time interaction. **Model Assumption**: first order autoregressive (AR[1]) covariance structure **Missing data approach:** Missing at random. Missing data will not be imputed **Data summaries:** observed absolute change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% CIs. *P*-value from the MMRM

Type	Objective	Endpoint	Statistical Method
	To characterize the effect of bexotegrast versus placebo for the proportion of participants with improvement in QLF at Week 52	• Proportion of participants with ≥2% reduction in QLF extent at Week 52 • Proportion of participants with ≥2% reduction or stable QLF extent at Week 52 • Proportion of participants with ≥2% increase QLF extent at Week 52	*Separate models with be constructed for each exploratory QLF extent endpoint.* **Statistical model:** A logistic regression (binomial distribution with logit link function), incorporating all the by-visit proportion of responders as the dependent variable. **Model assumption:** unstructured (UN) **Missing Data approach:** missing data will be imputed as non-responders **Data Summaries:** observed counts and proportions; least-square proportions and odd ratios; *P*-value from the logistic regression model
	To characterize the effect of bexotegrast versus placebo over 52 weeks of treatment on pharmacodynamic biomarkers	Absolute change from baseline at Week 52: [redacted]	*Separate models with be constructed for absolute change for each pharmacodynamic biomarker endpoint. Both absolute and percent change will be summarized.* **Statistical model:** mixed model repeated measures (MMRM) **Model terms**: Baseline biomarker, visit, and a treatment-by-visit interaction. **Model Assumption**: unstructured (UN) **Missing data approach:** Missing at random. Missing data will not be imputed. **Data summaries:** observed absolute change and observed difference from placebo; observed percent change and observed difference from placebo; LS mean absolute change; LS mean difference and 95% confidence intervals (CI). *P*-value from the MMRM.

3. OVERVIEW OF STUDY DESIGN

Study PLN-74809-IPF-206 is a randomized, double-blind, dose-ranging, placebo-controlled operationally seamless adaptive Phase 2b/3 study. The objective of the Phase 2b cohort is to evaluate the efficacy and safety of two dose levels and to select a bexotegrast dose(s) for final evaluation in the Phase 3 cohort. The objective of the Phase 3 cohort is to evaluate the efficacy and safety of the dose level(s) selected in the Phase 2b cohort. Both cohorts will evaluate the efficacy and safety of bexotegrast over 52 weeks in participants with IPF taking and not taking background therapy (ie, nintedanib or pirfenidone). Participants will be randomized in 3 groups with a separate data analysis for Group 1 (Phase 2b) and a separate data analysis for Groups 2 and 3 (Phase 3) with no data sharing between the primary analyses. Enrollment in Group 2 will be country specific depending on health authority approval.

In the Phase 2b cohort (Group 1), 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. Three-hundred and sixty (360) participants will be enrolled 1:1:1 to bexotegrast 160 mg, bexotegrast 320 mg, or placebo. Eligible participants will be stratified by type of background therapy at baseline (pirfenidone, nintedanib or none), gender-age-physiology index (GAP) for IPF stage (I or II/III), and Region (Americas/Europe/Middle East/Africa, Japan, India, or Asia-Pacific [APAC] excluding Japan and India) at study entry.

In the Phase 3 cohort (Groups 2 and 3), 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. Enrollment in the Phase 3 cohort will begin after the 360th participant is enrolled in the Phase 2b cohort. Thus, enrollment will be initiated in the Phase 3 cohort before the final bexotegrast dose(s) has been selected. As such, participants enrolled in the Phase 3 cohort prior to dose selection will be randomized 1:1:1 to bexotegrast 160 mg, bexotegrast 320 mg, or placebo. Initially, up to 504 participants will be enrolled in the Phase 3 cohort (up to 168 participants per group). If enrollment in the Phase 3 cohort is ongoing after bexotegrast dose selection (ie, has not enrolled up to n=504), participants in Group 3 will be enrolled using equal randomization to the selected bexotegrast dose(s) and placebo, until 168 participants have been enrolled in each selected group. Eligible participants will be stratified by type of background therapy at baseline (pirfenidone, nintedanib or none), gender-age-physiology index for IPF stage (I or II/III), and Region (Americas/Europe/Middle East/Africa, Japan, India, or APAC excluding Japan and India) at study entry.

A blinded sample size re-estimation for the Phase 3 cohort will be conducted after [redacted] participants in Group 1 have had the opportunity to complete 52 weeks of treatment. If the sample size is re-estimated to be higher to meet the Phase 3 primary objective, no greater than [redacted] additional participants per group will be added for a maximum of [redacted] participants per treatment group (N=[redacted] in total). In this scenario, the total sample size for the study will be increased from N=864 to N=[redacted].

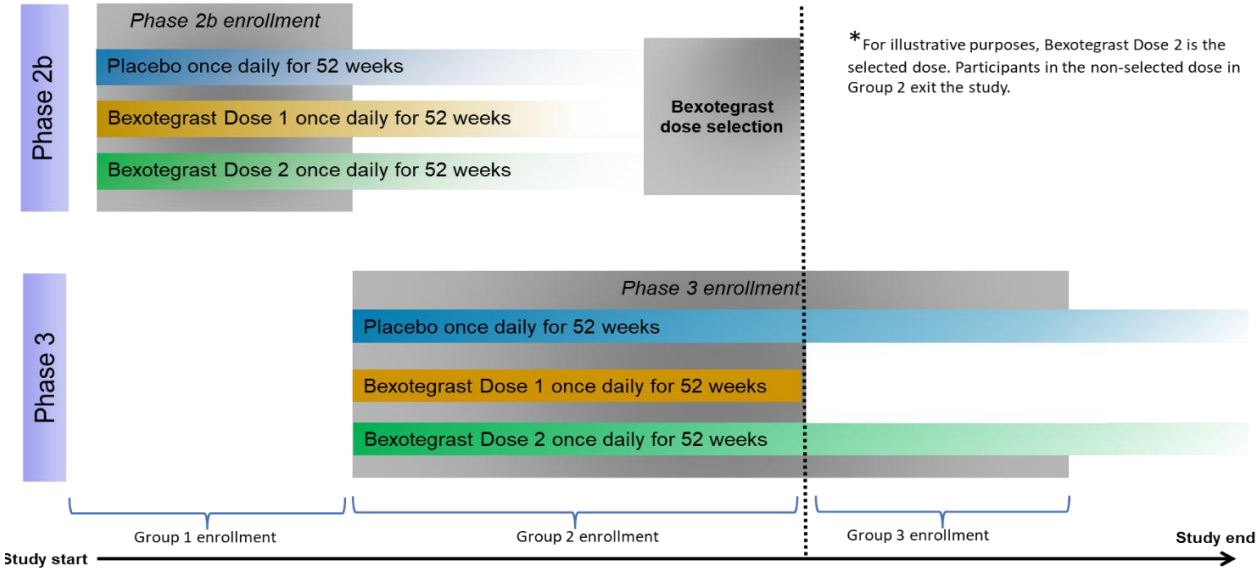
Approximately 30% of participants will not be taking background therapy at study entry which is managed using a cap on randomization for participants taking background therapy. Of note, participants who are not taking background therapy at study entry will be allowed to initiate either therapy at any time during the study. Thus, the study is designed to evaluate the efficacy

and safety of bexotegrast 160 and 320 mg in participants taking or not taking background therapy.

All participants who complete 52 weeks of treatment may be eligible to enroll in an extension study (under a separate protocol).

A study schematic is presented in Figure 1. The extension study will be conducted under a separate protocol and is not represented in the study schematic.

Figure 1. Study Schematic



Efficacy will be assessed via change from baseline in FVC, time to disease progression (including components of ≥10% absolute decline in FVCpp, adjudicated IPF acute exacerbations, adjudicated respiratory-related hospitalization, or all-cause mortality through Week 52), the proportion of participants with a ≥10% absolute decline in FVCpp or all-cause mortality through Week 52, change from baseline in diffusing capacity for carbon monoxide percent predicted (DLCOpp), change from baseline in several PROs, L-PF, K-BILD, EQ-5D-5L and change from baseline in quantitative lung fibrosis (QLF) extent (%). Samples for PD biomarker analysis and samples for PK analysis will also be collected.

Safety and tolerability will be assessed via TEAEs. Post baseline clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations that are clinically meaningful will be captured as TEAEs.

A Data Safety Monitoring Board (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 11.1.

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

Study 206 was discontinued early due to a recommendation of the Study Data Safety Monitoring Board. As such, the SAP has been modified (Version 2.0) to a smaller subset of analyses pertinent to only the Phase 2b cohort. No participants were enrolled in the Phase 3 cohort.

4. SAMPLE SIZE AND POWER

4.1. Phase 2b Sample size and Power

For Phase 2b (Group 1), 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.

5. RANDOMIZATION

5.1. Phase 2b (Group 1)

Three-hundred and sixty (360) participants will be randomized 1:1:1 to bexotegrast 160 mg, bexotegrast 320 mg, or placebo. Eligible participants will be stratified by type of background therapy at baseline (pirfenidone, nintedanib or none), gender-age-physiology index (GAP) for IPF stage (I or II/III), and Region (Americas/Europe/Middle East/Africa, Japan, India, or Asia-Pacific [APAC] excluding Japan and India) at study entry.

5.2. Blinding

Matching placebo tablets will resemble the bexotegrast tablets in shape, size, and color. 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 is utilized to maintain blinding between the 2 dose levels (160 and 320 mg) and placebo. Participants randomized to bexotegrast 160 mg will receive one 160 mg bexotegrast tablet and 1 matching placebo tablet. Participants randomized to bexotegrast 320 mg will receive two 160 mg bexotegrast tablets. Participants randomized to placebo will receive 2 placebo tablets.

6. GENERAL ANALYSIS CONSIDERATIONS

6.1. General Conventions

The Statistical Analysis Plan (SAP) must be approved prior to database lock for each cohort. If post database lock, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post Database Lock Statistical Analysis Plan Addendum.

The study treatment unblinding for final statistical analyses will occur after all subjects in a cohort have completed the Randomized Treatment Period and the End of Study Period. (See Appendix 1) and the database has been cleaned and locked.

All clinical data programming will be performed using SAS® statistical software package (Statistical Analysis System, Version 9.4 or higher) and based on Clinical Data Interchange Standards Consortium (CDISC) data standards.

Study Data Tabulation Model (SDTM) programming will follow SDTM version 1.7 together with SDTM implementation guide 3.3. Analytical Data Model (ADaM) programming will follow ADaM implementation guide 1.1. Specifications for SDTM and ADaM datasets are described in a separate document.

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

PK concentration-time data will be summarized using a 7-point summary, the number of nonmissing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%).

Categorical data will be summarized using the frequency and percentage of participants. Percentages will be based on the number of nonmissing observations or the participant population, unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Incidences of AEs, medical history, and concomitant medications will be reported at the participant level. Participants can only be counted once within each preferred term and system organ class under the highest severity and relationship to study drug. Percentages will be calculated using the number of participants in the treatment group for the safety population.

Model-based data will be summarized with LS means or LS proportions, standard errors, 95% CIs and *P*-values

All data from scheduled and unscheduled visits will be presented in the participant listings; however, unless noted otherwise, only data from scheduled visits will be included in the summaries, statistical analysis, and calculation of derived parameters. Early Termination (ET) assessments will not be summarized unless the ET visit falls on a scheduled visit.

Reporting structures for data summaries are presented in Appendix 2.

6.2. Decimal places

Means, medians, and percentiles will be displayed to 1 more decimal place than the data**,** dispersion statistics (eg, standard deviation and standard error) will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data.

Where appropriate, less decimal places may be used on a case-by-case basis as denoted in the table shells. Percentages will be displayed with 1 decimal place.

6.3. P-values

P-values will be displayed to 4 decimal places. *P*-values < 0.0001 will be presented as $p<0.0001$.

6.4. Data Displays

All TFLs will be generated as individual Rich Text Format (.rtf) files. Data summaries and graphical analyses will be reported within Section 14 of the CSR and individual participant data listings within Appendix 16.2 of the CSR.

Participant disposition, baseline characteristics, and demographics, will be presented by treatment group (PLN-74809 or placebo) and overall. Other summaries will be presented by treatment group (PLN-74809 or placebo) only.

Treatment group labels will be displayed as follows:

Bexotegrast 160 mg (N=XX)	Bexotegrast 320 mg (N=XX)	Placebo (N=XX)	Overall (N=XX)

Listings will be sorted in the following order treatment group, participant, parameter (alphabetical), and visit (ascending) unless otherwise stated. All data will be listed, participants who were not randomized will be displayed after the randomized treatment groups.

6.5. Colors

The following colors will be used:

- Placebo (#ADADAD/ RGB: 173, 173, 173 / circle-filled),
- Bexotegrast 160 mg (#4C70EE / RGB: 76, 112, 238 / triangle-filled),
- Bexotegrast 320 mg (#0E2A8F / RBG: 14, 42, 143 / square-filled).

In figures that contain multiple subgroups on same figure (eg, forest plots), no color (default black) will be used.

6.6. Medical Coding

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1. Conditions will be assigned to a system organ class and preferred term based on the Investigator-reported verbatim term.

Any medications taken (other than study drug) will be coded using the World Health Organization Drug Dictionary (WHO Drug) B3 SEP 2023 Version. Medications (both prior and concomitant) will be assigned to an Anatomical Therapeutic Chemical (ATC) Level 4 drug classification and preferred name based on the medication name reported on the eCRF. Oxygen use is considered a concomitant medication for the purposes of these summaries.

6.7. Baseline Definition

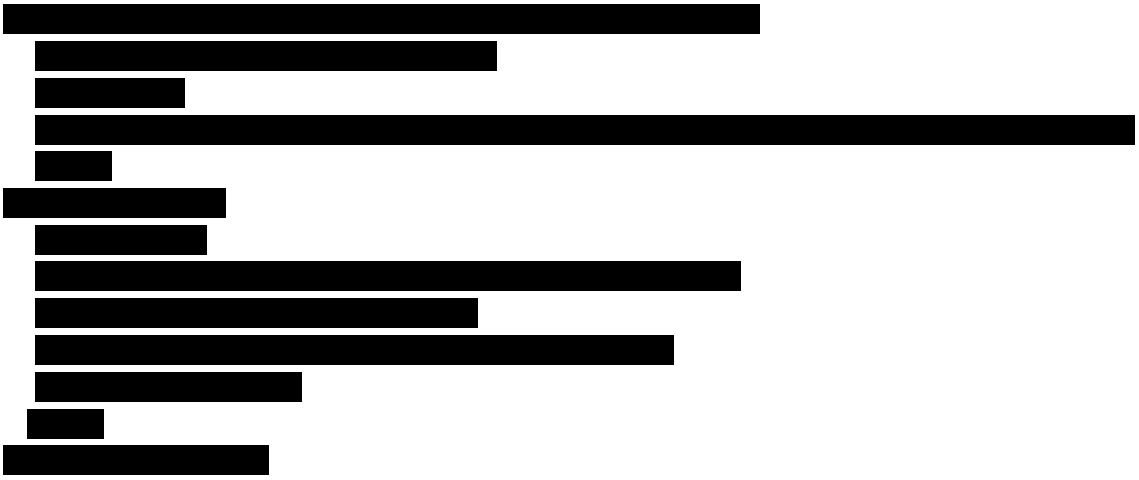
Baseline data is defined as data collected prior to and closest to administration of the first dose of study medication (bexotegrast or placebo).

