Statistical Analysis Plan

A randomized, double-blind, dose-ranging, placebo-controlled Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with idiopathic pulmonary fibrosis (IPF) (INTEGRIS-IPF)

Protocol Number: *PLN-74809-IPF-202*

Protocol Version: *3.0,* [redacted]

SAP Version *2.0,* [redacted]

Addendum 1.0, [redacted]

Addendum 2.0, [redacted]

Addendum 3.0, [redacted]

Addendum 4.0, [redacted]

Addendum 5.0, [redacted]

Post Final database lock Addendum, [redacted]

[redacted]

Previous SAP Versions

SAP Version 1.0, [redacted]

SAP Amendments Before Database Lock for Parts A/B/C Week 12

Version	Issue Date	Section	Revision / Addition
2.0	17 June 2022	6.1.7	Definition of Efficacy Per Protocol Population was amended.
		6.2.4	Procedure for early termination assessments was defined.
		6.2.5	Handling of spirometry assessments was clarified.
		6.2.13	Compliance calculation was refined.
		6.2.17	Definition of electrocardiogram abnormalities was amended and clarified.
		6.6	Handling of DLCO lung function assessment at screening was clarified.
		6.6	Duration Since Diagnosis at Screening and Duration of Standard of Care at Randomization was defined and will be summarized in Participant Disposition.
		[redacted]	[redacted]
		6.11.1	Clarification added. FVC in mL will be analyzed.
		6.13	Clarification added. Result adjusted for dilution factor will be used.
		[redacted]	[redacted]
		6.15.1	Tabulations and listings for serious adverse events were added.
		6.15.2	Clarification added. Système International (SI) units will be used to report laboratory results.
		6.15.4	Definition of 'Confirmed Abnormality' was clarified.
		9	Changes to Planned Protocol Analyses was updated.
		11	List of Tables, Figures and Listings was updated.

SAP Amendments Post Database Lock for Parts A/B/C Week 12 and pre database lock for Part D Week 12

Version	Issue Date	Section	Revision / Addition
Addendum 1.0	02 Dec 2022	6.15.2	CTCAE grading for laboratory test parameters removed
		6.11.1	Added new pooled placebo groups and Wilcoxon rank sum test for FVC at Week 12
		7	Added text to clarify data cut off day for Part D interim
		11	List of Tables, Figures and Listings was updated.
Addendum 2.0	06 Dec 2022	11	List of Tables, Figures and Listings was updated.
Addendum 3.0	12 Dec 2022	11	List of Tables, Figures and Listings was updated.

SAP Amendments Post Database Lock for Parts A/B/C/D Week 12 and pre database lock for Part D Week 24

Version	Issue Date	Section	Revision / Addition
Addendum 4.0	31 Jan 2023	[redacted]	[redacted]
		6.2.20	Addition of SAS code to determine outliers
		11	List of Tables, Figures and Listings was updated.
Addendum 5.0	30 Mar 2023	6.6	Added summary of pulmonary function at baseline
		[redacted]	[redacted]
		11	List of Tables, Figures and Listings was updated.

SAP Amendments Post Final Database Lock

Version	Issue Date	Section	Revision / Addition
Post database lock	09 May 2023	6.6	Added baseline summaries by study part
		[redacted]	[redacted]
		11	List of Tables, Figures and Listings was updated.

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for Pliant Therapeutics Inc., protocol number "PLN-74809-IPF-202" study titled "A randomized, double-blind, dose-ranging, placebo-controlled Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with idiopathic pulmonary fibrosis (IPF) (INTEGRIS-IPF)".

The proposed analyses are based on the contents of Protocol Amendment 3, dated 19 October 2021.

This is a Phase 2a, multicenter, 4-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of once-daily (QD) treatment with PLN-74809 in participants with idiopathic pulmonary fibrosis (IPF).

Each study part consists of an up to 28-day screening period, a 4-week (Part A), 12-week (Parts B and C), or at least 24-week (Part D) treatment period, and a 2-week (±3 days) post-treatment follow-up period.

2 STUDY OBJECTIVES

2.1 Primary Objective

- Assessment of the safety and tolerability of PLN-74809.

2.2 Secondary Objective

- Assessment of PK of PLN-74809.

2.3 Exploratory Objectives

The exploratory objectives of this study are as follows:

- Assessment of change from baseline in Forced Vital Capacity (FVC)
- Assessment of change from baseline in Quantitative Lung Fibrosis (QLF) score
- Assessment of change from baseline in a visual analog scale (VAS) for cough
- Assessment of changes in selected biomarkers.

