Lung Therapeutics, Inc.

LTI-03-1002

A Randomized, Double-Blind, Placebo-Controlled, Phase 1b, Dose Escalation, Safety, Tolerability and Pharmacodynamic Biomarker Study of Caveolin-1-Scaffolding-Protein-Derived Peptide (LTI-03) in Recently Diagnosed, Treatment Naïve Subjects with Idiopathic Pulmonary Fibrosis

10OCT2024

Statistical Analysis Plan

Version *2.0*

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Client:	**Lung Therapeutics Inc.**
Protocol Number:	***LTI-03-1002***

Document Description:	Final Statistical Analysis Plan
SAP Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 1b, Dose Escalation, Safety, Tolerability and Pharmacodynamic Biomarker Study of Caveolin-1-Scaffolding-Protein-Derived Peptide (LTI-03) in Recently Diagnosed, Treatment Naïve Subjects with Idiopathic Pulmonary Fibrosis
SAP Version Number:	2.0
Effective Date:	10OCT2024

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7ED091F404EE412284998939BB80C4B7

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Signing Time: 17-Oct-2024 | 5:56:04 PM GMT
7B3A3A801DEE4B9688DF9FC97DD6D19C

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DOCUMENT HISTORY

Version	Date	Changes
Version 1.0	01Sep2023	Initial version
Version 2.0	10Oct2024	Protocol deviation severity and significant status defined, 15% baseline FEV1 replaced by 15% decrease from Baseline FEV1, rule for BLQ value in biomarkers data

TABLE OF CONTENTS

LIST OF ABBREVIATIONS VI

1. INTRODUCTION 1

2. OBJECTIVES 1

2.1. Primary Objective 1
2.2. Exploratory Objectives 1

3. INVESTIGATIONAL PLAN 1

3.1. Overall Study Design and Plan 1
3.2. Study Endpoints 2
3.2.1. Primary Endpoint 2
3.2.2 Other Safety Endpoints 2
3.2.3. Exploratory Endpoints 2
3.3. Treatments 3
3.4. Dose Adjustment/Modifications 3

4. GENERAL STATISTICAL CONSIDERATIONS 3

4.1. Baseline, End of Study and Study Day 4
4.2. Missing/Incomplete Start and Stop Dates 4
4.3. Sample Size 5
4.4. Randomization and Blinding 5
4.5. Analysis Sets 5
4.5.1. Enrolled Set 5
4.5.2. Randomized Set 5
4.5.3. Safety Set 6
4.5.4. Pharmacokinetics (PK) Set 6
4.5.5. Pharmacodynamics (PD) Set 6

5. SUBJECT DISPOSITION AND PROTOCOL DEVIATIONS 6

5.1. Subject Disposition 6
5.2. Protocol Deviations 6

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS 7

6.1. Demographics and Baseline Characteristics 7
6.2. Medical History 7
6.2.1. General Medical History 7
6.2.2. Disease-Specific History 7
6.3. Inclusion and Exclusion Criteria 7

7. TREATMENTS AND MEDICATIONS 8

7.1. Prior and Concomitant Medications 8
7.1.1. Prior Medications 8
7.1.2. Concomitant Medications 8
7.2. Concomitant Procedures 8
7.3. Extent of Exposure and Treatment Compliance Rate 8

8. SAFETY ANALYSIS 8
8.1 ADVERSE EVENTS 9
8.1.1. Incidence of Treatment-Emergent Adverse Events 9
8.1.2. Relationship of Adverse Events to Study Drug 9
8.1.3. Severity of Adverse Event 10
8.1.4. Serious Adverse Events 11
8.1.5. Adverse Events Leading to Treatment Discontinuation 11
8.1.6. Adverse Events Leading to Death 11
8.2. CLINICAL LABORATORY EVALUATIONS 11
8.2.4. Hematology 12
8.2.5. Serum Chemistry 12
8.2.6. Coagulation 13
8.2.7. Pregnancy Test 13
8.3. VITAL SIGN MEASUREMENTS 13
8.4. PHYSICAL EXAMINATION 13
8.5. ELECTROCARDIOGRAM 14
8.6. SPIROMETRY 14
8.7. LEICESTER COUGH QUESTIONNAIRE 15
8.8. COUGH VISUAL ANALOGUE SCALE 15
9. PHARMACOKINETICS 15
10. EXPLORATORY BIOMARKER SAMPLING 15
11. INTERIM ANALYSIS 16
12. CHANGES IN THE PLANNED ANALYSIS 17
13. REFERENCES 18
14. APPENDICES 19
14.1. SCHEDULE OF ASSESSMENTS 19
14.2. LEICESTER COUGH QUESTIONNAIRE 21
14.3. COUGH VISUAL ANALOGUE SCALE 22

List of Abbreviations

AE	Adverse Event
AEC2	Alveolar Epithelial Type 2 Cells
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AV	Atrioventricular
BA	Bronchoabsorption
BAL	Bronchoalveolar Lavage
BALF	Bronchoalveolar Lavage Fluid
BID	Twice daily
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CSD	Caveolin-1 Scaffolding Domain
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DLCO	Diffusion Capacity of the Lungs for Carbon Monoxide
ECG	Electrocardiogram
ECM	Extracellular Matrix
EOS	End of Study
ERS	European Respiratory Society
EU	European Union
FEV_1	Forced Expiratory Volume 1
FLF	Fibrotic Lung Fibroblast
FN	Fibronectin
FOCBP	Female of Childbearing Potential
FVC	Forced Vital Capacity