Measurements taken after the start of administration of study drug will be considered on-treatment values and will be assigned to visits for statistical analysis, if applicable, as defined in Section 6.9.

6.8. Definition of FVC outlier

Outliers can confound assessment of efficacy. Grubb's test (Grubbs FE 1969) will be applied to FVC data to identify statistical outliers.

The following SAS® code is used for the determination of outliers:



In this code, VAR are the FVC (mL) spirometry values at each visit.

Outliers will be examined prior to database lock. If a statistical outlier was identified and confirmed by the clinical study lead to not be physiologically possible, then the outlier will be censored from the mITT analysis set.

Physiologically impossible applies only to increases from baseline and not decreases from baseline. This process may be repeated to test the presence of outliers in the reduced analysis set.

6.9. Analysis Windows

All assessments will be summarized using analysis windows, Table 2 - Table 5.

Only one observation per time window will be selected for statistical analysis at a particular visit. The terminology of unscheduled will be applied to assessments that are outside an analysis window regardless of the nominal label associated with the assessments in the EDC system.

In general, if multiple observations exist at a visit or collection time point then records will be chosen based on the following rules:

1. The record closest to the nominal day and timepoint in question, or,
2. The later record if the two visits are equidistant from the day and timepoint, or,
3. The average (arithmetic mean) if there is more than one planned record on the day and timepoint (only applies to assessments done in triplicate, eg, ECGs).
4. If multiple, evaluable spirometry sessions, within the same day for the same time point, exist:
    a. Use the highest-grade best effort attempt (only among grades A, B, C) across all evaluable sessions.
    b. If multiple records exist of the same grade, use the highest numerical FVC value as the record for best effort.
5. If multiple spirometry sessions are conducted within the same window:
    a. Only assessments with an acceptable or borderline acceptable quality grade will be selected.
    b. If two or more quality assessments are available, revert to step 1.

For multiple records that are within a visit window, the records(s) that do not meet the above selection criteria will be labelled as “Week X unscheduled”.

Table 2: Analysis windows for pulmonary function, laboratory assessments, physical exam, vital signs and 12-lead ECG

Start day	End Day	Length of the time-window [nominal days]	Visit number	Visit name (Nominal Label)	Nominal Day
-35	-1	35	-1	Screening	
-35[1]	Prior to first dose	1	1	Day 1 Baseline	1
Post first dose	End of first dose day	1	1.5	Day 1 Post Dose	1
First dose day+1	57	56	2	4 weeks	29
58	127	70	3	12 weeks	85
128	211	84	4	24 weeks	169
212	309	98	5	36 weeks	253
310	last dose day + 1	70	6	52 weeks	365

Start day	End Day	Length of the time-window [nominal days]	Visit number	Visit name (Nominal Label)	Nominal Day
Day of last dose+2	End of Study visit	14	7	Follow-up	379

[1] Participants without a baseline assessment prior to first dose have a Day 1 baseline analysis window overlapping with the screening analysis window; screening assessments will be windowed as Day 1 Baseline.

Table 3: Analysis windows for PROs

Start day	End Day	Length of the time-window [nominal days]	Visit number	Visit name (Nominal Label)	Nominal Day
-35	Prior to first dose	1	1	Baseline	1
First dose day+1	127	126	3	12 weeks	85
128	211	84	4	24 weeks	169
212	309	98	5	36 weeks	253
310	last dose day + 1	70	6	52 weeks	365
Day of last dose+2	End of Study visit	14	7	Follow-up	379

Table 4: Analysis window for HRCT

Start day	End Day	Length of the time-window [nominal days]	Visit number	Visit name (Nominal Label)	Nominal Day
-35	Prior to first dose	35	1	Baseline	1
Post first dose	139 (Week 19)	139	99	Unscheduled	NA
140 (Week 20)	196 (Week 28)	56	4	24 weeks	169
197 (Week 29)	335 (Week 34)	139	99	Unscheduled	NA
336 (Week 48)	378 (Week 54)	43	6	52 weeks	365
Day of last dose	End of Study visit			Follow-up	

Table 5: Analysis Windows for adverse events and medications

Window	Start	Stop
Adverse events	Signing of ICF	Maximum of follow-up visit or last contact
Treatment-emergent Adverse events, ECGs and Labs	Post first dose	Last dose + 14 days
Prior Medications	Up to 2 years prior to randomization	Prior to first dose
Concomitant Medications	Post first dose	Last dose + 24 hours
Medical History	Up to 2 years prior to randomization	NA

6.10. Conventions for Missing and Partial Dates

Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition. All dates presented in the individual participant listings will be as recorded on the electronic case report form (eCRF).

Missing / Partial Start / Stop Date of Adverse Events, Medical History and Concomitant Medication

Missing and partial start dates will be imputed solely for the purpose of determining whether an AE is treatment-emergent, medical history is ongoing at screening, or a medication is concomitant to study drug.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the participant has stopped taking the concomitant medication, the stop date will be imputed as the date of the participant's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the participant's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the participant's last clinic visit in which case the date of participant's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the participant's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing):

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing):

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

Missing Date of Last Dose:

If date of last dose is not present, the date of completion/termination will be imputed as the date of last dose for calculation of study drug exposure.

6.11. Definition of Major Analysis Protocol Deviations

The following protocol deviations are considered major analysis protocol deviations impacting the interpretation of efficacy and/or safety and which result in exclusion from the per protocol analysis set:

- Non-compliance with study drug < 80%;
- Does not meet inclusion criteria [redacted]
- Meets exclusion criteria [redacted]

6.12. Analysis Sets

The analysis sets (populations) for this study are as follows:

6.12.1. Screened Population (SCR)

The screened analysis set includes all participants screened who gave and signed an informed consent.

6.12.2. Intent-to-Treat (ITT)

The ITT analysis set will include all randomized participants, regardless of study drug exposure.

Treatment assignment will be based on the treatment randomized. The ITT analysis set is the primary analysis set for general and efficacy analyses.

6.12.3. Modified Intent-to-treat (mITT)

The mITT analysis set will include all participants in the ITT population who receive at least 1 dose of study drug, have at least 1 postdose FVC assessment. The ITT population participant's data will be included in the mITT analysis set if the data was collected while the participants was on treatment (ie, taking study drug). Data collected during off-treatment visits (ie, due to the pause in dosing) will be set to missing. Treatment assignment will be based on randomized treatment.

6.12.4. Per-Protocol (PP)

The PP analysis set includes all participants in the ITT population who complete the study without any major protocol analysis violations will be included in the per protocol population. Treatment assignment will be based on randomized treatment.

6.12.5. Safety (SAF)

The Safety analysis set will include all participants who were randomized into the study and received at least one dose of study drug.

Treatment assignment will be based on actual treatment. The Safety analysis set is the primary analysis set for safety analyses.

6.12.6. Pharmacokinetic (PK)

The PK analysis set includes all participants in the SAF population who have any evaluable PK concentration data (>below the limit of quantification). The PK analysis set will be the primary population for the summarization of PK analyses. Treatment assignment is by actual treatment.

6.12.7. CT Protocol (CT)

The CT analysis set will include all participants in the ITT analysis set with evaluable HRCT imaging data per the following criteria:

- Baseline HRCT scans are <35 days from randomization
- Participant did not experience an exacerbation or progression of IPF adverse event within approximately 2 weeks prior to a HRCT scan
- No identification of HRCT quality issues per the HRCT Imaging Charter as identified by HRCT overread vendor.

Treatment assignment will be based on randomized treatment. The CT population is the primary analysis set for the summary of HRCT data.

6.12.8. Modified CT Protocol (mCT)

The mCT analysis set will include all participants in the CT population who receive at least 1 dose of study drug, have at least 1 postdose HRCT assessment. The CT population participant's data will be included in the mCT analysis set if the data was collected while the participants was on treatment (ie, taking study drug). Data collected during off-treatment visits (ie, due to the pause in dosing) will be set to missing. Treatment assignment will be based on randomized treatment.

6.13. Examination of Subgroups

To characterize the consistency of the treatment effect, the primary endpoint analysis and select secondary endpoint analyses will be repeated for the following subgroups using an interaction term in the statistical model to assess the differential effect across subgroups.

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 following subgroup are prespecified:

- Age 1: a) <70 years; b) ≥70 years
- Age 2: age by quartiles
- Sex: a) Male; b) Female
- Race category: a) Asian b) non-Asian
- Baseline background therapy use 1: a) yes; b) no
- Baseline background therapy use 2: a) pirfenidone; b) nintedanib; c) none
- Baseline Background therapy use and Race category: a) pirfenidone, Asian Race; b) nintedanib, Asian Race; c) none, Asian Race; d) pirfenidone, Non-Asian Race; e) nintedanib, Non-Asian Race; f) none, Non-Asian Race
- Screening GAP Stage 1: a) I; b) II/III
- Baseline FVC % predicted 1: a) ≤70%; b) >70%)
- Baseline FVC % predicted 2: by quartiles
- Time since IPF diagnosis: a) <median year; b) ≥median year
- Baseline ITGβ6 expression by quartiles
- Participants on nintedanib therapy dosage at baseline: a) >=150 mg; b) <150 mg
- Participants with and without a treatment-emergent adverse event with preferred term of idiopathic pulmonary fibrosis
- Participants with and without a Grade 3 or higher treatment-emergent adverse event with preferred term of idiopathic pulmonary fibrosis

7. DERIVED DATA

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be recalculated.

7.1. Race

Where more than one race category has been selected for a participant, these race categories will be combined into a single category labelled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

7.2. Body Mass Index

Body mass index (BMI) will be calculated as follows:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight at Screening (kg)} / \text{Height at Screening (m)}^2$$

7.3. Best Effort Spirometry

Quality control of spirometry data will be conducted by a blinded overread Clinical Specialist based on ATS/ERS 2019 Guidelines. In each spirometry session, up to 8 attempts may be available for overread. The clinical specialist will assign a quality and replicability grade for each session. The quality grades are Acceptable, Borderline Acceptable and Unacceptable. The Acceptable and Borderline Acceptable quality grades indicate evaluable assessments and Unacceptable indicate non-evaluable assessments.

The clinical specialist will assign a replicability grade to the highest value “evaluable” effort within a spirometry session for each participant and visit (Table 6).

[redacted]

If no values meet the acceptability standards, participants can repeat the spirometry session later in the day or on a subsequent unscheduled visit.

Table 6: FVC Spirometry Assessment Grades

Grade	Criteria
Grade A	≥3 Acceptable maneuvers with repeatability ≤ 150 mL
Grade B	≥2 Acceptable maneuvers with repeatability ≤ 150 mL
Grade C	≥2 Acceptable maneuvers with repeatability (150, 200] mL
Grade D	≥2 Acceptable maneuvers with repeatability (200, 250] mL
Grade E	≥2 Acceptable maneuvers with repeatability > 250 mL OR 1 Acceptable Maneuver
Grade U	0 Acceptable and ≥ 1 Useable

Grade	Criteria
Grade F	0 Acceptable and 0 Useable Maneuvers

7.4. GAP Stage

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) (Table 7). GAP stage is determined from the GAP score per Table 8.

The screening assessments will be used to determine GAP stage.

Table 7: GAP Score Criteria

Predictor	Points Allocated
Gender	Female = 0; Male = 1
Age	≤ 60 = 0; 61 - 65 = 1; >65 = 2
Physiology - FVC, % Predicted	>75 = 0; 50 - 75 = 1; <50 = 2
Physiology - DLCO, % Predicted-hemoglobin adjusted	>55 = 0; 36 – 55 = 1; ≤ 35 = 2; Cannot perform = 3*
Total Point Score	**0-8**

*Cannot perform is only 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.

Table 8: GAP Stage

Stage	I	II	III
GAP score	**0-3**	**4-5**	**6-8**

7.5. Change from Baseline

Change from baseline is defined as the difference between baseline and any post-baseline records. A negative change from baseline indicates decline.

Percent change from baseline will be calculated as change from baseline multiplied by 100 then divided by the baseline value.

7.6. Study Day

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

7.7. Exposure to Study Drug and Study Drug Compliance

Exposure to study drug will be calculated as follows:

date of last dosing - date of first of dosing + 1

The exposure calculation will not take into account interruptions in study drug.

Study drug compliance will be calculated by comparing the amount of drug dispensed and drug returned for each participant as follows:

Number of tablets taken = Total dispensed – Total returned (if the number returned is missing, a value of 0 will be used).

Expected number of tablets = Number of days on study×2.

Compliance (%) = (Number of tablets taken / Expected number of tablets taken)×100.

7.8. Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

7.9. Electrocardiogram Abnormalities

Any QTcF interval (ms) result meeting the following criteria will be identified as an electrocardiogram abnormality:

Table 9: Electrocardiogram Abnormalities

Grade	Abnormality
1	Postbaseline value >450 and ≤480 msec
2	Postbaseline value >480 and ≤500 msec or postbaseline increase >30 and ≤60 msec
3	Postbaseline value >500 msec or postbaseline increase >60 msec
4	Incidence of Torsade de pointes, Ventricular tachycardia, Arrhythmia

7.10. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

8. CHANGES TO PROTOCOL SPECIFIED ANALYSES

The following changes to protocol specified analyses occurred prior to database lock of the Phase 2b cohort.

- Pharmacodynamic population was not used; ITT population used in place of pharmacodynamic population
- [redacted]
- Updated the definition of per protocol analysis set to include major analysis protocol deviations as opposed to major protocol deviations.
- mITT population was amended to include an on-treatment data requirement due to the study pause in dosing
- Multiplicity adjustment was removed due to the early discontinuation of the trial
- Several sensitivity analyses to the primary analyses were removed due to the early discontinuation of the trial
- Subgroup analyses by region and race were removed due to the early discontinuation of the trial.
- Summary of the EQ-5D-5L was not done due to the early discontinuation of the trial and limited Week 52 values ($n < 5$).

9. GENERAL ANALYSES

9.1. Sequence of Analyses

Due to the early discontinuation of the trial, only analyses of the Phase 2 cohort will be conducted.

9.2. Enrollment by Investigator

Enrollment by Investigator will summarize the number of participants enrolled by country and investigator by treatment group and total, sorted by highest enrolling country first and then by highest enrolling investigator. The randomized analysis set is used for this summary.