3 ENDPOINTS

3.1 Primary Safety Endpoint

The primary safety endpoint is the nature and proportion of AEs between PLN-74809 and placebo groups (descriptive).

Other safety endpoints include clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis), [redacted], vital sign measurements, changes in physical examination and concomitant medications.

3.2 Secondary Pharmacokinetic Endpoints

Plasma PLN-74809 concentrations ([redacted]) at each sampling timepoint will be presented in listings and descriptive summary statistics by dose and visit. The data will also be presented graphically.

3.3 Secondary Pharmacodynamic Endpoints

- Presence or actual concentration of biomarkers in urine, plasma, or serum samples.
- Levels of biomarkers markers as well as relative (and/or absolute) change in levels for each participant and the relationship between these markers.
- Relationships between PK and PD may be evaluated in an exploratory fashion and presented in graphical manner.

3.4 Exploratory Endpoints

3.4.1 Exploratory Efficacy Endpoints

- FVC including percent of predicted and absolute volume (mL).
- QLF score assessed by high-resolution computerized tomography (HRCT).
- Patient-reported outcome (PRO) measured by visual analog scale (VAS) for cough.

3.4.2 Other Assessments or Analyses

[redacted] concentrations of PLN-74809 will be determined in plasma samples. Exploratory metabolite evaluation may be performed in plasma samples.

4 SAMPLE SIZE

Recruitment for Part A is complete with 1 participant enrolled.

For Parts B, C and D, the sample size of approximately 21 participants receiving PLN-74809 per treatment group is expected to provide a meaningful evaluation of PLN-74809 safety, tolerability and PK in the target population.

Approximately 112 participants may be enrolled in study Parts B (n = 28), C (n = 56), and D (n=28).

5 RANDOMIZATION

In Part A, participants were randomized 1:1:1 to receive PLN-74809 (20 mg), PLN-74809 (40 mg) or Placebo. Recruitment for Part A is complete with 1 participant enrolled.

In Part B, 28 eligible participants were randomized 3:1 on Day 1 (Visit 2) to receive PLN-74809 (40 mg) or Placebo.

In Part C, 56 eligible participants per cohort will be randomized 3:3:2 on Day 1 (Visit 2) to receive PLN-74809 (80 mg), PLN 74809 (160 mg) or Placebo.

In Part D, 28 eligible participants will be randomized 3:1 on Day 1 (Visit 2) to receive PLN-74809 (320 mg) or Placebo.

Randomization will be stratified by use of Standard of Care (SoC) IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no).

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

6 PLANNED ANALYSES

Any statistical analysis plan (SAP) prepared in advance of final participant data cannot be definitive, therefore the Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

Please note: Since study Part A is considered complete, data from the one enrolled participant in Part A will be listed only. Analyses described herein refer to analysis of data from participants taking part in study parts B, C, and D only.

6.1 Analysis Populations

Participants excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.1.1 Screened Participants

Screened Participants are any participants who gave informed consent to participate in the study.

6.1.2 Randomized Participants

Randomized Participants are any participants who were assigned a randomization number.

6.1.3 Safety Population

The Safety Population includes all randomized participants who receive at least one dose of study drug.

6.1.4 PK Analysis Population

The PK Analysis Population includes all randomized participants who have concentration data (including below the limit of quantification (BLQ)) for PLN-74809, nintedanib or pirfenidone.

6.1.5 PD Analysis Population

The PD Analysis Population includes all randomized participants who receive any amount of study drug and who have results from baseline and from at least one post-baseline PD assessment.

6.1.6 Efficacy Intent-to-Treat Population

The Efficacy Intent-to-Treat (ITT) Population includes all randomized participants.

6.1.7 Efficacy Per Protocol Population

The Efficacy Per Protocol Population will include the subset of the ITT Population who complete the study without any protocol deviations that may significantly impact the interpretation of safety and/or efficacy analyses.

6.1.8 Efficacy Modified Intent-to-Treat Population

The Efficacy modified Intent-to-Treat (mITT) Population includes all randomized participants who do not have FVC values that meet outlier criteria. [redacted].

6.2 Derived Data

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

6.2.1 Race

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

6.2.2 Body Mass Index

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

BMI (kg/m^2) = Weight at Screening (kg) / [Height at Screening $(m)^2$]

6.2.3 Baseline

In general, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug, unless otherwise specified.