GGT	Gamma Glutamyltransferase
HDL-C	High Density Lipoprotein Cholesterol
Hgb	Hemoglobin
HR	Heart Rate
HRCT	High-resolution Computed Tomography
IB	Investigator's Brochure
ICH	International Council for Harmonization
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IVRS	Interactive Voice Response System
LCQ	Leicester Cough Questionnaire
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein Cholesterol
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	Pharmacodynamic
PR	P to R interval
PK	Pharmacokinetic
PT	Prothrombin Time
QD	Once Daily
QRS	QRS wave
QT	Q to T interval
QTcF	QT interval corrected for heart rate calculated using Fridericia's formula
RBC	Red blood cell
RDW	Red cell Distribution Width
RR	R to R interval for ECGs
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

SOA	Schedule of Assessments
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) defines the statistical methods and data presentations for the Lung Therapeutics, Inc. protocol LTI-03-1002 study entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 1b, Dose Escalation, Safety, Tolerability and Pharmacodynamic Biomarker Study of Caveolin-1-Scaffolding-Protein-Derived Peptide (LTI-03) in Recently Diagnosed, Treatment Naïve Subjects with Idiopathic Pulmonary Fibrosis".

This SAP covers all specified analysis for the final study reports based on the study protocol Version 5.0 dated 04 May2023.

2. Objectives

2.1. Primary Objective

- To determine the safety and tolerability of inhaled LTI-03 in subjects diagnosed with IPF within 3 years of Screening.

2.2. Exploratory Objectives

- To assess the plasma pharmacokinetic (PK) of inhaled LTI-03 after the first dose and at steady state in subjects with IPF diagnosed within 3 years of Screening.
- To evaluate the pharmacodynamic (PD) biomarkers of inhaled LTI-03 in subjects diagnosed with IPF within 3 years of Screening.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multi-center, dose escalation, safety and tolerability study of LTI-03 or placebo administered by inhalation in subjects with IPF without prior treatment with anti-fibrotic agents within 2 months of the Baseline bronchoscopy. An IPF diagnosis will be confirmed by high-resolution computed tomography (HRCT) of chest or lung biopsy within 3 years prior to Screening. The study will contain 2 dose cohorts which will run sequentially. Subjects in the first, low-dose cohort (Cohort 1) will receive 2.5 mg of study drug (LTI-03 or placebo), administered twice daily approximately 10-12 hours apart (5 mg per day). If the 5 mg per day dose is well tolerated, a second, high-dose cohort (Cohort 2) will receive 5 mg of study drug (LTI-03 or placebo), administered twice daily approximately 10-12 hours apart (10 mg per day).

Eligible subjects will be randomized in a 3:1 ratio to either LTI-03 or placebo. Each cohort will have 9 subjects randomized to LTI-03 and 3 subjects randomized to placebo. Safety data will be reviewed on an ongoing basis by the Sponsor's medical officer and the Contract Research Organization (CRO)'s medical monitor. A review of safety data including but not limited to adverse events, laboratory assessments, vital signs, and spirometry will be conducted after all 12 subjects from Cohort 1 have completed Day 14 assessments. Enrollment in the second cohort will not begin until the Cohort 1 safety data has been reviewed and a dose decision made. A lower dose cohort may be added (2.5 mg administered once daily) or additional subjects (up to 12 subjects) may be added to the low-dose cohort (2.5 mg administered twice daily) if doses of

5 mg twice daily (10 mg per day) are not tolerated. In total, a maximum of approximately 24 subjects will be randomized in the study.

The Treatment Period will be 14 days, with subjects self-administering the study drug using the provided commercially available dry powder inhaler. All subjects will be trained on the proper methods of inhaler use and will have access to site personnel trained to assist subjects remotely if questions arise. Retraining may occur on Day 1 and 7, if required. During the Treatment Period, there will be on-site visits on Day 1, Day 7, and Day 14 and study assessments will occur at the investigational site on these days. The first dose of study drug will be administered at the investigational site and subjects will be monitored for at least 1 hour after dosing.

Screening assessments may take place over no more than 21 days prior to the Treatment Period. Screening assessments will include but not be limited to a complete physical examination including vital signs, electrocardiogram (ECG), spirometry, safety laboratory parameters, medical history, and concomitant medications. A Baseline bronchoscopy will be performed during the Screening Period in subjects who meet the Screening criteria and will include bronchoalveolar lavage (BAL) and/or bronchoabsorption (BA), and deep bronchial brushings.

Treatment Period will include but not be limited to physical examinations with vital signs, ECG, spirometry, clinical laboratory assessments, adverse event (AE) assessment, Leicester cough questionnaire, cough visual analogue scale (VAS), and concomitant medications. Bronchoscopies with BAL and/or BA and deep bronchial brushings will also be performed on Day 14 approximately 2-3 hours after morning dosing.

Follow-up study assessments will be completed at Day 21 with all Day 14 assessments repeated except dosing, bronchoscopy, and blood collection for biomarkers and PK. Also, a complete physical examination will be replaced by a brief physical examination. The end of the study is defined as the date of the last visit of the last participant in the study.

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Incidence of Treatment Emergent Adverse Events (TEAE).