9.3. Analysis Sets

Participant status in each analysis set will be summarized by treatment group and overall for the screened population, as follows:

- The number of participants in each analysis population (SCR, SAF, ITT, mITT, PP, CT, mCT and PK).

Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone).

9.4. Participant Disposition

Participant disposition will be summarized by treatment group and overall for the ITT population, as follows:

- The number of participants who complete the study drug.
- The number of participants who terminate study drug early and the reason for early termination.
- The number of participants who complete the study.
- The number of participants who terminate early from the study and the reason for early termination.

A listing of participant disposition will include the ITT analysis set status, the date of informed consent signed, the date of first dose and last dose of study drug, primary reason for subject discontinuation of study medication, the date of last visit, study completion status, primary reason for study termination, and the date of last contact.

9.5. Protocol Deviations

Protocol deviations will be summarized by classification (critical, major, minor, intentional and total) and reason by treatment group and overall, for the ITT population. A listing of protocol deviations will be provided.

The ITT analysis set will be used for the summary.

9.6. Demographics and Baseline Characteristics

Demographics (age, age category (40-64, ≥65), sex, race, ethnicity, height, weight, and BMI) and baseline characteristics (time since IPF diagnosis, baseline background therapy, duration of background therapy, Screening GAP stage, supplemental oxygen use, Baseline HRCT categorical assessment, proportion of participants by QLF % quartile and proportion of participants by QGG % quartile will be summarized for the ITT analysis set.

Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone). A listing will also be provided.

The ITT analysis set will be used for the summary.

9.7. Baseline Pulmonary Function

A summary of pulmonary function (FVC, FVCpp, FEV1, FEV1pp, FEV1/FVC) at screening and at baseline will be provided.

A summary of DLCO (DLCO and DLCOpp) at screening and at baseline will be provided.

Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone). A listing will also be provided.

The ITT analysis set will be used for the summary.

9.8. Key Baseline Characteristics by Region

The following parameters will be summarized by region (US, EU/LATAM/Isreal/Canada, China, Japana, India, APAC) and in total: number randomized, age, sex, race, ethnicity, baseline background therapy, duration of background therapy, Screening GAP stage, baseline FVC, and FVCpp and Baseline HRCT categorical assessment.

Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone). A listing will also be provided.

The ITT analysis set will be used for the summary.

10. EFFICACY ANALYSES

Efficacy analyses will be presented by randomized treatment for the Intent-to-Treat (ITT) Population (unless otherwise specified). Tabulations will be presented overall, and by SoC (Yes/No) by GAP stage (I or II/III), and by Region (Americas/Europe/Middle East/Africa, Japan, India, or Asia-Pacific [APAC] excluding Japan and India) at study entry.

10.1. Primary Endpoint

The primary estimand 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 (Table 10).

Table 10: Attributes of the Primary Estimand

Attribute	Description
Study Objective	Investigation of the mean difference in the change in FVC from baseline to 52 weeks between bexotegrast and placebo treatment groups
Variable	Absolute change in absolute FVC (mL) from baseline to Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy, as defined by the inclusion and exclusion criteria, regardless of changes in their background therapy
Population Level Summary	Adjusted mean difference in change from baseline in absolute FVC (mL).
Estimator	The treatment difference for a continuous efficacy endpoint will be estimated using a mixed model repeated measures (MMRM) analysis
Intercurrent Events	Changes in background therapy while on treatment Start use of restricted medication Lung transplant Premature treatment discontinuation Study-wide pause in dosing Death

Hypothesis

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.

The statistical hypothesis of the primary endpoint includes a detection of significance in FVC with a 2-sided alpha of 0.05.

Analysis model

Change in FVC from baseline to Week 52 will be analyzed using a mixed model repeated measures (MMRM) analysis, with timepoints at Weeks 4, 12, 24, 36 and 52, to assess the difference between treatment groups with respect to change from baseline in absolute FVC volume. The change of absolute FVC volume from baseline will be considered the dependent variable, whereas treatment group, visit, treatment*visit interaction, baseline background therapy status, treatment*background therapy status*visit interaction, Screening GAP stage, and Region are considered in independent variables. Baseline FVC will be included as a covariate.

A first order autoregressive (AR[1]) covariance structure will be used to estimate the within subject variance covariance. If the model fails to converge, an unstructured (UN) covariance structure will be substituted.

Example SAS code for MMRM model is provided below. SAS options may be added or adjusted for ease of output and interpretation.

```
PROC MIXED DATA = DATAIN;
CLASS USUBJID TRT SOCYN GAP SEX REGION VISIT;
MODEL CHG = BASE TRT VISIT SOCYN GAP SEX REGION TRT*VISIT
              TRT*VISIT* SOCYN / SOLUTION CL DDFM = KR;
REPEATED VISIT / SUBJECT=USUBJID TYPE = AR(1);
LSMEANS TRT*VISIT / CL PDIFF DIFF;
RUN;
```

where

BASE: FVC value at baseline
CHG: FVC change from baseline
SEX: Participants sex
SOCYN: Participant’s background therapy use at baseline (Yes or No)
GAP: Screening GAP stage collapsed into a category I, II/III
SEX: Participants sex
REGION: Region for each participant at study entry
TRT: Randomized treatment group
USUBJID: Participant id
VISIT: visit number

The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (bexotegrast vs. placebo), corresponding SE, 95% CI, and p-value for each dose group will also be presented.

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

Missing data are assumed to be missing at random (MAR) for the primary analysis model and will not be imputed. Sensitivity analyses to examine the impact of missing data on the primary estimand are specified in Section 10.1.1.

10.1.1. Sensitivity Analyses to the Primary Endpoint

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

10.1.2. [redacted]

[redacted]

[redacted]

10.2. Secondary Endpoints

The following statistical analyses are designed to support the secondary estimands (with estimand attribute tables in Appendix 3).

10.2.1. Time to Disease Progression Endpoints

The following time to disease progression endpoints will be analysed as secondary endpoints:

- Key endpoint: Time to disease progression, defined as time to first occurrence of adjudicated respiratory-related hospitalization, adjudicated IPF exacerbation or all-cause mortality through Week 52
- Additional endpoint: Time to disease progression, defined as time to first occurrence of ≥10% absolute decline from baseline in forced vital capacity percent predicted (FVCpp), adjudicated respiratory-related hospitalization, adjudicated IPF exacerbation, or all-cause mortality through Week 52
- Additional Endpoint: Time to a ≥10% absolute decline in DLCOpp from baseline or all-cause mortality

For the purposes of efficacy presentations, TEAEs meeting the disease progression criteria will be summarized as identified by the adjudication committee. For the purposes of safety presentations, TEAEs will be summarized as recorded by the Principal Investigator, ie, non-adjudicated.

The primary analysis set for this summary is the ITT analysis set.

Hypothesis

The following hypothesis testing schema will be employed to assess the time to disease progression endpoints: the null hypothesis for the treatment comparison will be that there is no difference in the time to disease progression between at least one dose level of bexotegrast and placebo treatment groups at Week 52. The alternative hypothesis is that there is a longer time to disease progression in at least one bexotegrast treatment group.

Analysis Model

For each composite time to disease progression endpoint, estimates and 95% CIs for each treatment group will be presented using Kaplan-Meier estimates and the p-value will be calculated using a stratified log rank test. Hazard ratios (i.e., rate ratio) comparing each dose level of bexotegrast relative to placebo and 95% CIs will be calculated using a Cox proportional hazard model adjusting for baseline stratification factors. Breslow's method for handling ties will be used.

The following SAS code will be used to perform the Cox proportional hazard model analysis for each endpoint and produce the HR and 95% CIs.

```
PROC PHREG DATA= DATAIN;
CLASS TRT SOCYN GAP SEX REGION;
MODEL DAYS*EVENT(0) = TRT GAP SOCYN TRT*SOCYN SEX REGION /
RL;
HAZARDRATIO TREATMENT/DIFF=REF CL = WALD;
ODS OUTPUT HAZARDRATIOS = HREST;
RUN;
```

The binary indicator variable (EVENT) with a value of 0 indicates event was observed or a value of 1 indicates the time to the event is censored. DAYS is a time to event variable.

The following example SAS codes will be used to perform stratified analyses to generate stratum-specific median time to event estimates and confidence intervals, stratum-specific Kaplan-Meier curves, and to perform the log-rank test. For any unstratified analyses, code can be used after the removal of the strata line.

```
PROC LIFETEST DATA=DATAIN PLOTS =(S);
TIME DAYS*EVENT(0);
STRATA TRT;
TEST TRT;
ODS OUTPUT QUARTILES=DATACI(WHERE=(PERCENT=50))
PRODUCTLIMITESTIMATES=ESTIMATE(KEEP=TRT TIMETO SURVIVAL
STDERR WHERE=(SURVIVAL>=0 AND TIMETO>0.0))
PRODUCTLIMITESTIMATES=ATRISK(KEEP=TRT TIMETO FAILED LEFT);
RUN;
```

A survival plot and inverse survival plot of the Kaplan-Meier estimates will be provided.

Censoring rules for this model are defined as follows:

- Participants who are lost to follow-up or terminate their participation will be censored at the day of their last clinical date in clinical database.
- Participants who complete follow-up but do not have an event observed by Week 52, time is censored at the date of last follow-up.

The proportional hazard assumptions will be tested, and alternative parametric survival models will be used if the proportionality assumption is not sustained.

If the proportion of patients experiencing an event is less than 5%, only frequencies of events by treatment group will be provided for this endpoint. In this case no other analyses will be performed.

10.2.2. Proportion-based Disease Progression Endpoints

The following proportion-based disease progression endpoint will be analysed as a secondary endpoint:

- Proportion of participants with a ≥10% absolute decline from baseline in FVCpp or all-cause mortality through Week 52

The primary analysis set for this summary is the ITT analysis set.

Hypothesis

The following hypothesis testing schema will be employed to assess the proportion-based disease progression endpoints: the null hypothesis for the treatment comparison will be that there is no difference in the proportion of participants with disease progression between at least one dose level of bexotegrast and placebo treatment groups at Week 52. The alternative hypothesis is that there is a difference in at least one bexotegrast treatment group.

Analysis model

For the analysis of the proportion of participants with a ≥10% absolute decline (ie, disease progression) in FVCpp from baseline or all-cause mortality at Week 52, a logistic regression (binomial distribution with logit link function), incorporating all the by-visit proportion of responders as the dependent variable to assess this secondary endpoint.

An unstructured covariance matrix will be used.

A summary of participants who are FVC responders will include observed counts and proportions (using frequency reporting format) and observed least-square proportions and odd ratios on the differences between treatment groups. Nominal *p*-values will be reported.

The following example SAS codes will be used to perform the logistic regression analysis:

```
PROC GLIMMIX DATA=DATAIN;
CLASS TRT SOCYN SEX REGION;
MODEL FVCPP10 (EVENT="1") = TRT SOCYN SEX REGION TRT*SOCYN
       / SOLUTION DIST=BINOMIAL LINK=LOGIT DDFM=KR;
RANDOM INTERCEPT/SUBJECT=USUBJID;
LSMEANS TRT / DIFF PDIFF ODDSRATIO ILINK;
LSMEANS TRT*SOCYN / DIFF PDIFF ODDSRATIO ILINK;
RUN;
```

where

FVCPP10 Binary indicator for meeting criteria
SOCYN: Participant's background therapy use at baseline (Yes or No)
SEX: Participants sex
TRT: Randomized treatment group
USUBJID: Participant id

10.2.3. FVC by Background therapy subgroup

The following secondary endpoints are subgroup analyses of the primary endpoint:

- 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 primary analysis set for this summary is the ITT analysis set.

Hypothesis

The following hypothesis testing schema will be employed to assess the secondary 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 for a by-background-therapy subgroup. The alternative hypothesis will be that there is a difference.

Analysis Model

The same MMRM analysis model as the primary endpoint will be used exchanging the LSmeans statement for the interaction term for background therapy use-by-treatment to construct estimates.

A first order autoregressive (AR[1]) covariance structure will be used to estimate the within subject variance covariance. If the model fails to converge, an unstructured (UN) covariance structure will be substituted.

```
PROC MIXED DATA = DATAIN;
CLASS USUBJID TRT SOCYN  GAP SEX REGION VISIT;
MODEL CHG = BASE TRT VISIT SOCYN GAP SEX REGION TRT*VISIT
              TRT*VISIT*SOCYN / SOLUTION CL DDFM = KR;
REPEATED VISIT / SUBJECT=USUBJID TYPE = AR(1);
LSMEANS TRT*VISIT*SOCYN / CL PDIFF DIFF;
RUN;
```

where

BASE: FVC value at baseline
CHG: FVC change from baseline
SOCYN: Participant's background therapy use at baseline (Yes or No)
GAP: Screening GAP stage collapsed into categories I, II/III
SEX: Participants sex
REGION: Region for each participant at study entry
TRT: Randomized treatment group
USUBJID: Participant id
VISIT: visit number

The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (bexotegrast vs. placebo by subgroup), corresponding SE, 95% CI, and p-value for each dose group will also be presented.

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.

10.2.4. HRCT based endpoints

HRCT scans will be conducted at Baseline, Weeks 24 and/or Week 52. The following HRCT endpoint is a secondary endpoint:

- Change from baseline in QLF extent (%)

The primary analysis set for this summary is the CT analysis set.

Hypothesis

The following hypothesis testing schema will be employed to assess the secondary endpoint: the null hypothesis for the treatment comparison will be that there is no difference between the mean change in QLF extent (%) 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.

Analysis Model

An unstructured covariance structure will be used to estimate the within subject variance covariance

Example SAS code for MMRM model is provided below. SAS options may be added or adjusted for ease of output and interpretation.

```
PROC MIXED DATA = DATAIN;
CLASS USUBJID TRT SOCYN  GAP SEX REGION VISIT;
MODEL CHG = BASE TRT VISIT SOCYN  GAP SEX REGION TRT*VISIT
TLV TRT*VISIT* SOCYN / SOLUTION CL DDFM = KR;
REPEATED VISIT / SUBJECT=USUBJID TYPE = UN;
LSMEANS TRT*VISIT / CL PDIFF DIFF;
RUN;
```

where

BASE: QLF(%) value at baseline
CHG: QLF (%) change from baseline
SOCYN: Participant's background therapy use at baseline (Yes or No)
SEX: Participants sex
GAP: Screening GAP stage collapsed into categories I, II/III
REGION: Region for each participant at study entry
TLV: Total lung volume at baseline

TRT: Randomized treatment group
USUBJID: Participant id
VISIT: visit number

The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (bexotegrast vs. placebo), corresponding SE, 95% CI, and p-value for each dose group will also be presented.

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.

A supportive analysis using percent change will also be provided.

10.2.5. Patient Reported Outcome Endpoints

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

- 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.