6.2.4 Early Termination Assessments

Early termination assessments will not be summarized. Early termination assessments will appear in the listings as recorded.

6.2.5 Spirometry Assessments

Raw spirometry data will be provided by an external data vendor and this data will be used for analyses. The vendor will identify the best value out of 5 attempts at each visit and the best value will be taken for summary and analysis. [redacted]

6.2.6 GAP Index and Staging System

The GAP index and staging system is a multidimensional prognostic staging system derived from four commonly measured clinical and physiologic variables (Gender, Age and two lung physiology variables (FVC and D_{LCO})[2]. Points are allocated to each clinical or physiological variable and points are summed to provide a total score (from 0-8). The total score is then used to assign a stage (I, II, or III) as follows:

GAP Scoring

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 - D_{LCO}, % Predicted	> 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 D_{LCO} maneuver. If D_{LCO} is unavailable for a non-respiratory reason (e.g., an operational reason), the GAP index and staging system cannot be applied.

Staging System

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

6.2.7 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

6.2.8 Unscheduled Visits

Only scheduled post-baseline values will be tabulated. Post-baseline repeat / unscheduled assessments will not be summarized but will be listed in the relevant appendices to the CSR.

6.2.9 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual participant listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

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

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 treatment.

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 "01-Jan" of the same year or 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.

6.2.11 Date of Last Dose of Study Drug

Date of Last Dose will be recorded at the Study Completion/Termination visit, if different from the from Date of Completion/Termination. If Date of Last Dose is not present, the Date of Completion/Termination will be taken as Date of Last Dose for calculation of study drug exposure.

6.2.12 Exposure to Study Drug

Exposure to study drug will be calculated as follows from the date of last dose (or the date of completion/termination if not present) minus the date of first dose + 1. The exposure calculation will not take into account breaks in therapy.

Duration of exposure (in days) will be calculated as follows:

- Date of Last Dose (or the Date of Completion/Termination if not present) of study drug (irrespective of dose) – Date of First Dose of study drug + 1

6.2.13 Study Drug Compliance

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

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

Expected [redacted] = Number of days on study (calculated as per Section 6.2.12 for duration of exposure) × [redacted] for the relevant study part and dose group (per the table below).

Compliance (%) = (Number of [redacted] / Expected number of [redacted]) *100

Number of [redacted] per study part and dose group

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

6.2.14 Imperial to Metric Unit Conversion

Measurements provided in inches (in), pounds (lb) and degrees Fahrenheit (°F) will be converted to centimeters (cm), kilograms (kg) and degrees Celsius (°C) respectively, using the following conversion calculations:

- $x\ (cm) = x\ (in) \times 2.54$
- $x\ (kg) = x\ (lb) \times 0.45359237$
- $x\ (°C) = [x\ (°F) - 32] / 1.8$

6.2.15 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.

[redacted]

[redacted].

[redacted]

[redacted]

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

[redacted]

[redacted]

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

[redacted]

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

[redacted]

[redacted]

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

[redacted]

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

[redacted]

6.2.20 Determination of FVC outliers

[redacted]

6.3 Conventions

6.3.1 Medical Coding

Adverse events and medical history will be coded using the Medical Dictionary of Regulated Activities (MedDRA) Version 24.1 (or higher). Conditions will be assigned to a System organ class (SOC) and preferred term (PT) based on the Investigator-reported verbatim term.

Any medications taken (other than study drug) will be coded using the World Health Organization Drug Dictionary ([redacted]) September 2021 Version (or higher). 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.

6.3.2 Data Handling

All clinical data programming will be performed using [redacted] 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.

6.3.3 Validation Methods

All programming of datasets and outputs will be validated by fully independent double programming of values and manual review of format compared to the SAP and agreed shell template. Figures will be validated by manual review of format and visual inspection of graphical display compared to tabulated data. All tables, figures and listings will be reviewed by a statistician prior to each milestone delivery.

6.3.4 Summary Statistics

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing 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 adverse events, medical history and concomitant medications will be reported at the participant level. Participants can only be counted once within each PT and SOC under the highest severity and most related. Percentages will be calculated using the number of participants in the treatment group for the Safety Population.

6.3.5 Decimal Places

For summary statistics, n will be reported as a whole number. Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place. All data presented in the individual participant listings will be as recorded on the eCRF.