3.2.2 Other Safety Endpoints

- Other safety endpoints include:
    - Physical examination findings
    - Vital signs
    - ECG
    - Clinical laboratory measurements
    - Spirometry
    - Leicester Cough Questionnaire (LCQ)
    - Cough VAS

3.2.3. Exploratory Endpoints

- To determine the plasma peak and trough concentration of LTI-03 after the first dose and at steady state.

- Change from baseline over time for biomarkers related to the pathophysiology of IPF.

3.3. Treatments

LTI-03 and matching placebo will be provided as inhalation powders for oral inhalation use. LTI-03, as an excipient-free, micronized dry powder, will be placed into white opaque hypromellose two-piece capsules. The placebo will be micronized lactose powder that is placed into white opaque hypromellose two-piece capsules and will be identical in appearance to LTI-03. Individual capsules containing 2.5 mg of study drug (LTI-03 or placebo) will not be labelled.

3.4. Dose Adjustment/Modifications

No dose adjustment is planned. A lower dose cohort may be added (2.5 mg administered once daily (QD)) or additional subjects may be added to the low-dose cohort (2.5 mg administered BID) if doses of 5 mg BID (10 mg per day) are not tolerated. If a lower dose cohort is added, the treatments will be appropriately described/updated and summarized in the TFLs.

4. General Statistical Considerations

This section presents general rules for the derivation and reporting of study data. If a subsequent section related to a specific derivation or analysis differs from this general guidance, the subsequent section takes precedence.

Continuous data will be presented using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Categorical data will be presented using frequency counts and percentages in each category. For the summary statistics of all numerical variables (unless otherwise specified), minimum and maximum will be displayed to the same level of precision of the raw data. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for missing values. The denominator for all percentages will be the number of subjects in that treatment group within the analysis set of interest, unless otherwise specified. Percentages will be presented to one decimal place except for the display of 100% frequency which will be displayed as ‘XX (100)’.

In general, all tables will be presented by treatment (active treatments, active treatment total, and pooled placebo). Subjects from all cohorts who took placebo will be combined to form a pooled placebo group for analyses. All study data will be presented in by-subject data listings.

“No data available for this report” will be presented when there are no data available to report.

The primary endpoint of the study is safety and no formal statistical hypotheses will be tested.

All descriptive statistical analyses will be performed using Statistical Analysis System (SAS) statistical software (version 9.4 or higher). Missing data will not be imputed unless otherwise stated.

4.1. Baseline, End of Study and Study Day

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to the date and time that the first dose of treatment is taken. Baseline values for spirometry are the mean of the Day 1 pre-dose and the value collected during screening using the same spirometry equipment (see Section 8.6).

A participant will have completed the study if all visits are completed and the End of Study eCRF is marked as completed. The end of study date for each participant is defined as the date of the last visit as recorded on the End of Study eCRF.

Study day is defined in relation to the date of first dose of study drug (on Day 1). Therefore, when an assessment date is before the first dose:

Study day = assessment date - first dose date of study drug

and when an assessment is on or after the first dose:

Study day = assessment date - first dose date of study drug + 1

4.2. Missing/Incomplete Start and Stop Dates

For the purpose of inclusion in tables, incomplete start and stop dates and times for AEs and prior/concomitant medications will be imputed as follows:

Missing start dates (where UK, UNK and UNKN indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY:
    - If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY.
    - If the month and year are the same as the first dose of study drug month and
        - the end date (after any imputation) is on or after the first dose of study drug, then the start date is assumed to be the date of the first dose of study drug.
        - the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date.

- DD-UNK-YYYY/UK-UNK-YYYY:
    - If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year.
    - If the year is the same as the first dose of study drug year and
        - the end date (after any imputation) is on or after the first dose of study drug, then the start date is assumed to be the date of the first dose of study drug.
        - the end date (after any imputation) is prior to the first dose of study drug, then the start date is assumed to be the end date for the start date.

If the start date is not recorded on eCRF then no date imputation will be performed.

Missing start times will be imputed as follows: If the missing time of an actual or imputed start date is the same as a study drug dosing date, the dosing time will be used as the imputed time. Otherwise, the earliest possible time of the actual or imputed start date (i.e. 00:01) will be used as the imputed time.

Missing stop dates (where UK and UNK indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY: Stop date is assumed to be the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Stop date is assumed to be 31-DEC-YYYY.

If a subject dies during the study, the stop date will be imputed as the date of death if the imputed stop date is after date of death.

Missing stop times will be imputed as the latest possible time of the actual or imputed stop date (i.e. 23:59).

4.3. Sample Size

Approximately 24 subjects are planned in 2 cohorts. Each cohort will include 12 subjects (9 on LTI-03 and 3 on placebo). Selection of sample size is based on prior experience to ensure that the safety and tolerability of LTI-03 will be adequately assessed while minimizing unnecessary subject exposure. With 18 subjects receiving LTI-03 there is a 60% chance of detecting an adverse event (AE) with a true incidence rate of 5% and an 85% chance of detecting a more common AE with a true incidence rate of 10%.

4.4. Randomization and Blinding

Subjects will be randomized to receive LTI-03: placebo in sequential cohorts, as per the study design. Randomization codes and unique subject identification numbers will be generated by the Interactive Voice Response System (IVRS). All study staff will remain blinded to study drug assignment throughout the trial.