The primary analysis set for this summary is the ITT analysis set.

Hypothesis

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

Analysis Model

An unstructured covariance structure will be used to estimate the within subject variance covariance.

Example SAS code for MMRM model is provided below. SAS options may be added or adjusted for ease of output and interpretation.

```
PROC MIXED DATA = DATAIN;
CLASS USUBJID TRT SOCYN GAP SEX REGION VISIT;
MODEL CHG = BASE TRT VISIT SOCYN GAP SEX REGION TRT*VISIT
              TRT*VISIT* SOCYN / SOLUTION CL DDFM = KR;
REPEATED VISIT / SUBJECT=USUBJID TYPE = UN;
LSMEANS TRT*VISIT / CL PDIFF DIFF;
RUN;
```

where

BASE: PRO score at baseline
CHG: PRO score change from baseline
SOCYN: Participant's background therapy use at baseline (Yes or No)
SEX: Participants sex
GAP: Screening GAP stage collapsed into categories I, II/III
REGION: Region for each participant at study entry
TRT: Randomized treatment group
USUBJID: Participant id
VISIT: visit number

The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (bexotegrast vs. placebo), corresponding SE, 95% CI, and p-value for each dose group will also be presented.

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 change over time, will also be included.

Missing data

Missing complete total or sub-domain scores will not be imputed.

Missing item scores are imputed based on the average of the non-missing item scores within the domain, rounded to the nearest integer. If the missing items are >50% per domain, then the domain score is set to missing.

If item 15 is missing, it will be replaced by the average of all available items 1-14.

If any of the domain scores are missing, the total score is set to missing.

10.3. Exploratory and Other Endpoints

10.3.1. Pharmacokinetic Concentration Endpoints

Blood samples for determination of total [redacted] PLN-74809 concentrations will be collected at predose (0 h), and at 2 hours post dose on Day 1 and at predose and at least 2 hours postdose on Weeks 4, 24, 36, and 52. Concentration-time data will be tabulated by Day/Week and nominal time using descriptive statistics. All BLQ values will be presented as "BLQ" in the concentration listings. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero.

Concentrations collected outside the sampling time window will be excluded from PK analysis and may be excluded from summary statistics.

The primary analysis set for this summary is the PK analysis set.

10.3.2. Pharmacodynamic Endpoints

The following are exploratory PD endpoints:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The primary analysis set for this summary is the ITT analysis set.

Analysis Model

An unstructured covariance structure will be used to estimate the within subject variance covariance.

Example SAS code for MMRM model is provided below. SAS options may be added or adjusted for ease of output and interpretation.

```
PROC MIXED DATA = DATAIN;
CLASS USUBJID TRT VISIT;
MODEL CHG = BASE TRT VISIT TRT*VISIT
                / SOLUTION CL DDFM = KR;
REPEATED VISIT / SUBJECT=USUBJID TYPE = UN;
LSMEANS TRT*VISIT / CL PDIFF DIFF;
RUN;
```

where

BASE: biomarker value at baseline
CHG: Change from baseline
TRT: Randomized treatment group
USUBJID: Participant id
VISIT: visit number

The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (bexotegrast vs. placebo), corresponding SE, 95% CI, and p-value for each dose group will also be presented.

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 change over time, will also be included.

In addition, biomarker results, will be summarized using descriptive statistics by treatment group and visit for each parameter. Actual biomarker concentration at each visit, the change from baseline and percent change from baseline will be presented.

The result adjusted for dilution factor will be used in summaries and listings. Samples hemolyzed, received ambient or with a note indicating improper storage will be excluded from summaries and listed only. If a sample has been excluded, then the change from baseline for that sample will not be calculated.

Actual biomarker concentrations will be presented as a line plot showing the mean (± SD) concentration at each visit by treatment group for each parameter.

10.3.3. Other Time to Disease Progression Endpoints

10.3.3.1. Other Component Time to Disease Progression Endpoints

For completeness to support interpretation of the composite time to disease progression endpoints, 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 ≥10% absolute decline in FVCpp from baseline
- Time to first adjudicated respiratory-related hospitalization
- Time to first adjudicated acute IPF exacerbation
- Time to all-cause mortality
- Time to a ≥10% absolute decline in DLCOpp

The primary analysis set for this summary is the ITT analysis set.

Analysis model

Each time to disease individual component endpoint (10% absolute decline in FVCpp, first adjudicated respiratory-related hospitalization, first adjudicated IPF exacerbation 10% absolute decline in DLCOpp and all-cause mortality) will analyzed using the sub-distribution function (Fine and Gray 1999) when death is a competing risk for the outcome on or before Week 52.

Risk sets will be constructed to include both individuals without any event and those who have had the competing event (i.e., death). Within this structure, a hazard function is calculated as the probability of the event given that an individual has survived up to time *t* without any event or has had the competing event prior to time *t*. Accordingly, any deaths that occur through Week 52 will be interpreted as events throughout the study duration (that is, at the time of analyses, deaths that occurred “remain in the denominator” [at-risk] and counted as “non-responders” [non-events] in the numerator). All deaths that occur before a component event will be considered censored at 365 days.

The hazard ratio for each treatment group versus placebo will be estimated using Cox regression under a competing risk framework, including treatment and baseline strata.

First, an ITT analysis will be performed in which subjects who die prior to experiencing a disease progression endpoint are treated as experiencing a competing risk in the Fine-Gray proportional hazard regression model. Second, a Cox model will be fit with binary indicators for treatment group and baseline strata as well as a treatment-by-baseline strata interaction. The treatment group hazard ratios and CIs and the interaction term p-value will be reported for the interaction models.

A forest plot will be generated to display the overall treatment hazard ratio estimate and CI from each of the within-stratum analyses.

The following SAS code will be used to generate the sub-hazard ratio and 95% confidence intervals for the competing risk analysis:

```
PROC PHREG DATA=DATAIN PLOTS(OVERLAY)=CIF;
CLASS TRT SOCYN SEX /ORDER = INTERNAL REF=FIRST PARAM =
GLM;
MODEL AVAL*EVENT(0) = TRT SOCYN SEX SOCYN*TRT/ RL
EVENTCODE=1;
HAZARDRATIO 'CASUE SPECIFIC HAZARD' TRT /DIFF= PAIRWISE
ODS OUTPUT HAZARDRATIOS = HREST;
RUN;
```

where

EVENT = 1 if the participant had the event by Week 52.
EVENT = 2 if the participant died before Week 52 and prior to having the event.
EVENT = 0 if the participant did not have the event and did not die.
Aval takes minimum of time of death and time to event.

10.3.3.2. Other Composite Time to Disease Progression Endpoints

The following composite time to disease progression endpoints will be analysed as exploratory endpoints:

- Time to a ≥ 10% absolute decline in FVCpp from baseline or all-cause mortality through Week 52
- Time to a ≥ 10% absolute decline in diffusing capacity for carbon monoxide percent predicted (DLCOpp) from baseline to Week 52 or all-cause mortality through Week 52

The primary analysis set for this summary is the ITT analysis set.

Analysis Model

For each composite time to disease progression endpoint, estimates and 95% CIs for each treatment group will be presented using Kaplan-Meier estimates and the p-value will be calculated using a stratified log rank test. Hazard ratios (i.e., rate ratio) comparing each dose level of bexotegrast relative to placebo and 95% CIs will be calculated using a Cox proportional hazard model adjusting for baseline stratification factors. Breslow's method for handling ties will be used.

The following example SAS codes will be used to perform stratified analyses to generate stratum-specific median time to event estimates and confidence intervals, stratum-specific Kaplan-Meier curves, and to perform the log-rank test. For any unstratified analyses, code can be used after the removal of the strata line.

```
PROC LIFETEST DATA=DATAIN PLOTS =(S);
TIME DAYS*EVENT(0);
STRATA TRT SOCYN GAP SEX REGION;
TEST TRT;
ODS OUTPUT QUARTILES=DATACI(WHERE=(PERCENT=50))
PRODUCTLIMITESTIMATES=ESTIMATE(KEEP=TREATMENT TIMETO
SURVIVAL STDERR WHERE=(SURVIVAL>=0 AND TIMETO>0.0))
PRODUCTLIMITESTIMATES=ATRISK(KEEP=TRT TIMETO FAILED LEFT);
RUN;
```

where

SOCYN: Participant's background therapy use at baseline (Yes or No)
GAP: Screening GAP stage collapsed into categories I, II/III
SEX: Participants sex
REGION: Region for each participant at study entry
TRT: Randomized treatment group

The binary indicator variable (EVENT) with a value of 0 indicates the event was observed or 1 indicates the time to the event is censored. DAYS is a time to event variable.

A survival plot and inverse survival plot of the Kaplan-Meier estimates will be provided.

10.3.4. Other Pulmonary Function Endpoints

The following other endpoints will be reported:

- Change from baseline in FVCpp
- Change from baseline in FEV1
- Change from baseline in FEV1/FVC ratio
- Change from baseline in DLCO
- Change from baseline in DLCOpp

The primary analysis set for this summary is the ITT analysis set.

Analysis model

The primary analysis FVC MMRM model will be applied to each other pulmonary function endpoint replacing the FVC baseline covariate with the corresponding baseline and replacing the individual independent FVC change variables with the corresponding change variable.

A first order autoregressive (AR[1]) covariance structure will be used to estimate the within subject variance covariance. If the model fails to converge, an unstructured (UN) covariance structure will be substituted.

Data summaries will include observed absolute 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.

10.3.5. Other HRCT Endpoints

For completeness to support interpretation of the HRCT QLF endpoint, the following other HRCT endpoints will be reported:

- Change from baseline in QLF (mL)
- Change from baseline in QILD (mL)
- Change from baseline in QILD (%)
- Change from baseline in QGG (mL)
- Change from baseline in QGG (%)
- Change from baseline in QHC (mL)
- Change from baseline in QHC (%)

The primary analysis set for this summary is the CT analysis set.

Analysis model

The QLF (%) MMRM model will be applied to each other HRCT endpoints replacing the QLF baseline covariate with the corresponding baseline and replacing the individual independent QLF change variables with the corresponding change variable.

An unstructured covariance structure will be used to estimate the within subject variance covariance.

Data summaries will include observed absolute 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.

10.3.6. Other Proportion-based HRCT Endpoints

The following proportion-based HRCT endpoints are exploratory endpoints:

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

The primary analysis set for this summary is the CT analysis set.

Analysis Model

For the analysis of the proportion of participants with HRCT threshold changes from baseline at Week 52 as described above, a logistic regression (binomial distribution with logit link function), incorporating all the by-visit proportion of responders as the dependent variable, will be used to assess this secondary endpoint hypothesis.

An unstructured covariance matrix will be used. The final model independent variables, as defined by the primary analysis, will also be used in this analysis.

A summary of participants who are responders will include observed counts and proportions (using frequency reporting format) and observed least-square proportions and odd ratios on the differences between treatment groups. The nominal p-value will be reported.

The following example SAS codes will be used to perform the logistic regression analysis:

```
PROC GLIMMIX DATA=DATAIN;
CLASS TRT SOCYN SEX REGION;
MODEL QLF2 (EVENT="1") = TRT SOCYN TLV TRT*SOCYN
       / SOLUTION DIST=BINOMIAL LINK=LOGIT DDFM=KR;
RANDOM INTERCEPT/SUBJECT=USUBJID;
LSMEANS TRT / DIFF PDIFF ODDSRATIO ILINK;
LSMEANS TRT*SOCYN / DIFF PDIFF ODDSRATIO ILINK;
RUN;
```

where

QLF2: Binary indicator for meeting criteria
SOCYN: Participant's background therapy use at baseline (Yes or No)
SEX: Participants sex
TLV: Total lung volume at baseline
TRT: Randomized treatment group
USUBJID: Participant id

10.3.7. Other Patient Reported Outcome Endpoints

The following sub-domain score for the PROs will be reported for completeness:

- Change from baseline in the KBILD breathlessness and activities score at Week 52,
- Change from baseline in the KBILD psychological score at Week 52,
- Change from baseline in the KBILD chest symptoms score at Week 52,
- Change from baseline in the 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 L-PF Symptoms score at Week 52.

The primary analysis set for this summary is the ITT analysis set.

Analysis model

The PRO score MMRM model will be applied to each other PRO score endpoints replacing the PRO score baseline covariate with the corresponding baseline and replacing the individual independent change variables with the corresponding change variable.

An unstructured covariance structure will be used to estimate the within subject variance covariance.

Data summaries will include observed absolute 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.

10.3.8. Patient Global Impression of Change (PGIC)

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. PGIC is collected only at Weeks 24 and 52.

Data summaries will include only descriptive statistics.

10.4. Multiplicity Algorithm

Due to the early discontinuation of the trial, endpoints will be reported with nominal p-values without adjustment for multiplicity.

11. 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.

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include adverse events, physical examination, vital signs, medical history, prior and concomitant medications, clinical laboratory results (hematology, chemistry, and urinalysis), and quantitative parameters from 12-lead ECGs.

For the purposes of safety presentations, TEAEs will be presented as recorded by the Principal Investigator, i.e., non-adjudicated. For the purposes of efficacy presentations, TEAEs will be presented as identified by the adjudication committee.

A summary comparing adjudicated status for each adjudicated event will be presented.

11.1. Data Safety and Monitoring Board and Adjudication Committee

A DSMB will periodically review the blinded and unblinded safety data from this study until the primary analysis for Phase 3 is performed. 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%, 100% of the Phase 2b (Group 1) participants have been enrolled, and approximately quarterly thereafter during the enrollment of the Phase 3 (Group 2 and Group 3) until the completion of all participants in the study.

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

An independent adjudication committee that is blinded to treatment assignment will assess IPF acute exacerbations, respiratory-related hospitalizations and respiratory-related deaths.

11.2. Medical History

A summary of prior and ongoing medical conditions at screening will be presented by randomized treatment group and overall, for the safety population. All reported medical history data will be listed.

Non-pharmacological procedures will be provided as a separate listing.

11.3. Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by randomized treatment group and overall for the safety population.

Both prior and concomitant medication verbatim terms (as recorded on the eCRFs) will be mapped to Anatomical Therapeutic Chemical (ATC) Level 4 and Drug Reference Names using the WHO dictionary [redacted]. Prior and concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 4.

Oxygen use is recorded as a medication.

11.4. Study Drug Exposure and Treatment Compliance

Duration of exposure (in days) to study drug will be summarized by treatment group for the Safety Population.

All exposure data will be listed.

In addition, treatment compliance will be summarized using descriptive statistics and by threshold (<80%, 81-90%, 91-95%, 96%-100%) by actual treatment group for the safety population. The summary will exclude the period under pause from calculations of compliance.

Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone).

11.5. 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 and 14 days post last dose of study drug.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version [redacted]. All AEs will be graded for severity per CTCAE grading scale.

AE analyses will be presented by the treatment received for the Safety Population. Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone).