6.3.6 Data Displays

All clinical data tabulations, figures and listings will be generated as individual Rich Text Format (.rtf) files using [redacted])[1]. 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, demographic, compliance, concomitant medication, and adverse event data will be presented by treatment group and overall. Other safety data will be presented by treatment group only.

Please note: Data from study Part A will be listed only.

Treatment group labels will be displayed as follows:

PLN-74809 (40 mg) (N=XX)	PLN-74809 (80 mg) (N=XX)	PLN-74809 (160 mg) (N=XX)	PLN-74809 (320 mg) (N=XX)	All PLN-74809 (N=XX)	Placebo (N=XX)

Listings will be sorted in the following order, study part (Parts B/C/D/A), treatment group, participant number, parameter, and visit unless otherwise stated. All data will be listed, participants who were not randomized will be displayed after the randomized treatment groups.

6.4 Participant Disposition

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

- The number of participants entering the study.
- The number of participants in each analysis population.
- The number of participants completing study treatment.
- The number of participants not completing study treatment and reason for non-completion of study treatment.
- The number of participants completing the study.
- The number of participants with early termination and the reasons for early termination.
- The reasons for exclusion from the Efficacy Per-Protocol Population will be listed.

6.5 Protocol Deviations

All reported protocol deviations (PD) will be summarized by treatment group, PD category and PD classification (Major, Minor, and total) as well as listed.

6.6 Baseline Comparability

Comparability of treatment groups with respect to participant demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Baseline summaries will be presented by treatment group and overall, for the following variables based on the Safety Population:

Demographic Data

- Age at Informed Consent (years)
- Sex
- Ethnicity

- Race, where more than one race is selected the participant will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing.

Baseline Characteristics

- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)
- Fertility Status (Childbearing Potential, Postmenopausal, Surgically Sterile)
- Participant taking nintedanib or pirfenidone at Screening

Clinical Characteristics

- Pulmonary Function at Screening
- Pulmonary Function at Baseline
- D_{LCO} Lung Function Assessment at Screening (if repeated, the last non-missing value before first dose will be taken)
- GAP Index Score and Staging
- Duration Since Diagnosis at Screening (first date reported for Idiopathic Pulmonary Fibrosis, Pulmonary Fibrosis or Interstitial Lung Disease)
- Duration of Standard of Care at Randomization (defined as the number of months from start date of nintedanib or pirfenidone to date of randomization)

Additional summaries will be completed for Part D only participants as well as placebo participants by study part.

6.7 Medical History

Separate tabulations of prior and ongoing conditions at screening will be presented by 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.

6.8 Prior and Concomitant Medications

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

Prior and concomitant medications will be presented by ATC Level 4 classification and Preferred Name for each treatment group in the Safety Population. All reported medications will be listed.

6.9 Exposure to Study Drug

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

6.10 Study Drug Compliance

Compliance (%) will be calculated for each participant and summarized by treatment group and overall. All compliance and study drug accountability data will be listed.

6.11 Efficacy Analyses

Efficacy analyses will be presented by randomized treatment for the Efficacy Intent-to-Treat (ITT) Population (unless otherwise specified). [redacted]

6.11.1 Spirometry

All spirometry parameters will be summarized using descriptive statistics by treatment group and visit for the [redacted] Population. Actual values, the changes from baseline and the percent changes from baseline will be presented for all scheduled visits along with 95% confidence intervals (CI) for the mean changes and mean percent changes from baseline.

The number and percent of participants showing an absolute decline in FVC (% Predicted) of ≥5% and ≥10% over the first 12 weeks will also be provided for each treatment group.

The number and percent of participants showing a relative decline in FVC (% Predicted) of ≥5% and ≥10% over the first 12 weeks will also be provided for each treatment group.

A categorical summary of participants by FVC change relative to baseline (increase/ decrease) will be provided for Part D participants at Weeks 12 and 24.

A mixed model for repeated measures (MMRM) will also be utilized to analyze the change from baseline to each post-baseline visit in FVC (mL).

The MMRM model will [redacted]

The LS means, corresponding SEs, and 95% CI for each treatment group at each visit will be obtained from the model. An estimate for the LS mean difference (PLN-74809 vs. placebo), corresponding SE, 95% CI, and p-value for each dose group at each visit will also be presented.

Separate MMRM analyses [redacted]

[redacted] will be provided showing all available data (scheduled and unscheduled) for each individual participant over the study for the parameters listed below. One panel will be displayed per treatment group.