An unblinded team of Biostatistics personnel will be set up to handle unblinded data until the study is unblinded after data lock.

4.5. Analysis Sets

The following analyses sets will be used for the various analyses outlined in this SAP.

4.5.1. Enrolled Set

The Enrolled Set will consist of all subjects who signed the informed consent form (ICF), to include screen failures.

A screen failure is defined as a subject who consents to participate in the study but is not subsequently randomized.

4.5.2. Randomized Set

The Randomized Set will consist of all subjects who were enrolled and randomized to study drug.

4.5.3. Safety Set

The Safety Set will consist of all subjects randomized to study drug and received at least one dose of study drug. The Safety Set will be used for all safety analyses and subjects will be analyzed according to the study drug actually received.

4.5.4. Pharmacokinetics (PK) Set

The PK Set will consist of all subjects who receive at least one dose of LTI-03 and have at least one evaluable PK concentration.

4.5.5. Pharmacodynamics (PD) Set

The PD Set will consist of all subjects who received at least one dose of LTI-03 and have at least one measured value at a scheduled PD time point after the start of dosing for at least one PD analyte.

5. Subject Disposition and Protocol Deviations

5.1. Subject Disposition

Subjects will be summarized by the number and percent of subjects dosed, completed the study, discontinued from the study (with discontinuation reasons), completed treatment, and discontinued from treatment (with treatment discontinuation reasons). The number of subjects randomized (i.e., subjects with a randomization date/time/number recorded on the eCRF) will also be summarized. Subject disposition summary will be presented by treatment (active treatments, active treatment total, and pooled placebo) and overall.

All subject disposition data recorded on the eCRF, including for subjects not randomized will be listed by subject using the Enrolled Set.

5.2. Protocol Deviations

All protocol deviations will be recorded and documented according to the Study Deviation Rules document in PPD's Clinical Trial Management System (CTMS) system. Once the deviations have been finalized, a MS Excel file with all deviations will be converted into a SAS dataset and used as the source for the SDTM DV domain to generate a listing. Protocol deviations will be tabulated by severity (i.e., Major/Minor). The summary table will include the number of subjects reporting protocol deviations and as a percent of the number of subjects dosed by treatment (active treatments, active treatment total, and pooled placebo) and overall. If a subject reports protocol deviations at more than one level of severity, both categories will be summarized during analysis.

The following definitions will be used:

- Major protocol deviations are defined as those deviations with substantial effect on patient safety or data integrity.
- Minor protocol deviations are defined as those deviations with non-substantial effect on patient safety or data integrity.
- Significant protocol deviations are defined as those deviations which affect the analysis population.

- Non-significant protocol deviations are defined as those deviations which do not affect the analysis population.

The summary and listing of the protocol deviations will be provided for the Safety Set.

6. Demographics and Baseline Characteristics

6.1. Demographics and Baseline Characteristics

The number and percentage of subjects by sex (Male, Female), reproductive status (Of Child-bearing Potential, Surgically Sterile, Post-menopausal), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Unknown and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported and Unknown) will be summarized.

The baseline characteristics consist of age (years), baseline height (cm), baseline weight (kg), baseline body mass index (BMI) (kg/m^2), number of cigarettes (or the equivalent) per day (pack-years (applicable only to subjects with past and/or current tobacco use)), and Diffusion Capacity of the Lungs for Carbon Monoxide (DLCO) (measured value only, in units of mmol/min/kPa), baseline spirometry (FVC), baseline LCQ total score and baseline cough VAS score. Demographics and baseline characteristics will be summarized descriptively.

Body mass index is calculated as (body weight in kilograms) / (height in meters)^2. A subject's age in years is calculated using the date of the informed consent and date of birth.

Cigarette consumption will be calculated in pack-years using: (the number of cigarettes smoked per day/20) * number of years smoked.

The summary of subject demographics and baseline characteristics will be presented by treatment (active treatments, active treatment total, and pooled placebo) and overall. Subject demographics and baseline characteristics will be listed. The summary and listing of demographics and baseline characteristics will be provided for the Safety Set.

6.2. Medical History

6.2.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher by system organ class (SOC) and preferred term (PT).

Subject medical history data including specific details as collected in the eCRF will be presented in a listing for the Safety Set.

6.2.2. Disease-Specific History

Details of IPF diagnosis (diagnostic method and date of test) will be listed for the Safety Set.

6.3. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in Sections 4.1.1 and 4.1.2 of the study protocol. The status of eligibility criteria met, inclusion criteria not met, or exclusion criteria met details will be listed for the Enrolled Set.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered within 30 days of the Screening Visit through Study Day 21 will be recorded on the Case Report Form (CRF), using generic names when possible.

Prior and concomitant medication will be coded according to the latest World Health Organization Drug Dictionary (WHODD) version March, 2023 or later. Missing/partial start and stop dates will be imputed as specified in Section 4.2.

The listing of prior and concomitant medications will be provided for the Safety Set. All prior and concomitant medications will be presented in the same listing.

7.1.1. Prior Medications

A prior medication is defined as a medication that ends prior to the first study drug administration.

7.1.2. Concomitant Medications

A concomitant medication is defined as a medication that ends at the time of or after the first study drug administration.

7.2. Concomitant Procedures

All concomitant procedures recorded during the study will be listed. The listing will be provided for the Safety Set.