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug through 14 days post last dose of study drug.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug through 14 days post last dose of study drug.

AEs occurring prior to first dose or beyond 14 days of last dose of study drug are considered non-treatment emergent and will be listed only.

The Investigator will determine the relationship of the AE to treatment (Related, Not Related). If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Severity of the AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) grading system (Version 5.0): Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening), Grade 5 (Fatal). Grade 3 (Severe) will be assumed for an AE with missing grade.

An overall summary of AEs (incidence and number of events) will be presented by treatment group and overall. Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone).

The following metrics will be summarized.

- Overall Summary of TEAE
- TEAE
- TEAE Related to Study Drug
- TEAE Related to a Study Procedure
- TEAE Related to Background therapy
- TEAE of CTCAE Grade 3 or Higher
- TEAE of CTCAE Grade 3 or Higher Related to Study Drug
- TEAE of CTCAE Grade 3 or Higher Related to Background therapy
- Serious TEAE
- Serious TEAE Related to Study Drug
- Serious TEAE Related to Background therapy
- TEAE by SOC and PT and maximum Grade
- TEAE by PT
- TEAE of CTCAE Grade 3 or Higher by PT
- SAE by PT
- TEAE Leading to Withdrawal of Study Drug
- TEAE Leading to Interruption of Study Drug
- TEAE Leading to Early Termination from Study
- TEAE Leading to Death

Summaries of TEAEs (incidence and number of events) will be presented by SOC and PT (unless noted as by PT only), by treatment group and overall. Summaries will be provided for all participants and by background therapy (Yes, No, nintedanib, pirfenidone).

Summaries for Asian participants only will also be presented as below.

- Overall Summary of TEAE (Asian Participants only)
- TEAE (Asian Participants only)
- TEAE of CTCAE Grade 3 or Higher (Asian Participants only)
- Serious TEAE (Asian Participants only)
- TEAE by PT Grade 3 or Higher (Asian Participants only)

In addition, the following summaries will be provided.

- TEAE by PT and Day of onset (D1-30, D31-60, D61-90, D91-240, D241+)
- IPF progression-related TEAEs by PT and LLT

- IPF progression-related TEAEs by PT and LLT (Asian Participants only)

System organ class will be presented in descending order of frequency in the total column and then alphabetically. Preferred terms will be displayed in descending order of frequency in the total column and then alphabetically.

For summary by severity, patients reporting more than one AE per system organ class and preferred term will only be counted once for the most severe event.

11.6. Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group at each visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Body weight (kg)
- Pulse oximetry (%)

All vital sign data will be listed.

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

11.7. Clinical Laboratory Parameters

Descriptive statistics of the observed values and change from baseline will be presented by treatment group and visit for each continuous hematology, serum chemistry, coagulation, and urinalysis parameter.

The required clinical laboratory tests are listed in Appendix 6.

Summaries and listings will be presented using the Système International (SI) unit for each parameter as received from the analytical laboratory.

Each measurement (for continuous data and for categorical data where provided) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

Clinical laboratory test parameters will be graded using the CTCAE grading scale for individual participants and values outside the reference ranges will be flagged. The incidence of treatment-emergent laboratory abnormalities (on or after first dose of study) will be summarized by severity and treatment group. For each parameter, summary statistics will be calculated for each measure and summarized by treatment and dose.

In addition, any confirmed liver abnormalities, identified per Section 7.10 will be summarized by treatment group and listed.

All individual laboratory data (i.e., including pregnancy testing data, local labs) will be listed. Any liver abnormalities identified will be provided as a separate listing.

11.8. 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 (Section 7.9) in observed value and change from baseline as well as ECG abnormalities will be provided.

Clinically significant ECG abnormalities will be reported as AEs.

Descriptive statistics for observed values and changes from baseline, based on central 12-lead ECG data, in the following ECG variables will be tabulated by treatment group at each visit:

- Heart rate (bpm)
- PR duration (ms)
- QRS duration (ms)
- RR interval (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcF interval (ms) [Fridericia's formula]

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS), from baseline to each follow-up visit will be presented.

All ECG data (supine 12-lead ECG and central 12-lead ECG), including details of any abnormalities, will be listed.

A separate listing of participants meeting the protocol-specified criteria (Section 7.9) will be presented.

12. REFERENCES

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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[c]	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		
K-BILD[j]		X		X	X	X	X		
L-PF		X		X	X	X	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)		
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	

DLCO: diffusing capacity for carbon monoxide; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; 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. 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 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. Measurements should be performed around the same time each visit based on Baseline assessments. Spirometry and DLCO results will be electronically transmitted and confirmed by central reading.

[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 theBaseline/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 predose 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 pharmacokinetic sample collection schedule in the protocol.

[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 EOT visit there will be no study drug administration.

APPENDIX 3. SECONDARY ESTIMAND ATTRIBUTE TABLES

Secondary Estimand 1:

Attribute	Description
Study Objective	Investigation of the effect of bexotegrast versus placebo over 52 weeks of treatment on disease progression
Variable	Time to disease progression, defined as time to first occurrence of ≥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
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Hazard ratio (i.e., rate ratio) and its 95% confidence interval will be calculated to compare each dose level of bexotegrast relative to placebo
Estimator	The treatment difference for this time-to-event efficacy endpoint will be estimated using a stratified Cox proportional hazard model
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

Secondary Estimand 2:

Attribute	Description
Study Objective	Investigation of the effect of bexotegrast versus placebo over 52 weeks of treatment on disease progression
Variable	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
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Hazard ratio (i.e., rate ratio) and its 95% confidence interval will be calculated to compare each dose level of bexotegrast relative to placebo
Estimator	The treatment difference for this time-to-event efficacy endpoint will be estimated using a stratified Cox proportional hazard model
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

Secondary Estimand 3:

Attribute	Description
Study Objective	Investigation of the effect of bexotegrast versus placebo over 52 weeks of treatment on disease progression
Variable	Proportion of participants with a ≥10% absolute decline in FVCpp from baseline or all-cause mortality through Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	A summary of participants who are FVC responders will include observed counts and proportions (using frequency reporting format) and observed least-square proportions and odd ratios on the differences between treatment groups
Estimator	The treatment difference for this categorical efficacy endpoint will be estimated using a logistic regression (binomial distribution with logit link function), incorporating all the by-visit proportion of responders as the dependent variable to assess the secondary endpoint hypothesis
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

Secondary Estimand 4:

Attribute	Description
Study Objective	Investigation of the mean difference in the change in FVC from baseline to 52 weeks between bexotegrast and placebo treatment groups in participants with and without background therapy at baseline with IPF at Week 52
Variable	Absolute change in absolute FVC (mL) from baseline to Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Mean difference in change from baseline in absolute FVC (mL)
Estimator	The treatment difference for a continuous efficacy endpoint will be estimated using a mixed model repeated measures (MMRM) analysis
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

Secondary Estimand 5:

Attribute	Description
Study Objective	Investigation of the mean difference in the change in FVC from baseline to 52 weeks between bexotegrast and placebo treatment groups in participants with and without background therapy at baseline with IPF at Week 52
Variable	Absolute change in absolute FVC (mL) from baseline to Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Mean difference in change from baseline in absolute FVC (mL).
Estimator	The treatment difference for a continuous efficacy endpoint will be estimated using a mixed model repeated measures (MMRM) analysis
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

Secondary Estimand 6:

Attribute	Description
Study Objective	Investigation of the effect of bexotegrast versus placebo after 52 weeks of treatment on overall symptom and functional improvement associated with IPF
Variable	Change in Living with Pulmonary Fibrosis (L-PF) Dyspnoea Domain score from baseline to Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Mean difference in change from baseline in Living with Pulmonary Fibrosis (L-PF) Dyspnoea Domain score at Week 52
Estimator	The treatment difference for a continuous efficacy endpoint will be estimated using a mixed model repeated measures (MMRM) analysis
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

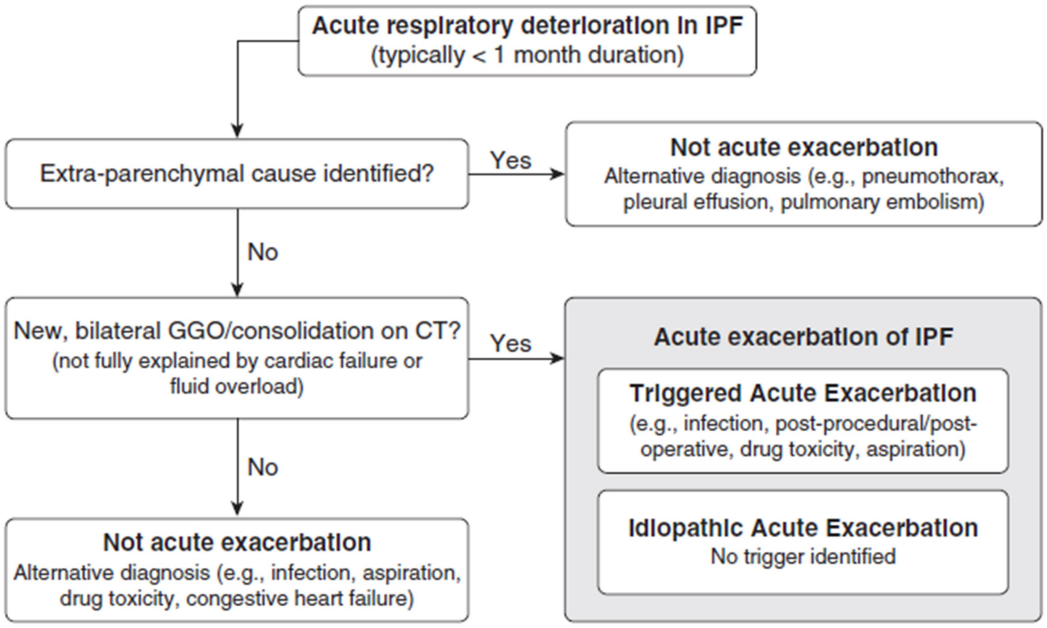
Secondary Estimand 7:

Attribute	Description
Study Objective	Investigation of the effect of bexotegrast versus placebo after 52 weeks of treatment on overall symptom and functional improvement associated with IPF
Variable	Change in L-PF Cough Domain score from baseline to Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Mean difference in change from baseline in L-PF Cough Domain score at Week 52
Estimator	The treatment difference for a continuous efficacy endpoint will be estimated using a mixed model repeated measures (MMRM) analysis
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

Secondary Estimand 8:

Attribute	Description
Study Objective	Investigation of the effect of bexotegrast versus placebo after 52 weeks of treatment on overall symptom and functional improvement associated with IPF
Variable	Change in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total score from baseline to Week 52
Population	Randomized participants with IPF in the ITT analysis set taking and not taking background therapy as defined by the inclusion and exclusion criteria regardless of changes in background medication.
Population level summary	Mean difference in change from baseline in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total score at Week 52
Estimator	The treatment difference for a continuous efficacy endpoint will be estimated using a mixed model repeated measures (MMRM) analysis
Intercurrent Events	• Changes in background therapy (standard of care) while on treatment • Start use of restricted medication (non-standard of care) • Lung transplant • Death • Premature treatment discontinuation

APPENDIX 4. ACUTE RESPIRATORY DETERIORATION IN IPF



Adapted from Collard et al, 2016.

[redacted]

[redacted]

APPENDIX 6. LIST OF LABORATORY TESTS

Hematology[a]
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell count
White blood cell count with differential
Coagulation[a]
International normalized ratio
Prothrombin time
Urinalysis
Appearance
Bilirubin
Color
Glucose
Ketones
Reflex microscopic examination of sediment
Nitrite
Occult blood
pH
Protein
Specific gravity
Urobilinogen
Screening Only
Urine drug screen, including, but not limited to[b]:
Amphetamines
Barbiturates
Benzodiazepines
Cocaine
Methadone
Phencyclidine
Opiates
Cotinine
Tetrahydrocannabinol
Alcohol metabolites

Serum Chemistry[a]
Alanine aminotransferase
Albumin
Alkaline phosphatase
Alpha-1-acid-glycoprotein[c]
Amylase (reflex lipase if amylase ≥1.5×ULN)
Aspartate aminotransferase
Bilirubin (total and direct)
Blood urea nitrogen
Calcium
Chloride
Creatinine
Creatine kinase
Gamma-glutamyl transferase
Glucose
Lactate dehydrogenase
Lipid panel[d]
Total cholesterol
High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol
Triglycerides
Phosphorus
Potassium
Sodium
Total protein
Uric acid
Pregnancy Testing
Serum pregnancy test (for women of childbearing potential)[e]
Urine pregnancy test (for women of childbearing potential)[f,g]
Screening Only
Serum follicle-stimulating hormone – to confirm postmenopausal status
Hepatitis A IgM antibody (HAV-IgM Ab)
Hepatitis B surface antigen (HBsAg)
Hepatitis C virus antibody (HCV Ab)
Human immunodeficiency virus (HIV)

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.

APPENDIX 8. PATIENT REPORTED OUTCOMES

Living with Pulmonary Fibrosis (L-PF) questionnaire

The Living with Pulmonary Fibrosis (L-PF) was developed with the input of patients with pulmonary fibrosis (PF) and thus is intended to capture perceptions specific to PF patients. The questionnaire is a 44-item questionnaire with two modules:

1. Symptoms (23 items)
2. Impacts (21 items)

In addition, there are 4 questions on supplemental oxygen use at the end of the L-PF.

Symptoms

The Symptoms module yields three domain scores and a total Symptoms Score (items 1-23)

1. Dyspnea (items 1-12)
2. Cough (items 13-18)
3. Fatigue (items 19-23)

Symptom domain scoring is as follows:

Dyspnea:

For items 1, 2, 4-10 and 12:

- If “yes is ticked, then score equals whichever box is ticked (0-4)
- if “No” is ticked and “A” is ticked, the score is 5
- if “No” is ticked and “B” is ticked, the item is not scored and does not contribute to the denominator
- if “No” is ticked and neither “A” nor “B” is ticked, the item is counted as missing and handled per “Instructions for Missing Items”. Items for which this occurs DO contribute to the denominator

For items 3 and 11, scores equal whichever box is ticked (0-4)

$$Dyspnea\ Score = \frac{Sum\ of\ responses\ for\ items\ 1-12}{total\ score\ of\ possible\ items\ without\ "No"/\mathrm{B}\ response}\ x\ 100$$

Cough:

$$Cough\ Score = \frac{Sum\ of\ responses\ for\ items\ 13-18}{24}\ x\ 100$$

Fatigue:

For items 19-22, score equals whichever box is ticked (0-4)

For item 23:

- If "yes is ticked, then score equals whichever box is ticked (0-4)
- If "no" is ticked, the item is not scored and does NOT contribute to the denominator

$$Fatigue\ Score = \frac{Sum\ of\ responses\ for\ items\ 19-23}{total\ score\ possible\ (20\ or\ 16\ if\ response\ for\ item\ 23\ is\ \text{"No"})}\ x\ 100$$

Symptoms Total Score:

$$Symptom\ Total\ Score = \frac{(\text{Dyspnea Symptoms} + \text{Cough Symptoms} + \text{Fatigue Symptoms})}{3}$$

The **Impacts** module yields a single Impacts score (sum of item responses 1-21).