Plots will also be provided showing mean (± SD) for all treatment groups at each scheduled visit for all parameters. Each treatment group will be identified using different plot symbols. Plots will be shown for actual values, change from baseline and percent change from baseline. Baseline will be set to zero for change from baseline plots.

Spirometry parameters to be summarized by treatment group and visit include:

- FVC (mL) Actual
- % FVC Predicted
- [redacted]
- [redacted]

[redacted]

All spirometry data will be listed.

Sensitivity Analyses:

The MMRM will be repeated in the [redacted] as sensitivity analyses. In addition, a sensitivity analysis will be conducted using the [redacted]

A trimmed mean analysis trimming the participants [redacted] will also be conducted for Part D participants.

In addition, FVC will be summarized using descriptive statistics by the following treatment groups at baseline and Week 12 for the Efficacy Intent-to-Treat Population:

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

Actual values, the changes from baseline and the percent changes from baseline will be presented along with 95% confidence intervals (CI) for the mean changes and mean percent change from baseline.

The two comparisons below will be performed via the MMRM on (a) FVC change from baseline at each visit, and (b) FVC percent change from baseline at each visit. Additionally, [redacted] will test (a) FVC Week 12 change from baseline endpoint, and (b) FVC week 12 percent change from baseline :

- [redacted]
- [redacted]

As a further exploratory analysis, [redacted] will be utilized to analyze the change from baseline to Week 12 in FVC between subjects in each of the treatment group selections above, as well as in Part D alone (not pooled).

6.11.1 Patient-Reported Cough

Descriptive statistics for the patient-reported VAS for cough and change from baseline will be summarized by treatment group and visit for the Safety Population. The number and percent of participants with VAS ≥ 40 at Baseline and reduction in VAS of ≥ 30 at Week 12 (as described in [redacted][3]) will also be provided by treatment group. Mean (± SD) change from baseline will also be presented graphically by treatment group. All collected VAS data will be listed.

6.11.2 Quantitative Lung Fibrosis

Collection data for HRCT scans performed will be listed. Analysis of QLF (assessed by HRCT) will be described in a separate analysis plan.

6.12 Pharmacokinetic Analyses

6.12.1 Concentration-Time Data

In study Parts B and C, plasma samples will be taken [redacted] relative to PLN-74809 dosing on [redacted] In study Part D, plasma samples will be taken [redacted] relative to PLN-74809 dosing on [redacted]

Concentration data will be obtained for PLN-74809 [redacted]

[redacted] PLN-74809 concentration [redacted] will be calculated as follows:

- [redacted]
- [redacted]

PLN-74809 concentration data ([redacted]) will be summarized by dose level and visit at each scheduled sample time (nominal time) using descriptive statistics: number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%). Scatter plots will also be provided showing mean (SD). Similarly, [redacted] will be

summarized. Concentrations that are below the limit of quantification (BLQ) will be set to zero for summary statistics. BLQ concentrations will be retained as BLQ in listings. The data will be reported to 3 significant figures.

Individual PLN-74809 [redacted]), nintedanib, and pirfenidone concentration data will be provided in listings. Data may be pooled with data from other studies for population PK and reported outside of the clinical study report.

6.12.2 PK Parameters

Not applicable.

6.13 Pharmacodynamic Analyses

Biomarker results obtained from urine, plasma or serum samples 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 percentage 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 also 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.

For biomarkers with at least 2 post-baseline scheduled assessments, absolute change from baseline and percentage change from baseline will be presented as a line plot showing baseline (0) and the mean (± SD) concentration at each post-dose visit by treatment group for each parameter.

For biomarkers with only one post-dose scheduled assessment, absolute change from baseline and percentage change from baseline will be presented by box and whisker plot for each treatment group.

Change from baseline to each visit will also be analyzed for all biomarkers using an MMRM [redacted] LS means (±SE) for each treatment group and estimate for treatment difference compared to placebo, with corresponding SE, 95% CI and p-value will be provided .

6.14 Pharmacogenomic Analyses

Pharmacogenomic sampling data will be listed only. Future cross-study pharmacogenomic analyses will be described in a separate analysis plan.

6.15 Safety Analyses

Safety analyses will be presented by the treatment received for the Safety Population.

6.15.1 Adverse Events

AE analyses will be presented by the treatment received for the Safety Population. Tabulations will be presented overall and by SoC (Yes, No).

AEs will be collected from the time of informed consent through completion of the participant's last study visit.

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 completion of the last study visit.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug through completion of the last study visit.