7.3. Extent of Exposure and Treatment Compliance Rate

Exposure to study drug is defined as administration of any amount of study drug. Duration of exposure is defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dose date and time (Day 1) to the last dose date and time (date of last dose minus the date of first dose + 1) as recorded in the eCRF.

Drug compliance over the total dosing period will be assessed as the rate of compliance. The rate of compliance (%) will be calculated as follows and recorded on the eCRF: [(number of capsules used/number of capsules expected to be used)]*100.

The extent of exposure and rate of compliance will be summarized by treatment (active treatment arms, total of active arms, pooled placebo) and overall. A listing of exposure and compliance rate data will be presented.

The summary table and listing of exposure and compliance rate will be provided for the Safety Set.

8. Safety Analysis

Safety will be evaluated through continuous monitoring of AEs, physical examinations, vital signs, clinical laboratory measurements, spirometry, and ECGs.

Safety summaries and listings will be presented for the Safety Set.

8.1 Adverse Events

According to the International Council for Harmonization (ICH) guideline for GCP, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., Screening invasive procedures such as biopsies).

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA® Version 26.0 or higher). Missing/partial AE dates and times will be imputed as specified in Section 4.2. In general, summaries will be provided for the Safety Set and presented by SOC, PT and treatment (active treatments, active treatment total, and pooled placebo) and overall. Participants will be counted only once within each SOC or PT.

All AEs will be presented in a listing.

8.1.1. Incidence of Treatment-Emergent Adverse Events

AEs which begin or increase in severity or frequency at or after the administration of first dose of study drug are to be considered as TEAEs.

An overall summary of TEAEs will include the number and percentage of participants with at least one TEAE, any TEAE with CTCAE severity Grade 3 or higher, any related TEAE, any serious TEAE, any fatal TEAE, and any TEAEs leading to discontinuation of study drug.

The number and percentage of participants with TEAEs and the total number of TEAEs will be summarized by SOC and PT for each treatment (active treatments, active treatment total, and pooled placebo) and overall.

8.1.2. Relationship of Adverse Events to Study Drug

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE.

- Not related: The AE is clearly not related to the study drug, or the temporal relationship of the onset of the AE relative to administration of the product is not reasonable, or the AE can

be explained by another cause such as an underlying medical condition or other concomitant medication, or the AE has no plausible relationship to study drug.

- Related: The AE is probably related to the study drug. The temporal relationship of the AE to administration of the product is reasonable and there is no other cause to explain the event. Adverse events should be classified as related if the Investigator feels there is evidence to suggest a causal relationship between the study drug and the AE.

Study drug related TEAEs will be summarized by SOC and PT for each treatment (active treatments, active treatment total, and pooled placebo) and overall.

8.1.3. Severity of Adverse Event

All AEs will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

Table 1 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 1: Adverse Event Severity Grading Scale for Events not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event, per the definition of serious adverse event in Section 8.1.4.
d. Grade 4 and 5 events must be reported as serious adverse events, per the definition of serious adverse event in Section 8.1.4.

Reference source: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 published on November 27, 2017.

CTCAE severity grade will be presented in the AE listing. TEAEs by maximum severity will be summarized by SOC and PT for each treatment (active treatments, active treatment total, and pooled placebo) and overall.

8.1.4. Serious Adverse Events

Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity, result in a congenital anomaly/birth defect, or are a significant medical event in the Investigator's judgement.

All serious TEAEs will be presented in a separate listing.

8.1.5. Adverse Events Leading to Treatment Discontinuation

The AEs where the answer to "Action Taken" on the AE eCRF is "Drug Withdrawn" will be identified in the AE listing.

8.1.6. Adverse Events Leading to Death

The AEs where the answer to "Outcome" on the AE eCRF is "Death" will be identified in the AE listing.

8.2. Clinical Laboratory Evaluations

Clinical laboratory assessments will be performed by a central laboratory and collected according to the SOA (see Appendix 14.1).

For all numeric serum chemistry and hematology laboratory values, descriptive statistics for observed and change from baseline values will be presented for each laboratory test by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set. Listings will include all measured values.

All relevant clinical laboratory tests will be classified as Low, Normal, and High according to the normal ranges. This categorical data will be summarized in shift tables comparing the minimum post-baseline value, maximum post- baseline value, and the results at timepoint of interest post-baseline visit with those at the baseline visit. Shift table summaries will be

presented by treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

8.2.4. Hematology

The following hematology laboratory tests will be included:

- red blood cell (RBC) count
- mean corpuscular hemoglobin concentration (MCHC)
- mean corpuscular hemoglobin (MCH)
- mean corpuscular volume (MCV)
- red cell distribution width (RDW)
- hematocrit (Hct)
- hemoglobin (Hgb)
- white blood cell (WBC) count
- including differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes)
- platelet count

Summary tables will be presented as described in Section 8.2 and data will be provided in a listing.

8.2.5. Serum Chemistry

The following serum chemistry laboratory tests will be included:

- bilirubin (total and conjugated)
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- alkaline phosphatase (ALP)
- gamma glutamyl transferase (GGT)
- lactate dehydrogenase (LDH)
- creatine kinase (CK)
- protein
- albumin
- cholesterol (total, low density lipoprotein cholesterol (LDL-C))
- high density lipoprotein cholesterol (HDL-C)
- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- chloride
- calcium
- magnesium
- C-reactive protein (CRP)

Summary tables will be presented as described in Section 8.2 and data will be provided in a listing.