The Impacts module yields four domain scores and a total Impacts Score (items 1-21)

1. Dyspnea (items 1-6)
2. Cough (items 7-11)
3. Fatigue (items 13-14)
4. Global (items 12, 15-21)

Impact domain scoring is as follows:

$$Dyspnea\ Impacts\ Score = \frac{\text{sum of responses from items } 1-6}{24}\ x\ 100$$

$$Cough\ Impacts\ Score = \frac{\text{sum of responses from items } 7-11}{20}\ x\ 100$$

$$Fatigue\ Impacts\ Score = \frac{\text{sum of responses from items } 13-14}{8}\ x\ 100$$

$$Global\ Impacts\ Score = \frac{\text{sum of responses from items } 12, 15-21}{32}\ x\ 100$$

$$Impacts\ Total\ Score = \frac{(\text{Dyspnea impact} + \text{Cough impact} + \text{Fatigue impact} + \text{Global Impact})}{4}$$

If the missing items are ≥50% within a score, then the corresponding score is set to missing.

Oxygen use

Item 1: summarize the count of "Yes/1" and "No/0"

Item 2: summarize the count of " 1: Only When I sleep", "2: Only when performing physical activity", "3: When I sleep or perform physical activity", "4: All the time"

Item 3: summarize oxygen flow rate where the denominator for the group is only participants who answered 1, 3 or 4 to item 2.

Item 4: summarize oxygen flow rate where the denominator for the group is only participants who answered 2, 3 or 4 to item 2.

Item 4: summarize oxygen flow rate where the denominator for the group is only participants who answered "Yes/1" to item 1.

Instructions for Completing the

Living with Pulmonary Fibrosis (L-PF) Symptoms Questionnaire

Complete this questionnaire to assess the symptoms you may have experienced from pulmonary fibrosis (PF) over the last 24 hours.

Keep in mind:

- you are not being asked to compare yourself to anyone else
- you are not being asked to compare how you are now with any time in the past

---

Items 1-12: The first 12 items ask about your symptoms in relation to physical activities, some of which you may not have done in the last 24 hours. If you did not perform an activity, we would like to know whether it was because you did not have the opportunity to do it (for example, maybe your home doesn't have stairs, so you did not walk up a flight of stairs), or whether you avoided the activity because it was too difficult.

If you did the stated activity, then reflect on the last 24 hours, and consider whether, on average, doing the activity at your usual pace or intensity level made you short of breath—and if so, how much.

If you normally use oxygen when you perform a given activity, then consider your response as if you were using supplemental oxygen.

Please select the box that best describes your experience.

1. Did you get dressed in the last 24 hours?

☐ Yes — How short of breath did getting dressed make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No — I did not get dressed in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

2. Did you walk up one flight of stairs in the last 24 hours?

Yes How short of breath did walking up one flight of stairs make

Not at all 0 1 2 3 4 **Extremely**

No I did not walk up one flight of stairs in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

3. Over the last 24 hours, how short of breath have you been while sitting down, relaxing, reading, or watching TV?

Not at all 0 1 2 3 4 **Extremely**

4. Did you walk up a short, gradual incline (like a wheelchair ramp into a building) in the last 24 hours?

Yes

Not at all 0 1 2 3 4 **Extremely**

No I did not walk up a short, gradual incline in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

5. Did you perform a grooming activity (eg, brush teeth, shave, fix hair) in the last 24 hours?

Yes How short of breath did grooming make you?

Not at all 0 1 2 3 4 **Extremely**

No I did not perform a grooming activity in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

6. Did you walk outside on a level surface (approximately 150 feet/45 meters, or the distance of half a typical city block) in the last 24 hours?

Yes How short of breath did walking outside on a level surface make you?

Not at all 0 1 2 3 4 **Extremely**

No I did not walk outside on a level surface in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

7. Did you walk from room to room inside your home in the last 24 hours?

Yes How short of breath did walking from room to room inside your home

Not at all 0 1 2 3 4 **Extremely**

No I did not walk from room to room inside my home in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

8 Did you leave your home in the last 24 hours?

Yes How short of breath did getting ready to leave your home (eg, find keys, put on coat, lock doors) make you?

Not at all 0 1 2 3 4 **Extremely**

No I did not leave my home in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

9. Did you bathe or shower in the last 24 hours?

Yes How short of breath did bathing or showering make

Not at all 0 1 2 3 4 **Extremely**

No I did not bathe or shower in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

10 Did you do light cleaning around the house in the last 24 hours?

Yes How short of breath did doing light cleaning around the house make

Not at all 0 1 2 3 4 **Extremely**

No I did not do light cleaning around the house in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity

11. Over the last 24 hours, how short of breath were you after eating a meal or

Not at all 0 1 2 3 4 **Extremely**

12. Did you lift and carry a light load (e.g., less than 10 lbs) a short distance (e.g., from one room to another) in the last 24 hours?

☐ Yes How short of breath did lifting and carrying a light load a short distance make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No I did not lift or carry a light load a short distance in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

Items 13-18: Each item focuses on cough. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

13. Over the last 24 hours, how often did you

Not at all 0 1 2 3 4 **Constantly**

If you chose "0", please skip to Item 19.

14. Over the last 24 hours, how often did you cough when you took a deep

Not at all 0 1 2 3 4 **Constantly**

15. Over the last 24 hours, how often did you cough when you were breathing hard

Not at all 0 1 2 3 4 **Constantly**

16. Over the last 24 hours, how often did you cough when you over-exerted

Not at all 0 1 2 3 4 **Constantly**

17. Over the last 24 hours, how often did coughing make you short of

Not at all 0 1 2 3 4 **Constantly**

18. Over the last 24 hours, how often did you feel an annoying tickle in your

Not at all 0 1 2 3 4 **Constantly**

Items 19-23: These items primarily focus on your energy level. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

19. Over the last 24 hours, how was your energy

Extremely low 0 1 2 3 4 **Excellent**

20. Over the last 24 hours, of all that you wanted to get done, how much did you actually

Nothing 0 1 2 3 4 **Everything**

21. Over the last 24 hours, how much energy did you have to do all the things you

No energy 0 1 2 3 4 **A lot**

22. Over the last 24 hours, how much did coughing have a negative effect on your

No effect at all 0 1 2 3 4 **A lot**

23. Did you become short of breath in the last 24 hours?

Yes How long did it take you to recover when you became short of

No time at all 0 1 2 3 4 **An extremely long time**

No Please continue to the next

Finally, we would like to ask you 5 questions about your supplemental oxygen use.

Oxygen Question 1. Do you ever use supplemental oxygen?

(Place an "X" in one box)

Yes	→→ proceed to Oxygen Question #2.
No	→→ skip Oxygen Questions #2-5

Oxygen Question 2. I use supplemental oxygen

(Place an "X" in one box)

1	→→ only when I sleep (answer Oxygen Question #3)
2	→→ only when I perform a physical activity (such as getting dressed or walking) (answer Oxygen Question #4)
3	→→ when I sleep or perform a physical activity (such as getting dressed or walking) but not at rest (answer Oxygen Questions #3 and #4)
4	→→ all the time (answer Oxygen Questions #3-5)

Oxygen Question 3. When I sleep, I most often use an oxygen flow rate of L/min.

(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12

Oxygen Question 4. When I perform a physical activity (such as getting dressed or walking), I most often use an oxygen flow rate of_L/min.

(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12

Oxygen Question 5. At rest, I most often use an oxygen flow rate of__L/min.

(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12

King's Brief ILD Questionnaire (K-BILD)

The K-BILD health status questionnaire is a 15-item questionnaire split into three domains: psychological (items 3, 5, 6, 8, 10, 12, and 14), breathlessness and activities (items 1,4,11, and 13), and chest symptoms (items 2,7, and 9). A final item is used to assess the impact of the respondent's lung condition on their financial state.

Scores are weighted, and a Rasch analysis confirmed the 15 items can be combined into a total score (Patel et al 2012). The domain scores and the total score range from 0 to 100, with higher scores indicating a better health status.

Response options for all 15 items are on a 7-point Likert scale, ranging from 1 to 7. For each of the items, the response options vary, including: item 1 (1 = "Every time," 7 = "Never"); items 2–4, and 6–14 (1 = "All of the time," 7 = "None of the time"); item 5 (1 = "None of the time," 7 = "All of the time"); and item 15 ("A significant amount," 7 = "Not at all").

If an item is not completed it will not be counted in the numerator. The final K-BILD questionnaire consists of 15 items and three domains:

Scoring Algorithm

To score the K-BILD, the Likert response scale weightings for individual items are combined, to ensure they detect progressive change in health status. Raw domain and total scores are then calculated by summing the recoded scale values provided below:

Item	Response						
	1	**2**	**3**	**4**	**5**	**6**	**7**
1	0	1	2	3	4	5	6
2	0	0	1	1	2	2	3
3	0	1	2	3	4	5	6
4	0	0	1	1	2	2	3
5	0	0	1	1	1	2	2
6	0	1	2	3	4	5	6
7	0	0	1	1	2	2	3
8	0	0	1	1	2	2	3
9	0	0	1	1	1	2	2
10	0	1	2	3	4	5	6
11	0	1	2	3	4	5	6
12	0	1	2	3	4	5	6
13	0	1	2	3	4	5	6
14	0	1	2	3	4	4	5
15	0	0	1	1	1	2	2

Finally, the raw domain and total scores are transformed to a range of 0–100 by using logit values where higher scores indicate better health status. To perform this transformation, the following look up table is provided.

Breathlessness and Activities		Chest Symptoms		Psychological		Total	
Raw Score	**Transformed Score**	**Raw Score**	**Transformed Score**	**Raw Score**	**Transformed Score**	**Raw Score**	**Transformed Score**
0	0	0	0	0	0	0	0
1	10.4	1	17.3	1	10.6	1	9.2
2	17.7	2	32.1	2	17.5	2	15.3
3	2.9	3	44	3	21.9	3	19.4
4	27	4	54.3	4	25.3	4	22.6
5	30.3	5	63.7	5	28	5	25.1
6	33.1	6	73.4	6	30.2	6	2.2
7	35.6	7	85.2	7	32.2	7	29
8	37.8	8	100	8	33.8	8	30.5
9	39.9			9	35.5	9	32
10	41.9			10	37	10	33.3
11	43.9			11	38.5	11	34.4
12	45.9			12	39.8	12	35.5
13	48			13	41.2	13	36.5
14	50.2			14	42.5	14	37.5
15	52.5			15	43.8	15	38.4
16	555.2			16	45.1	16	39.3
17	58.5			17	46.4	17	40.1
18	62.7			18	47.7	18	40.9
19	68.8			19	49.1	19	41.7
20	79.9			20	50.5	20	42.4
21	100			21	52	21	43.2
				22	53.5	22	43.9
				23	55.2	23	44.6
				24	56.9	24	45.2
				25	58.8	25	45.9
				26	60.8	26	46.5

Breathlessness and Activities		Chest Symptoms		Psychological		Total	
Raw Score	Transformed Score	Raw Score	Transformed Score	Raw Score	Transformed Score	Raw Score	Transformed Score
				27	63	27	47.2
				28	65.5	28	417.8
				29	68.3	29	48.5
				30	71.6	30	49.1
				31	75.6	31	49.7
				32	80.9	32	50.4
				33	88.6	33	51
				34	100	34	51.6
						35	52.2
						36	52.9
						37	53.5
						38	54.1
						39	54.8
						40	55.4
						41	56.1
						42	56.7
						43	57.4
						44	58.1
						45	58.8
						46	59.5
						47	60.2
						48	61
						49	61.8
						50	62.6
						51	63.5
						52	64.4
						53	65.3
						54	66.4
						55	67.5
						56	68.7

Breathlessness and Activities		Chest Symptoms		Psychological		Total	
Raw Score	**Transformed Score**	**Raw Score**	**Transformed Score**	**Raw Score**	**Transformed Score**	**Raw Score**	**Transformed Score**
						57	70
						58	71.5
						59	73.2
						60	75.2
						61	77.6
						62	80.6
						63	84.6
						64	90.8
						65	100

King's Brief ILD Questionnaire (K-BILD)

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, I have been short of breath climbing stairs or walking up an incline or hill.

1. Every time
2. Most times
3. Several Times
4. Sometimes
5. Occasionally
6. Rarely
7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight.

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. In the last 2 weeks have you worried about the seriousness of your lung symptoms?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks have you avoided doing things that make you short of breath?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

5. In the last 2 weeks have you felt in control of your lung condition?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A lot of the time
6. Most of the time
7. All of the time

6. In the last 2 weeks, have your lung symptoms made you feel annoyed or down?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, I have felt the urge to inhale deeply and frequently known as "air hunger."

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious.

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, how often have you experienced "wheezing" or whistling sounds from your chest?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. In the last two weeks how much of the time have you felt your lung disease is getting worse?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

12. In the last 2 weeks have you expected your lung symptoms to get worse?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount
2. A large amount
3. A considerable amount
4. A reasonable amount
5. A small amount
6. Hardly at all
7. Not at all

Patients' Global Impression of Change (PGIC) scale

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. PGIC is planned to be collected at the Weeks 24 and 52 visit.