AEs occurring prior to first dose 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, for the following:

- Any AE
- TEAE
- TEAE Related to Study Drug

- TEAE Related to a Study Procedure
- Serious TEAE
- Serious TEAE Related to Study Drug
- TEAE of CTCAE Grade 3 or Higher
- TEAE of CTCAE Grade 3 or Higher Related to Study Drug
- TEAE Leading to Interruption of Study Drug
- TEAE Leading to Withdrawal 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, by treatment group and overall, for the following:

- TEAE
- TEAE Related to Study Drug
- Serious TEAE
- Serious TEAE Related to Study Drug
- TEAE Related to a Study Procedure
- TEAE of CTCAE Grade 3 or Higher
- TEAE of CTCAE Grade 3 or Higher Related to Study Drug
- TEAE Leading to Interruption of Study Drug
- TEAE by SOC, PT and Maximum Grade (incidence only)
- [redacted]

The following listings of TEAEs will be presented in Section 14.3.2 of the CSR.

- TEAE Leading to Withdrawal of Study Drug
- TEAE Leading to Early Termination from Study
- TEAE Leading to Death
- Serious TEAE

In addition, listings of all reported AEs and SAEs will be provided in Appendix 16.2.7 of the CSR.

[redacted]

System organ class will be presented in descending order of frequency in the pooled PLN-74809 group and then alphabetically. Preferred terms will be displayed in descending order of frequency in the pooled PLN-74809 group 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.

6.15.2 Laboratory Data

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. Shift tables for the change from baseline in categorical parameters will presented in the natural order of the outcome where possible.

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.

In addition, any confirmed liver abnormalities, identified per Section 6.2.19, will be summarized by treatment group and listed.

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

6.15.3 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.

[redacted]

6.15.5 Physical Examination

Shift tables for the observed change in status of each of the body systems, i.e., Normal, Abnormal NCS (Not Clinically Significant), and Abnormal CS (Clinically Significant) from baseline to each

follow-up visit will be tabulated by treatment group. All data, including details of clinically significant findings will be listed.

7 INTERIM ANALYSIS

Interim analyses will be conducted at the following milestones:

- Upon completion of Parts B and C (following full enrollment and 12-week treatment duration with 40, 80, or 160 mg PLN-74809).
- Upon completion of 12-week treatment duration with 320 mg PLN-74809 in Part D.

A database freeze will occur upon completion of study Part C by the last participant. All data for study part A, B and C will be 100% cleaned and signed off by the investigators. After database freeze, participants will be unblinded and these data will be used for the statistical analysis and reporting of Parts A, B and C.

Blinding measures for interim analyses performed on data up to Week 12 for all participants in Part D will be described in a separate blinding plan.

Interim data from Part D will include all assessments up to the Week 12 assessments, [redacted] Adverse events or concomitant medications started/initiated post Day [redacted] will not be summarized in the in the interim analysis and will be presented in the final analysis. Participants who discontinue treatment or the study post the Week 12 assessment date up to Day [redacted] will be summarized as on treatment/on study for the purposes of the interim analyses.

8 DATA SAFETY MONITORING BOARD ANALYSIS

Data Safety Monitoring Board (DSMB) analyses [redacted] will be performed by an external vendor.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

1. Adverse event summaries and efficacy assessments will be presented overall and [redacted]
2. Change from Baseline at Week 12 in efficacy assessments will also be presented by [redacted]

3. [redacted]
4. A mixed model for repeated measures [redacted].
5. Definition of Efficacy Per Protocol Population was revised from:

   [redacted]

   [redacted]
6. Removed CTCAE grading summaries for laboratory test parameters.
7. [redacted]
8. Added additional pooled placebo groups for comparison purposes.

10 REFERENCES

1. [redacted]

11 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures, and listings to be included within each section of the electronic common technical document (eCTD). The eCTD section is shown in bold.

Number	Title	Population
[redacted]	[redacted]	[redacted]

Number	Title	Population
[redacted]	[redacted]	[redacted]

Number	Title	Population
[redacted]	[redacted]	[redacted]

Number	Title	Population
[redacted]	[redacted]	[redacted]

Number	Title	Population
[redacted]	[redacted]	[redacted]

Number	Title	Population
[redacted]		

Number	Title	Population
[redacted]		

Number	Title	Population
[redacted]	[redacted]	

Number	Title	Population
[redacted]	[redacted]	[redacted]

Number	Title	Population
[redacted]	[redacted]	[redacted]