8.2.6. Coagulation

The following coagulation laboratory tests will be included:

- prothrombin time (PT)
- INR
- activated partial thromboplastin time (aPTT)

Since coagulation data are collected only at the screening visit, only a listing will be presented.

8.2.7. Pregnancy Test

Females of childbearing potential must have a negative urine or serum pregnancy test during screening. A urine or serum pregnancy test will also be performed on study days as mentioned in the schedule of assessments (SOA) (see Appendix 14.1).

A listing showing pregnancy test date and time, test result and reason for not doing pregnancy test (if not done) will be presented for the Safety Set.

8.3. Vital Sign Measurements

Vital signs will be obtained after subject has been sitting for at least 1 minute and will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), body temperature (C) and hemoglobin oxygen saturation (%) (via pulse oximetry).

Descriptive statistics for observed and change from baseline values will be presented for each vital sign test by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

Vital signs data will be presented in a listing for the Safety Set.

8.4. Physical Examination

A complete physical examination will include an evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline (Screening Physical Exam) will be recorded as medical history.

A brief physical examination will focus on systems affected by AEs and at a minimum should include the cardiovascular and respiratory systems. Height and weight will be recorded at screening.

Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as TEAEs. A categorical summary of physical examination results will be presented by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

Physical examination data will be presented in a listing for the Safety Set.

8.5. Electrocardiogram

A single standard 12-lead ECG will be performed at each scheduled visit. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a supine position for at least 5 minutes.

ECG parameters to be evaluated include heart rate (HR) and the R to R interval (RR), Q to T (QT), P to R (PR) intervals and QRS duration. In addition, Fridericia's formula should be used to calculate the QT interval corrected for heart rate (QTcF). ECG morphology statements will also be evaluated with particular attention paid to waveform morphology findings of: ST segment abnormal, T wave changes, abnormal U waves, atrioventricular (AV) block, arrhythmia (supraventricular, ventricular, atrial fibrillation/flutter, etc.), and others including infarction, ischemia, and hypertrophy. ECG abnormalities will be recorded as AEs only if they are considered to be clinically significant by the Investigator.

Descriptive statistics for observed and change from baseline values will be presented for each ECG measurement by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

All ECG data will be listed with flags for QTcF values > 450 msec and increase from baseline > 30 msec.

8.6. Spirometry

Spirometry to assess forced expiratory volume 1 (FEV1), FVC, FEV1/FVC and the percent predicted for each of the parameters will be performed during Screening, Day 1, Day 7, Day 14, and Day 21. DLCO will be assessed only at Screening. Percent predicted will be calculated based on height, age, and ethnicity. Spirometry will be performed according to the current American Thoracic Society (ATS) / European Respiratory Society (ERS) Task Force guidelines (Miller et al., 2005). Spirometry will be performed on Days 1, 7, and 14 pre-dose and post-dose at 30 and 60 minutes (See Protocol section 7). Unscheduled spirometry may as be performed as needed for respiratory symptoms. If bronchospasm is suspected, spirometry may also be performed before and after a rescue beta-adrenergic agonist inhalation.

It is important to note that baseline values for spirometry are the mean of the Day 1 pre-dose and the value collected during screening using the same spirometry equipment. For example, if the initial spirometry for screening is done in a central spirometry laboratory, but Day 1 and subsequent spirometry is done with portable equipment in the clinic, then a second spirometry should be done in the screening period using the same portable equipment used in the clinic. The baseline value for each spirometry would thus be the mean of screening value using portable equipment and the Day 1 pre-dose value using portable equipment.

Descriptive statistics for observed and change from baseline values will be presented for each spirometry measurement by scheduled visit, timepoint, and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

Line graphs of FEV1, FVC and 15% decrease from Baseline FEV1 will be presented by subject and visit for the Safety Set.

Spirometry data will be presented in a listing for the Safety Set.

8.7. Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ) is a subject self-report, health related quality of life questionnaire (see Appendix 14.2) that will be collected per SOA (see Appendix 14.1). The LCQ consists of three domains where domain scores are equal to the total score from the questions in the domain divided by the number of questions in the domain (domains scores range from 1 to 7):

1. Physical: Questions 1, 2, 3, 9, 10, 11, 14, and 15
2. Psychological: Questions 4, 5, 6, 12, 13, 16, and 17
3. Social: Questions 7, 8, 18, and 19

LCQ total score is equal to the sum of the domain scores (total score range from 3 to 21) with a lower score indicating greater impairment of health status due to cough. The LCQ domain and total scores will be derived for use during analysis. If a response is not provided to a question, the domain score will be calculated as the average of the scores to the answered questions within the domain. If a subject responds to less than 80% of questions in a domain, the LCQ domain score will not be calculated and will be treated as missing during analysis. If it is not possible to calculate all domain scores following this criteria, total score will not be calculated and will be treated as missing during analysis.

Descriptive statistics for observed and change from baseline values will be presented for LCQ domain and total scores by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

LCQ data will be presented in a listing for the Safety Set.

8.8. Cough Visual Analogue Scale

The cough VAS is a 100 mm scale (See Appendix 14.3) on which a subject will be asked to mark between ‘no cough’ (0 mm) and ‘the worst cough severity’ (100 mm).

Descriptive statistics for observed and change from baseline values will be presented for cough severity VAS by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for the Safety Set.