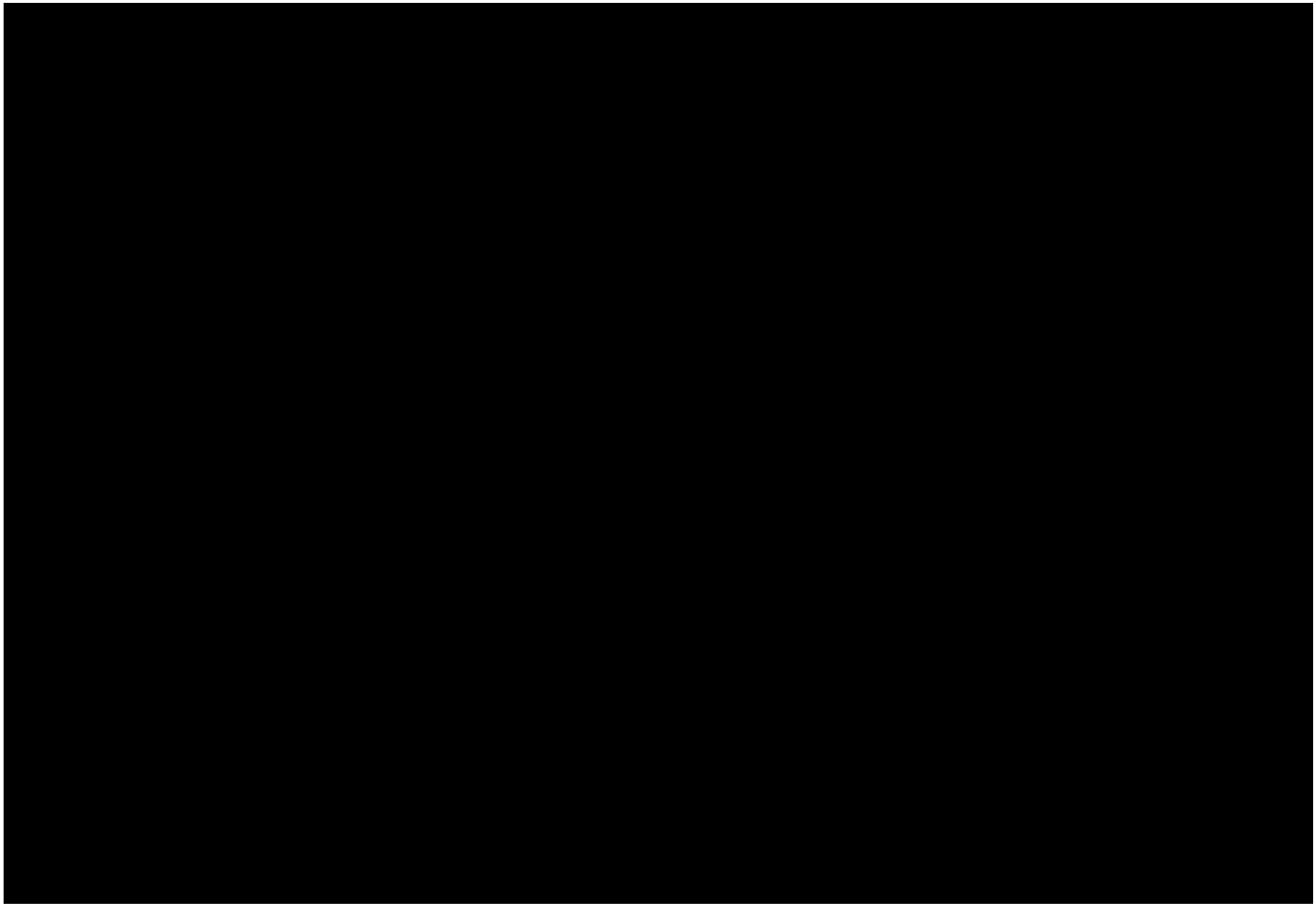
The PGIC scale is administered to each participant as follows:

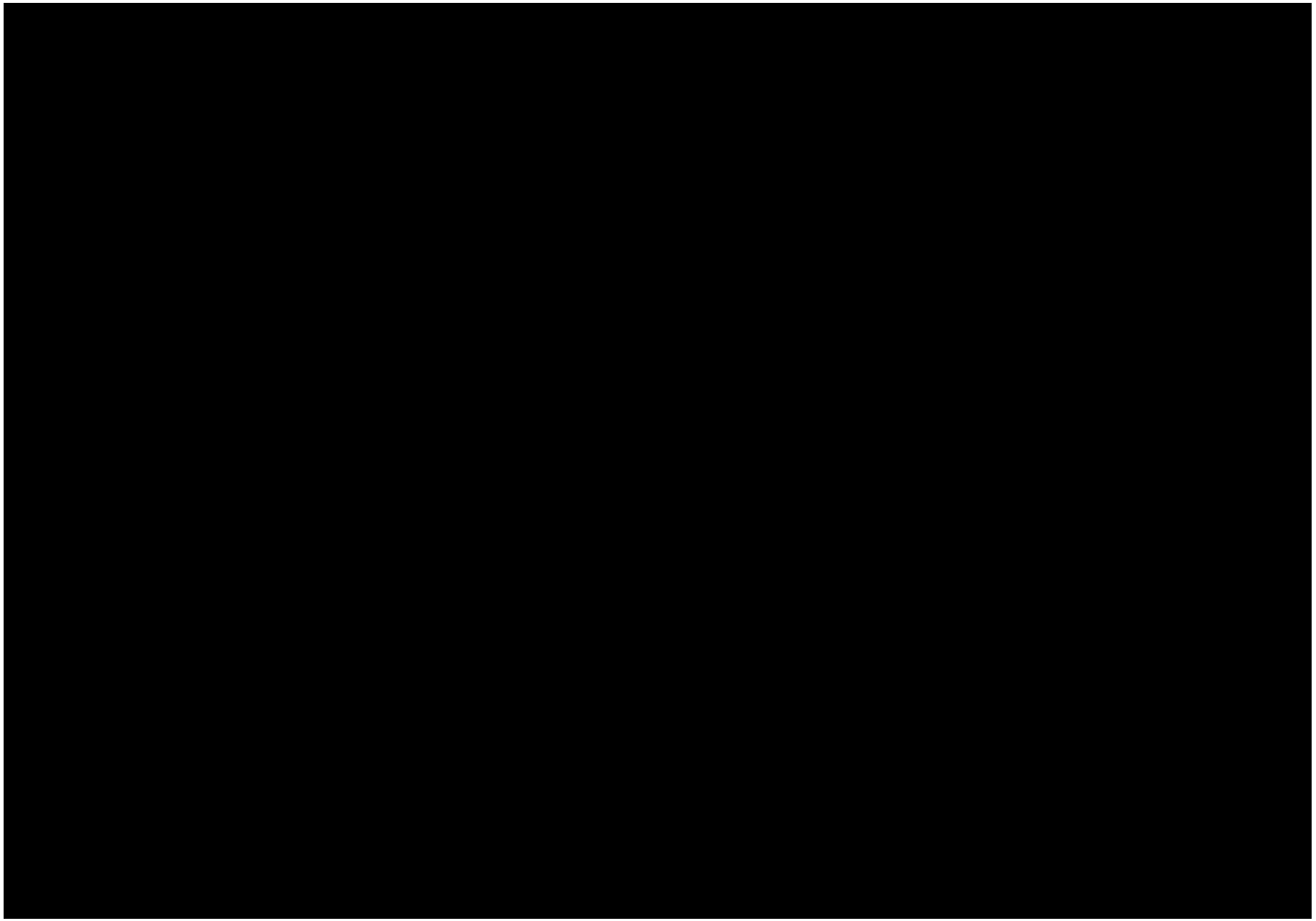
Patient Global Impression of Change (PGI-C)

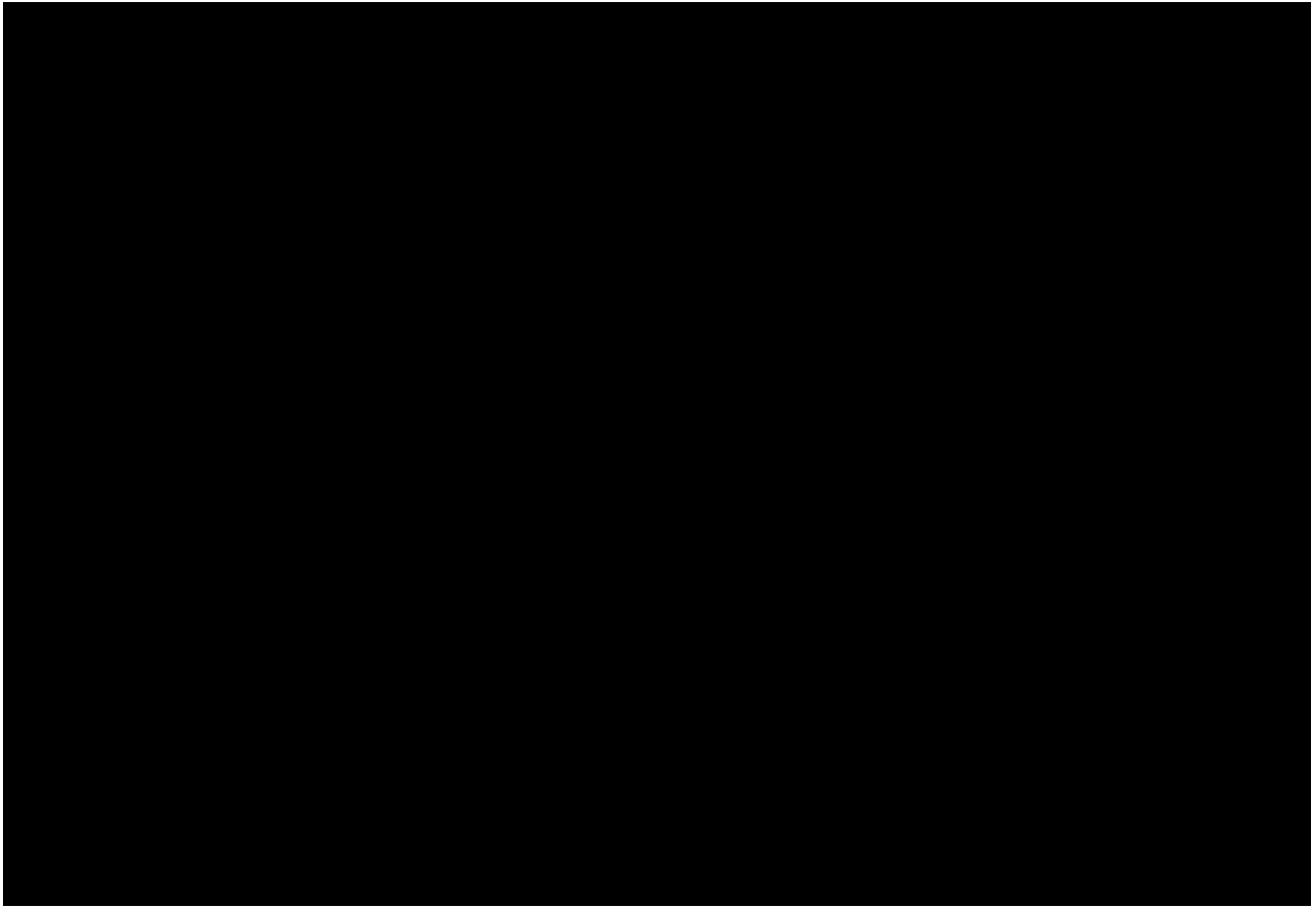
Since the start of the study, please rate your overall status using the scale below:

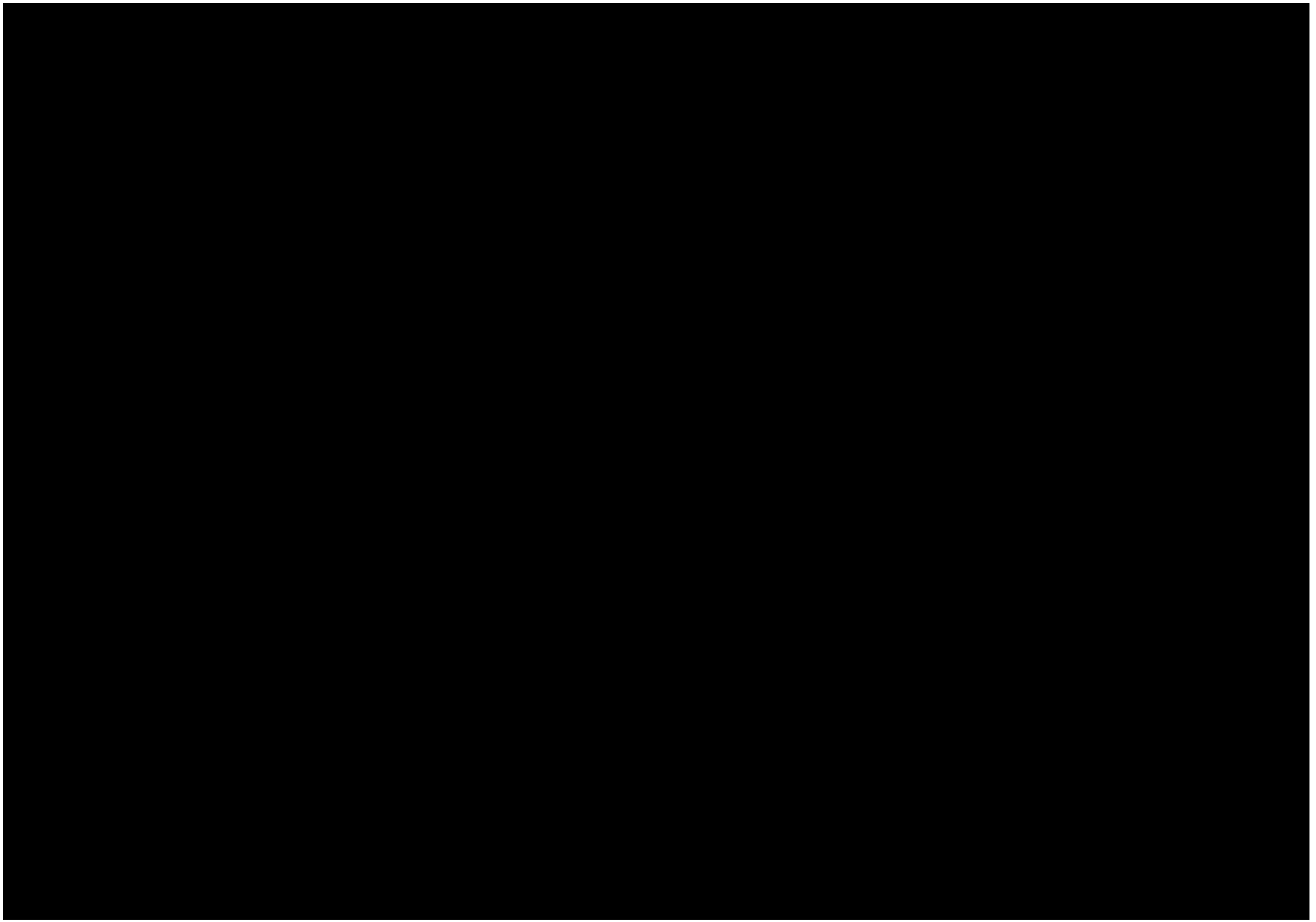
✓ *Check one box only:*

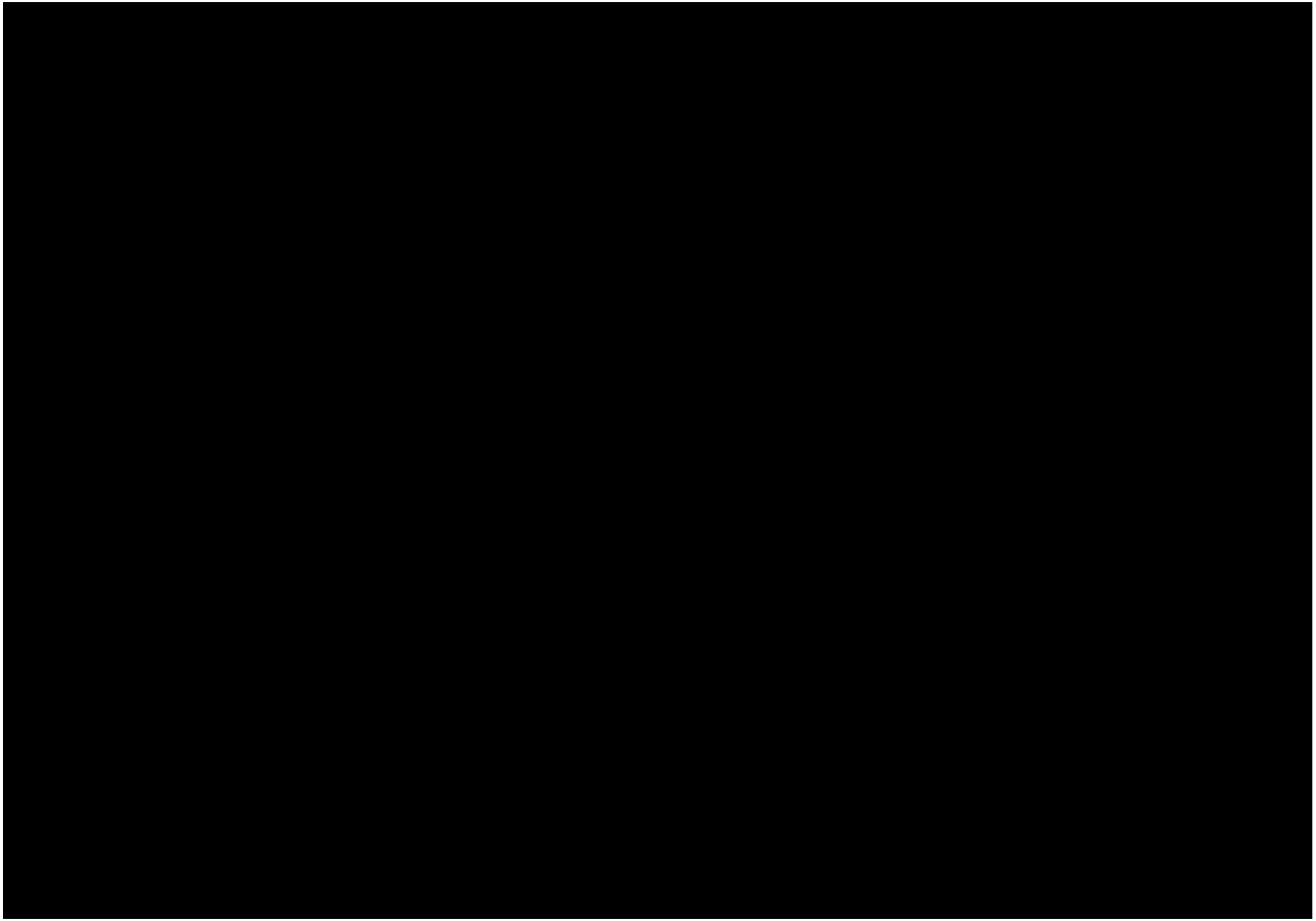
☐ **-5 – Very Much Worse** ☐ **-4** ☐ **-3** ☐ **-2** ☐ **-1** ☐ **0 – Unchanged** ☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ **5 –Very Much Better**

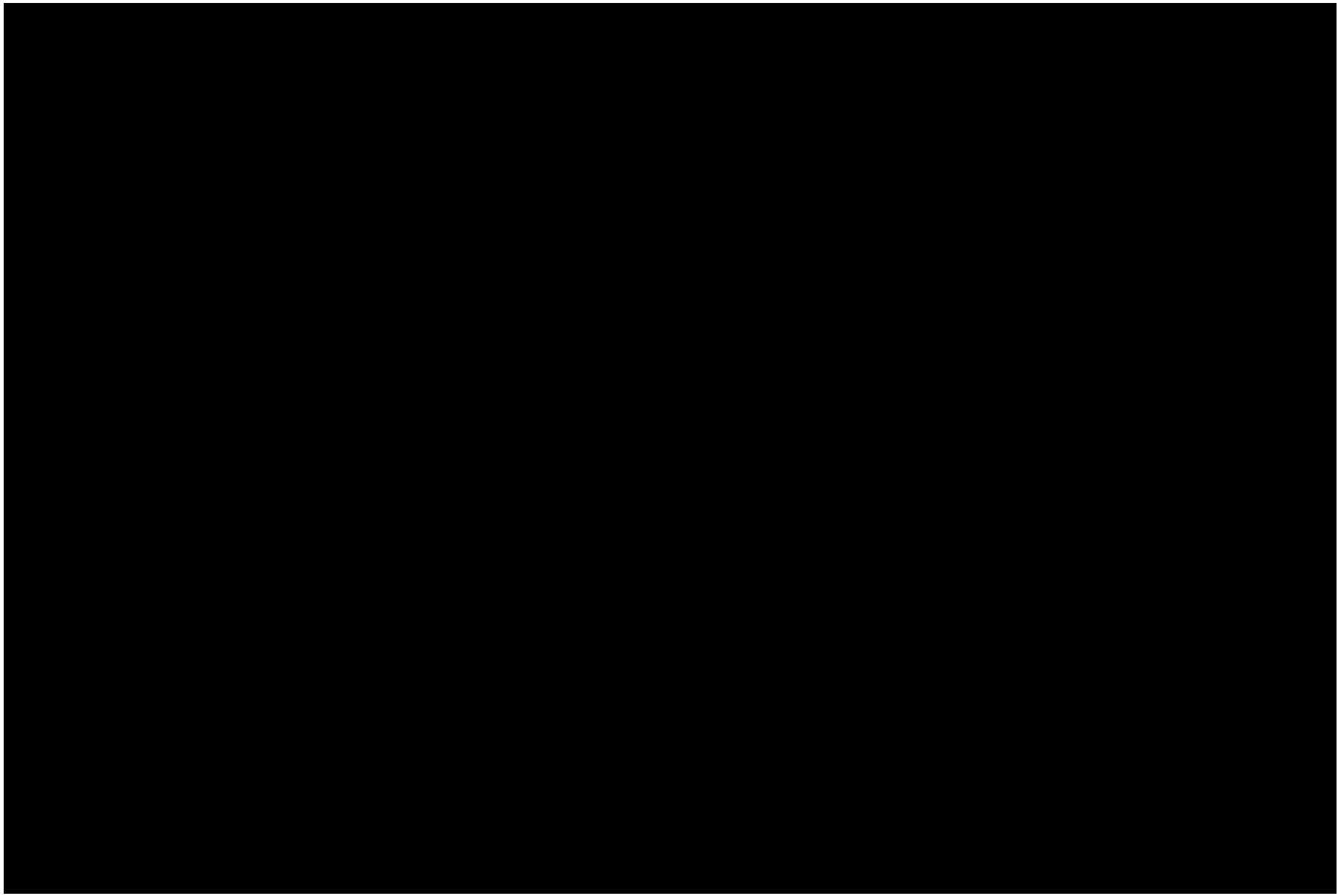


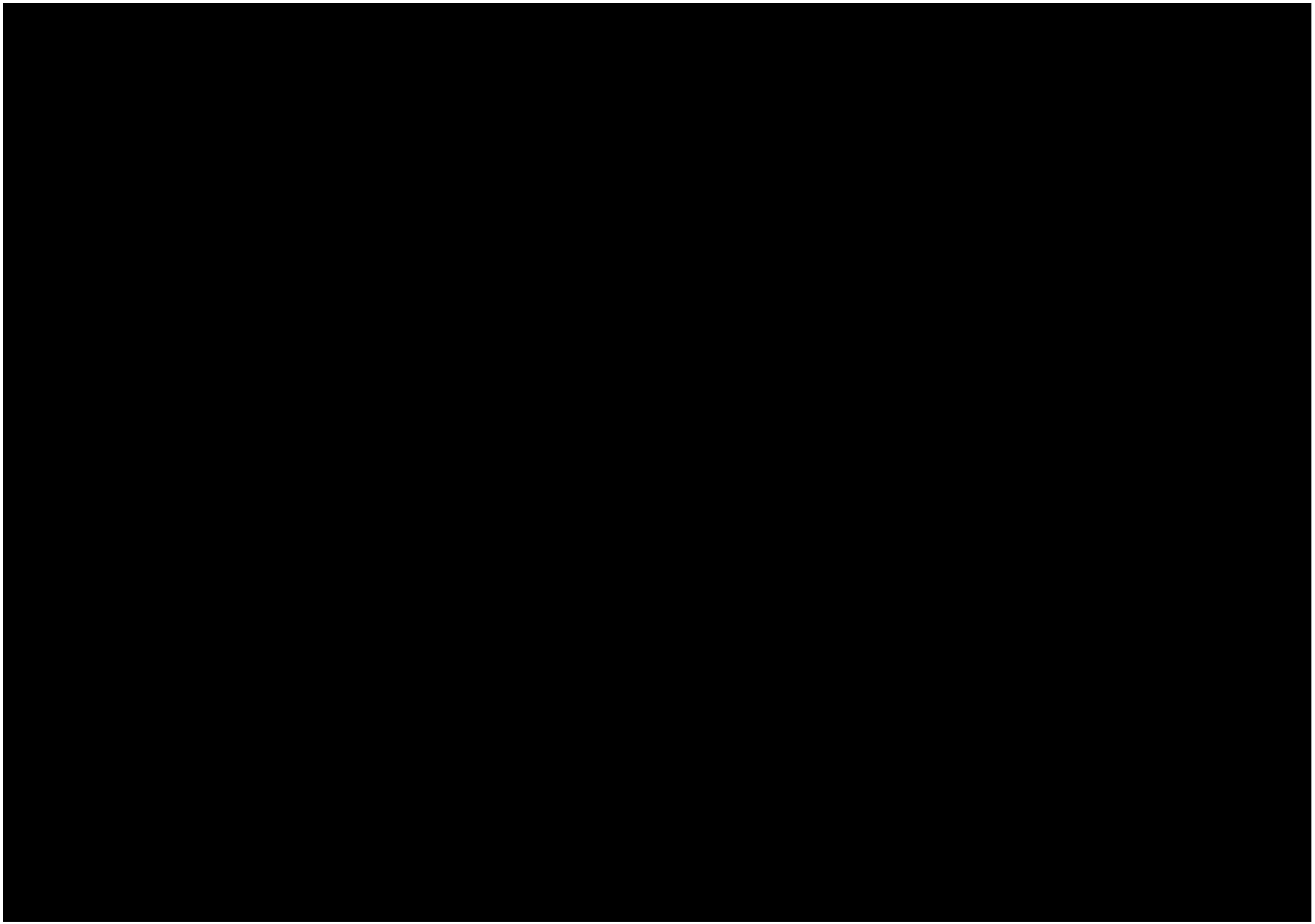


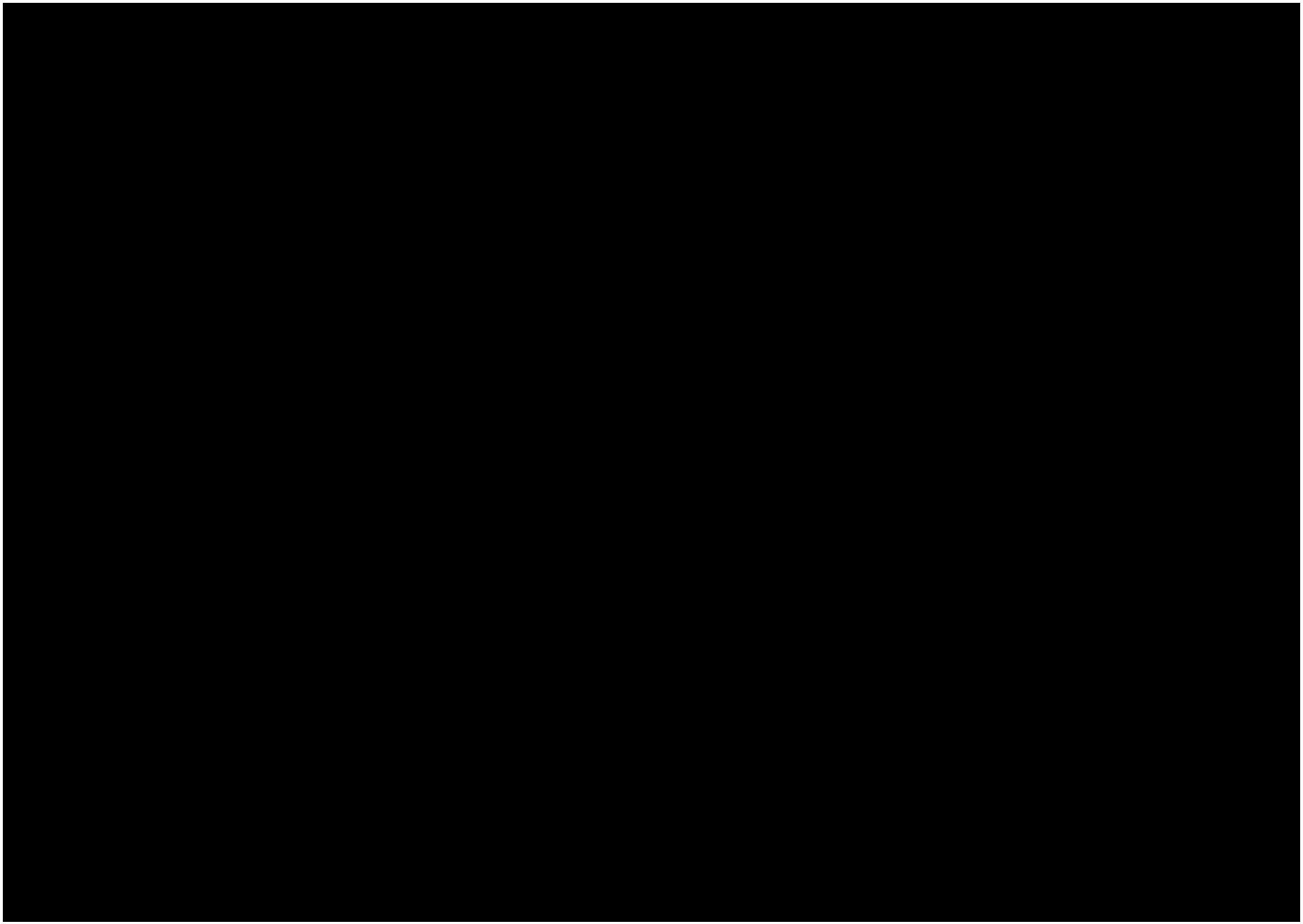












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Approval Task	[redacted] 03-Apr-2025 20:46:31 GMT+0000

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