Cough VAS data will be presented in a listing for the Safety Set.

9. Pharmacokinetics

Plasma and BAL samples for PK assessment will be collected as indicated in the SOA (see Appendix 14.1). Plasma PK analyses and BAL bioanalytical results will be covered by a vendor reported by the sponsor in a separate document.

10. Exploratory Biomarker Sampling

Exploratory biomarkers will be assessed in peripheral blood cells (as feasible), platelet rich plasma, BALF, BA samples, and deep bronchial brushings as outlined in Table 2. Ribonucleic acid (RNA) transcription analysis from whole blood may be substituted for any assays using peripheral blood cells. Samples will be collected at the time of bronchoscopy during the screening period and Day 14 as shown in Appendix 14.1. Additional biomarkers may be added as new information is generated about the potential effects of CSD (caveolin-1 scaffolding domain) signaling.

Table 2: Exploratory Biomarkers by Sample Source and Assumed Indicator Function

Sample source / Indicator of	Epithelial damage / repair	Fibrosis	Inflammation	Thrombosis
Peripheral blood cells [b]	-	p-AKT[b], IL-11	CXCL7	-
Platelet rich plasma (PRP)	CYFRA 21-1, SP-D, CA-19-9, KL-6, sRAGE, Galectin 7	MMP-7, Tenascin C (TNC), Periostin, IL-11, MYDGF, MMP-2	CCL18, CXCL13, slCAM1, IL-11, sCD163, CXCL7	PAI-1
BAL and/or BA[a]	Galectin 7, SP-D, sRAGE	MYDGF, MMP-2, TNC, MMP-7, periostin, IL-11	CCL18, CXCL13, slCAM1, IL-11, sCD163, CXCL7	PAI-1
Deep bronchial brushings	-	p-SMAD2/3	-	-

Abbreviations: BAL = bronchoalveolar lavage. BA = bronchoabsorption

[a] LTI-03 levels will also be measured on BAL samples. LTI-03 will not be measured in BA samples.

[b] Ribonucleic acid transcription analysis may be substituted for assays using peripheral blood cells.

For each PD biomarker, concentrations, change from baseline, percent change from baseline, and/or fold change, as applicable, will be summarized by scheduled visit and treatment (active treatments, active treatment total, and pooled placebo) and overall for all subjects in the Safety Set.

Biomarker results that are Below the Limit of Quantification will be treated as zero for calculation of concentration descriptive statistics. Percent change and fold change will be estimated for subjects with both baseline and post-baseline results, but will not be estimated in cases where the baseline result is zero.

Biomarker data will be presented in a listing for the Safety Set.

11. Interim Analysis

No formal interim analyses are planned for the study. Cohort 1 biomarker data may be analyzed before final database lock without changing the overall study conduct. If required, these analyses will be handled by Lung Therapeutics. PPD Biostatistics will provide relevant blinded SDTM and ADaM datasets to Lung Therapeutics to conduct the analyses. If requested, unblinded PPD Biostatistics personnel will be assigned and appropriate documentation updated to detail the unblinding event.

12. Changes in the Planned Analysis

Section 8.6: Line graphs of 15% Baseline FEV1 is updated to 15% decrease from Baseline FEV1.

13. References

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Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.

Snyder LD, Mosher C, Holtze CH, et al. Time to diagnosis of idiopathic pulmonary fibrosis in the IPF-PRO Registry. BMJ Open Respir Res 2020;7(1). DOI: 10.1136/bmjresp-2020-000567.

14. Appendices

14.1. Schedule of Assessments

	Screening Period	**Treatment Period**[1]			**Follow-Up**	**Early Termination**[2]
	(Day -21 to Day -1)	**Day 1**	**Day 7** (± 1 day)	**Day 14** (± 1 day)	**Day 21** (+ 2 days)	
Informed consent	x					
Inclusion/Exclusion Criteria	x	x				
Demographics, Medical History	x					
Prior medications	x					
Concomitant medications	→					
Complete physical examination[3]	x			x		x
Brief physical examination[4]		x	x		x	
Vital Signs	x	x	x	x	x	x
ECG (12-Lead ECG), single	x	x	x	x	x	x
Bronchoscopy with BAL and/or BA and deep bronchial brushings biopsy	x			x		x
Blood for biomarker assessments[5]	x			x		x
Pregnancy test[6]	x	x	x	x	x	x
Safety Laboratory parameters[7]	x	x	x	x	x	x
Randomization		x				
Blood collection for PK[8]		x	x	x		
Assessment of ability to use inhaler	x					
Leicester Cough Questionnaire & Cough VAS	x	x	x	x	x	x
Spirometry[9]	x	x	x	x	x	x

Dosing[10]		x	x	x		
Subjects returning unused study drug			x	x		
Adverse Events	x	→				

Abbreviations: BAL = bronchoalveolar lavage; BA = bronchoabsorption; DLCO = diffusion capacity of the lungs for carbon monoxide; ECG = electrocardiogram; PK = pharmacokinetics; VAS = visual analogue scale

Note:

1. On Days 2 to 6 and Days 8 to 13, subjects will self-administer study drug at home and will be contacted on Day 4 (± 2 days) and Day 10 (± 2 days) by study staff to check on compliance and for potential adverse events. Day 1, 7, and 14 will be clinic visit. Study be clinic visit. Study staff will monitor subjects self-administrating study drug (most likely the morning dose) on Day 1, Day 7, and Day 14.
2. If a subject discontinues study drug before Day 14, the Day 14 assessments (other than study drug dosing) where feasible should be performed in the clinic as close as possible to the day of discontinuation. The EOS assessments should be performed 7 days after the last dose of study drug (assuming the subject has not withdrawn consent).
3. A complete physical examination will include an evaluation of the head, eyes, ears, nose and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline (Screening Day) will be recorded as medical history.
4. A brief physical examination will focus on systems affected by AEs and at a minimum should include the cardiovascular and respiratory systems.
5. Biomarker assessment will be for peripheral blood cells, platelet rich plasma, bronchoalveolar lavage fluid (BALF), BA samples, and deep bronchial brushings.
6. Serum or urine test required for any FOCBP, defined as pre-menopausal or < 12 months of amenorrhea post-menopause or no history of surgical sterilization.
7. Safety laboratory assessments include hematology, chemistry, and coagulation. Coagulation will be performed only at Screening.
8. Blood for PK will be collected pre-dose (trough) and +5 minutes after dosing (peak).
9. Spirometry: DLCO on Screening only. On treatment days (Day 1, 7, 14), it will be done before dosing and post dose at 30 and 60 minutes.
10. Study staff will monitor subjects self-administrating study drug (most likely the morning dose) on Day 1, Day 7, and Day 14. On Day 1, the first dose of study drug will be administered at the investigational site and subjects will be monitored for at least 1 hour after dosing. Study drug is dispensed on Day 1 and Day 7.

14.2. Leicester Cough Questionnaire

This questionnaire is designed to assess the impact of cough 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, have you had chest or stomach pains as a result of your cough?

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

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

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

4. In the last 2 weeks, have you felt in control of your cough?

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

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

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

6. In the last 2 weeks, my cough has made me feel anxious

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

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

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

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

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

9. In the last 2 weeks, exposure to paints or fumes has made me cough

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

10. In the last 2 weeks, has your cough disturbed your sleep?

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

11. In the last 2 weeks, how many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

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

13. In the last 2 weeks, my cough has made me feel fed up

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

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

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

15. In the last 2 weeks, have you had a lot of energy?

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

16. In the last 2 weeks, have you worried that your cough may indicate serious illness?

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

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

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

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

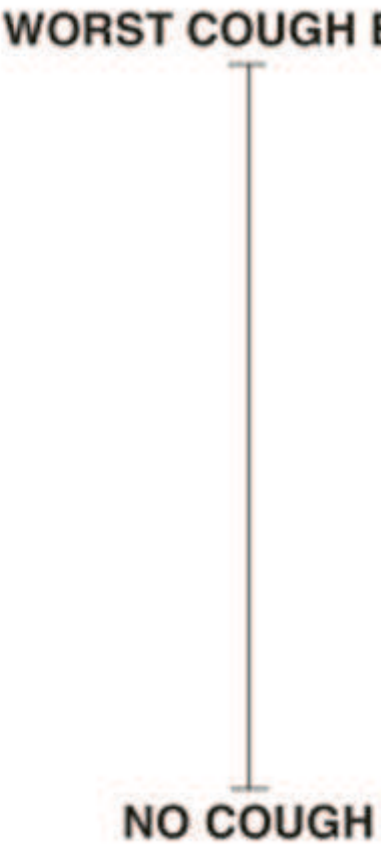
19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

14.3. Cough Visual Analogue Scale

Please put a cross on the line to indicate the severity of your cough in the past 2 weeks.



Note this scale is 100 mm long.

DocuSign

Certificate Of Completion

Envelope Id: 55C9ECD7E1DD44A38456B9DEE6502240
Status: Completed
Subject: Complete with Docusign: LTI LTI031002 SAP - V2.0.docx
Source Envelope:
Document Pages: 30
Signatures: 2
Certificate Pages: 3
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC) Monrovia, Reykjavik

Envelope Originator:
Katie Pottorff
929 N Front St
Wilmington, NC 28401
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IP Address: 208.127.228.158

Record Tracking

Status: Original
17 October 2024 | 15:05
Holder: Katie Pottorff
Katie.Pottorff@ppd.com
Location: DocuSign

Signer Events	Signature	Timestamp
Mikki Behnke mbehnke@lungtx.com Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 19 July 2023 | 15:05 ID: 43a759fc-8a24-4d43-88e6-089725d35c89	 Signature Adoption: Pre-selected Style Signature ID: 7B3A3A80-1DEE-4B96-88DF-9FC97DD6D19C Using IP Address: 174.22.239.59 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17 October 2024 | 15:13 Viewed: 17 October 2024 | 17:54 Signed: 17 October 2024 | 17:56
Ichraq Latar Ichraq.Latar@ppd.com Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	Ichraq Latar Signature Adoption: Pre-selected Style Signature ID: 7ED091F4-04EE-4122-8499-8939BB80C4B7 Using IP Address: 15.188.233.136 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17 October 2024 | 17:56 Viewed: 21 October 2024 | 13:23 Signed: 21 October 2024 | 13:24

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	17 October 2024 | 15:13
Certified Delivered	Security Checked	21 October 2024 | 13:23
Signing Complete	Security Checked	21 October 2024 | 13:24
Completed	Security Checked	21 October 2024 | 13:24

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

PPD has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures