Statistical Analysis Plan

Sponsor Name: Avalyn Pharma Inc.

Protocol Number: AP01-002

Protocol Title: A Randomized Open-Label, Phase 1b **S**tudy of the Safety of Pirfenidone So**l**ution for Inhalation (AP01) in P**a**tients with Idiopathic Pulmonary Fibrosi**s** (ATLAS Study)

Protocol Version and Date: Version 2.1 (12-OCT-2020)

Syneos Health Project Code: 1012435

Author: Dean Margeson, Principal Biostatistician

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	06-Dec-2019	Dean Margeson	Final Version 1.0
1.1	26-Feb-2020	Dean Margeson	Updated Version to Address Protocol Deviation Classification
2.0	24-Nov-2020	Dean Margeson	Final Version 2.0 – Updated analyses to account for COVID-19 effects on the data.
2.1	02-Jul-2021	Dean Margeson	Updated for changes due to patients in 50 mg once daily group switching to 100 mg twice daily group during Part B.
3.0	15-Jul-2021	Dean Margeson	Final Version 3.0

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

Dean Margeson, Principal Biostatistician	Dean Margeson	Electronically signed by: Dean Margeson Reason: I am the author Date: Jul 15, 2021 12:27 EDT
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
Jed Henke, Manager Biostatistics		Electronically signed by: Jed Henke Reason: I am the approver Date: Jul 15, 2021 11:31 CDT
Name, Title Senior Reviewer	Signature	Date (DD-Mmm-YYYY)

Avalyn Pharma, Inc. Approval

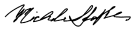
Michele Shaffer, Manager Biostatistics		Electronically signed by: Michele Shaffer Reason: I am the approver Date: Jul 15, 2021 09:37 PDT
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AP01	Pirfenidone Solution for Inhalation
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAL	Bronchoalveolar Lavage
BMI	Body Mass index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DSMB	Data and Safety Monitoring Board
D_{LCO}	Diffusion Capacity for Carbon Monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELF	Epithelial Lining Fluid
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in One Second
FOCBP	Female of Child-Bearing Potential
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLM	General Linear Model
HRCT	High-Resolution Computed Tomography
ICH	International Conference on Harmonization

Abbreviation	Description
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
KBILD	The King's Brief Interstitial Lung Disease
LCM	Leicester Cough Monitor
LCQ	Leicester Cough Questionnaire
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model Repeated Measures
N/A or NA	Not Applicable
NCI	National Cancer Institute
PE	Physical Exam
PFT	Pulmonary Function Tests
PP	Per-Protocol/Per-Protocol Set
PRO	Patient Reported Outcomes
PT	Preferred Term
QOL	Quality of Life
QTcB	Bazett-Corrected QT Interval
QTcF	Fredericia-Corrected QT Interval
RV	Residual Volume
SAE	Serious Adverse Event
SAF	Safety Set
SaO_2	Saturated Oxygen
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class

Abbreviation	Description
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
TLC	Total Lung Capacity
UIP	Usual Interstitial Pneumonia
VAS	Visual Analogue Scale
VC	Vital Capacity
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

An independent Data and Safety Monitoring Board (DSMB) will perform a review of safety data from the first 20 patients after Week 4 to confirm the safety of multiple dose administration. A decision to stop, continue or modify the study will be made based on this review. Throughout the course of the study, all serious adverse events (SAEs) will be sent to the DSMB for review.

An interim analysis will be performed at the completion of Part A. All endpoints will be analyzed and a full set of tables, listings and figures will be generated.

The final analysis of all safety and efficacy endpoints over Part A and Part B is planned after all patients complete the final study visit in Part B or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

The primary objective is to evaluate safety and tolerability of treatment with AP01 given once or twice daily to patients with idiopathic pulmonary fibrosis (IPF) by monitoring adverse events (AEs) and post-dose spirometry.

3.2. Secondary Objectives

The secondary objectives include:

- To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on absolute change in % predicted forced vital capacity (FVC) in patients with IPF
- To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on absolute change in % predicted Diffusion Capacity for Carbon Monoxide (D_{LCO}) in patients with IPF
- To compare the safety and efficacy of 50 mg once daily vs 100 mg twice daily dosing to provide guidance on dosing regimens for future studies
- To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on change in Patient Reported Outcomes (PROs) and cough in patients with IPF
- To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on change in the extent of fibrosis and lung volumes as measured by High Resolution Computed Tomography (HRCT) scans in patients with IPF
- To evaluate the following exploratory measurements:
    - Correlation between weekly home spirometry measurements and in-clinic spirometry values
    - Correlation of extent of fibrosis and lung volumes as measured by HRCT at Baseline and Week 24 to other measures of clinical status, e.g. spirometry
    - Change from baseline in serum biomarkers of alveolar epithelial injury (CA19-9 and CA-125).

3.3. Brief Description

This Phase 1b, 2-part, open-label study of AP01 will randomize approximately 100 patients with IPF. Patients will be randomized in a 1:1 ratio to one of two treatment groups: 50 mg once daily or 100 mg twice daily.

Figure 1: Part A Study Schema

PART A – Patients are randomized at Visit 2 to either 50 mg given once daily or 100 mg AP01 given twice daily

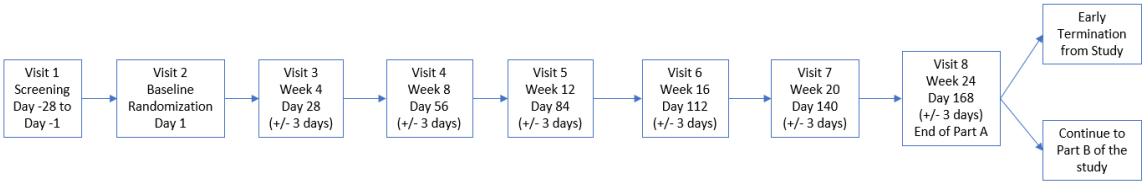


Figure 2: Part B Study Schema

PART B – Patients continue randomized treatment regimen of either 50 mg once daily or 100 mg AP01 twice daily

In Part A, eligible patients at least 40 years of age with a confident clinical and radiographic diagnosis of IPF according to pre-specified criteria, 40 ≤ %FVC ≤ 90, forced expiratory volume in 1 second (FEV_1)/FVC ratio ≥ 70% and 30 ≤ % D_{LCO} ≤ 90 will be randomized with equal probability to receive AP01 50 mg once daily or 100 mg twice daily for 24 weeks. Other than brief periods of medically appropriate treatment for acute IPF exacerbation, patients will not receive any other therapy for the treatment of IPF during Part A. If in the opinion of the investigator, a patient is in need of treatment with oral pirfenidone or nintedanib during Part A, the patient should be discontinued from the study and return to the clinic for their Early Termination visit. Supplemental oxygen will be allowed during the entire study.

The initial dose of drug will be administered in the clinic to confirm airway tolerance. If based on the investigator's opinion, the patient had tolerability issues during the first dose administration, a second dose, at least 4 hours later, will also be observed. Patients who experience cough that limits their ability to complete dosing will be given 1 - 2 puffs (90 - 100 microgram (µg)) of salbutamol in order to complete the in-clinic dose. These patients, as well as patients with a history of asthma or smoking history of 20 pack years or greater, or patients that have a ≥ 15% drop in FEV_1 % predicted in their pre-dose and post-dose readings will be required to use 1 - 2 puffs (90 - 100 µg) of salbutamol prior to

dosing throughout the study unless these patients are currently taking a long-acting beta-2-agonist therapy.

Patients will have a telephone assessment at Week 1 and in-clinic assessments at Weeks 4, 8, 12, 16, 20, and 24. The DSMB will perform a review of safety data from the first 20 patients after Week 4 to confirm the safety and airway tolerability of multiple dose administration. A decision to stop, continue or modify the study will be made based on this review.

Part B will collect long-term safety and efficacy data for an additional 48 weeks. Patients who complete Part A through Week 24 and, in the opinion of the investigator are compliant with treatment, may select to continue the treatment to which they were randomized. If one dosing regimen is determined to be superior either from an efficacy or safety standpoint, Part B may be converted to a single dose regimen and all patients who select to continue or start Part B at that point will be dosed with the selected regimen.

Study duration is up to 80 weeks for patients that complete both Part A and Part B of the study. If patients discontinue study treatment prior to Week 72 for any reason, they should return to the site for an Early Termination visit. All patients who complete the regular study visits through Week 72 in Part B will return for a Follow-up visit 28 days after their End of Study visit.

3.4. Patient Selection

3.4.1. Inclusion Criteria

Inclusion Criteria are described in Section 5.1 of the clinical study protocol.

3.4.2. Exclusion Criteria

Exclusion Criteria are described in Section 5.2 of the clinical study protocol.

3.5. Determination of Sample Size

This is an open-label study to determine safety and tolerability of AP01 50 mg once daily or 100 mg twice daily; both regimens being administered using the eFlow. With 50 patients per group, we have a 92% chance of detecting an AE with a true population rate of 5%, as displayed in Table 1:

Table 1: Probability of observing adverse events

	Actual probability of event		
	1%	**5%**	**10%**
Chance of observing ≥ 1 event	0.395	0.923	0.995

The Phase 3 study of oral pirfenidone in patients with IPF (ASCEND)[1] showed a standard deviation (SD) of 4.5 based on the imputed mean change in % of predicted FVC at Week 26. Assuming a SD of 4.5, with 50 patients per group, a two-sided 95% confidence interval (CI) for mean change from baseline in % of predicted FVC will extend 1.25 from the observed mean. The ASCEND[1] study showed a decrease of 1.5 and 3.9 in % of predicted FVC at Week 26 in the pirfenidone and placebo groups, respectively. Table

2 shows results of the ASCEND[1] active and placebo groups and potential observed differences in the AP01-002 study, assuming a similar SD.

Because we have no prior data on efficacy outcomes with our compound, we are unable to make well-informed predictions of effect size or variability. In lieu of that information, we have included some estimates of confidence intervals based on prior oral pirfenidone studies; however, we cannot be confident that our product will behave similarly and would not base hypothesis tests on this information. This study will give us an idea of which endpoints are most likely to be positively impacted by our product as well as solid estimates of both effect size and variability. In addition, if the effect is due to AUC or multiple peaks/day in the Epithelial Lining Fluid (ELF) rather than peak levels, based on our modeling from the BAL cohort in the AP01-001 study, we have around 75% power to show a difference between groups. With this sample size, we can be confident on selecting dosing regimen(s) for future trials.

Table 2: Observed and potential change in FVC

	ASCEND[1] Placebo (n = 262)	**ASCEND[1] Active (n = 255)**	**AP01-002 Potential Scenarios (n = 50)**		
Observed Change FVC % predicted (mean, SD)	-3.9, 5.2	-1.5, 4.5	-0.75, 4.5	-1.0, 4.5	-1.5, 4.5
95% CI	(-4.53, -3.27)	(-2.05, -0.95)	(-2.0, 0.5)	(-2.25, 0.25)	(-2.75, -0.25)

3.6. Treatment Assignment & Blinding

Patients will be randomized in a 1:1 ratio to receive Pirfenidone Solution for Inhalation (AP01) either 50 mg once daily or 100 mg twice daily; both regimens being administered by the eFlow. The randomization schema will be stratified by region (Asia-Pacific and Europe) and by disease severity (FVC < 50% predicted and FVC ≥ 50% predicted). The first 20 patients randomized in the study must have FVC ≥ 50% predicted at Screening. After the first 20 patients have been randomized, patients with FVC 40% < 50% predicted will be allowed to be randomized in the study but randomization for these patients will be capped at 20.

This is an open-label study; no blinding restrictions are required.

3.7. Administration of Study Medication

Patients will be trained on use of the eFlow and administration of the study drug at the Baseline visit. The first dose of study drug for each patient will be administered and observed at the clinical study site at the Baseline visit to confirm tolerability. All subsequent doses will be administered by the patient at home. All doses must be taken at least 4 hours apart.

Patients who experience cough that limits their ability to complete dosing will be given 1 – 2 puffs (90 -

100 µg) of an inhaled beta 2 agonist, such as salbutamol, in order to complete the in-clinic dose. These patients, as well as patients with a history of asthma or smoking history of 20 pack years or greater, or patients that have a ≥ 15% drop in FEV_1 % predicted in their pre-dose and post-dose readings and are symptomatic will be provided with and required to use 1 - 2 puffs (90 - 100 µg) of salbutamol prior to their second dose and for dosing throughout the study, unless these patients are currently taking a long-acting beta-2-agonist therapy. If symptoms persist with study treatment despite beta-2-agonist therapy, the Investigator will assess and discontinue the patient due to tolerability issues if he/she deems it necessary.

3.8. Study Procedures and Flowchart

3.8.1. Study Schedule

The study schedule can be found in Tables 3 and 4. At-home patient assessments are outlined in Table 5. Detailed information on study assessments is provided in Section 7 of the clinical study protocol.

Table 3: Study Schedule for Part A

	Study Phase – Part A							
	Screening	**Baseline**	**Treatment**					
Visit	1	2	3	4	5	6	7	8
Day	-30 to -1	1	28	56	84	112	140	168
Window (Days)	NA	NA	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3	+/- 3
Informed Consent	X							
Eligibility Assessments	X	X						
Assessment of IPF Diagnosis	X							
Demographics	X							
Medical History	X							
Physical Exam[2]	X	X	X	X	X	X	X	X
Height[3], Weight	X				X			X
Vital Signs	X	X	X	X	X	X	X	X
ECG	X							
Laboratory Tests[4]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Urinary Pregnancy Test[5]	X	X	X	X	X	X	X	X
Spirometry and D_{LCO}	X	X	X	X	X	X	X	X
SaO_2	X		X	X	X	X	X	X
LCM[6] and diary dispensation	X				X			X
Cough VAS, KBILD Questionnaire and LCQ		X	X	X	X	X	X	X

HRCT[7]		X						X
Pre-dose Spirometry		X						
Pre-dose SaO_2		X						
Randomization		X						
Study Material Training		X						
Study Drug Administration First Dose		X						
Post-dose Spirometry (≤ 10 min post-dose)		X						
Post-dose SaO_2		X						
Study Material Dispensation		X	X	X	X	X	X	X[8]
Home Spirometer Training and Dispensation		X						
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
End of Treatment/Study Form								X

Table 4: Study Schedule for Part B

	Study Phase – Part B				
	Treatment				
Visit	9	10	11	12	Follow-up
Day	252	336	420	504 End of Study	28 days after End of Study
Window (Days)	+/- 7	+/- 7	+/- 7	+/- 7	+/- 7
Cough VAS, KBILD and LCQ	X	X	X	X	X
Physical Exam[2]	X	X	X	X	X
Weight		X		X	
Vital Signs	X	X	X	X	X
Laboratory Tests[4]	X	X	X	X	X
Urinalysis	X	X	X	X	X
Urinary Pregnancy Test[5]	X	X	X	X	
Spirometry and D_{LCO}	X	X	X	X	X

Saturated Oxygen	X	X	X	X	X
Study Material Dispensation	X	X	X		
Concomitant Medications	X	X	X	X	X
Adverse Events	X	X	X	X	X
End of Treatment/Study Form				X	X

Notes for Tables 3 and 4:

1. Follow-up visit will occur 28 days after the End of Study visit in Part B of the study.
2. A complete physical exam will be performed at Screening and Baseline visits. A modified physical exam including the patient's lungs and cardiovascular body systems will be performed at all other visits.
3. Height is collected at the Screening visit only.
4. Blood samples for laboratory tests include: Chemistry (including AST and ALT), Hematology and Biomarkers (Blood samples for biomarkers will not be collected at Screening.)
5. Females of childbearing potential are required to take a urinary pregnancy test at each visit except the Follow-up visit.
6. Patients that pass screening and are scheduled to be randomized will receive a LCM to be worn for 24 hours and returned to the site at the Baseline visit. LCM will be worn for 24 hours at Visits 5 and 8. A paper diary will also be dispensed to the patient to record activities during the 24-hour period.
7. HRCT scans will be performed at Visits 2 and 8. The Baseline HRCT may be skipped if the HRCT for eligibility was performed less than 1 month prior to the Baseline visit.
8. Study material dispensation will occur at Visit 8 for those patients participating in Part B of the study.

Table 5 Patient At-Home Assessments

DAILY: Patients will administer AP01 50 once daily or 100 mg twice daily
WEEKLY: Patients will perform home spirometry readings on the same day each week at approximately the same time of day (+/- 2 hours)

3.8.2. Study Visits

Part A will consist of one Screening visit and 7 study visits, within the 24-week treatment period. Part B will consist of quarterly visits through study termination. A Follow-up visit will occur 28 days after the patient's End of Study visit in Part B.

Details of Study Visits are described in Sections 6.2.1 through 6.2.10 of the clinical study protocol.

4. Endpoints

4.1. Primary Efficacy Endpoint

- Change from baseline in absolute FVC % predicted.

4.2. Secondary Efficacy Endpoints

- Change from baseline in cough frequency as measured by LCM
- Change from baseline in the total KBILD score and in KBILD breathlessness and activity domains
- Change from baseline in the total LCQ score.
- Change from baseline in cough severity as measured by VAS
- Change from baseline in extent of fibrosis and lung volumes as assessed by HRCT
- Change from baseline in D_{LCO}.

4.3. Exploratory Endpoints

- Correlation between weekly home spirometry measurements and in-clinic spirometry values
- Correlation of extent of fibrosis and lung volumes as measured by HRCT at Baseline and Week 24 to other measures of clinical status, e.g. spirometry.
- Change from baseline in serum biomarkers of alveolar epithelial injury (CA19-9 and CA-125).

4.4. Safety Endpoints

- Treatment-emergent adverse events (AEs)
- Change from pre-dose to post-dose FEV_1 after initial dose
- Treatment-emergent deaths
- Treatment-emergent changes in clinical laboratory findings
- Changes in Vital signs.

5. Analysis Sets

5.1. Safety Set

The Safety Set (SAF) will include all randomized patients who were administered at least one dose of study medication. Patients will be analyzed according to treatment received. The SAF will be used for all analyses of safety endpoints.

5.2. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized patients. Patients will be analyzed according to randomized treatment. The FAS will be used for all analyses of patient disposition and baseline analyses and as a supportive sensitivity analyses for all efficacy endpoints. The FAS will also be used for the presentation of patients in all patient listings.

5.3. Per Protocol Set

The Per-Protocol Set (PP) will include all patients who were administered at least one dose of study medication, who have sufficient data to assess the primary efficacy endpoint, and who have no Major Protocol deviations that would impact the ability to appropriately assess the primary endpoint. Patients will be analyzed according to randomized treatment. Criteria for exclusion from the PP includes the following Major Protocol deviations:

- Violation of Inclusion/Exclusion Criteria
- Informed Consent not provided
- Study Drug Deviation
- Concomitant Medicine Restrictions

Summaries of all efficacy endpoints will be created using the PP.

5.4. Protocol Deviations

Protocol deviations will be collected and will be categorized as:

- Informed Consent
- Enrollment Criteria
- Dosing
- Concomitant Medications
- Visits/Procedures Required
- Visit Schedule
- Non-compliance
- Regulatory
- Laboratory
- Other

They will also be graded as Major or Minor.

Major protocol deviations are defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the subject's rights, safety or well-being. Major protocol deviations will be included in the Clinical Study Report (CSR). These include: Enrollment Criteria (violation of inclusion/exclusion criteria, Informed Consent (informed consent not provided), Dosing (study drug deviation), Non-compliance, Concomitant Medications (administration of prohibit medication) and Other Good Clinical Practice (GCP) deviations. All protocol deviations will be tracked and corrective live actions implemented.

Protocol deviations will be summarized by grade and category for each treatment group and overall in the following ways:

- Patients with Any Protocol Deviations (Major or Minor)
- Patients with Major Deviations Only
- Patients with Minor Deviations Only (i.e. excluding those patients with Major deviations).
- Protocol Deviations Attributable to COVID-19

All protocol deviations will be listed.

6. General Aspects for Statistical Analysis

6.1. General Methods

Unless otherwise specified, all data will be summarized by treatment group and overall. A separate summary of data from Part A of will be provided in addition to a full study summary including both Part A and Part B data. Categorical data will be summarized as number and percent of total. Continuous data will be summarized using mean, median, SD and range. Dose response will be evaluated by comparing safety and changes in efficacy variables across the dose regimens.

All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings.

Pulmonary function tests (PFTs) (including D_{LCO}) are performed at each study visit.

The following PFTs will be performed at all visits (including Screening) using spirometry (and documented on the PFT eCRF form):

- FVC Liters (L)
- FEV_1 Liters (L)
- % Predicated FVC
- % Predicted FEV_1.

Pre-dose and post-dose spirometry will be performed at the Baseline visit.

At every visit, D_{LCO} ($mL/min^{-1}/mmHg^{-1}$) and % Predicted D_{LCO} will be obtained using the site's standard methodology.

FEV_1/FVC ratio will be derived as: 100 x FEV_1/FVC.

For comparisons to baseline, data from Visit 2 prior to the first dose of study drug will be used as baseline, unless otherwise noted. For PFTs, the pre-dose result will be used as baseline. Subgroup analyses will be performed based on baseline groupings for FVC, region, age, sex, D_{LCO} and progression-related biomarkers (CXCL13**,** CCL18, MMP3).

If either regimen is eliminated based on Part A outcomes, patients may be switched to the selected regimen for the remainder of their participation. Data summaries will be created to mimic this switch by using the following treatment grouping for Part B: (1) randomized to 100 mg twice daily; (2) randomized to 50 mg once daily and stayed on 50 mg once daily; (3) randomized to 50 mg once daily and switched to 100 mg twice daily; (4) randomized to 50 mg once daily total [groups 2 and 3 combined]; (5) overall total for Part B data. Descriptive within-patient analyses will be included for those patients who switch from 50 mg once daily to 100 mg twice daily. These analyses will include spider plots of change from baseline showing when the dose switch took place. Data listings will include a variable to denote the regimen switch and flag the time of the switch for affected patients.

No formal hypothesis tests are planned.

6.2. Key Definitions

6.2.1. First Dose Date

First dose date in the study is defined as the first dose date of AP01 in Part A.

6.2.2. Cut-Off Date of Final Analysis

For the purpose of final analysis, the cut-off date of final analysis defined as the date at which all patients in the SAF either discontinue from treatment or 18 months has elapsed from the date of the first day of treatment for the last patient enrolled, whichever occurs first.

6.2.3. Baseline and Change from Baseline

Baseline is defined as the last non-missing measurement prior to or on the first dose of study drug.

Change from baseline = (post-baseline value – baseline value). For the purpose of tabulations, the unscheduled post-baseline values generally will be excluded.

6.2.4. Last Dose Date

The last dose date is defined as the last dose date of AP01 in Part B (or Part A if the patient discontinues treatment prior to Part B).

6.2.5. Study Day

The study day in the study is the days relative to the first dose date in the study. The day of the first dose of study medication in Part A will be defined as study day 1. The day prior to the first dose of study medication is study day -1. There is no study day 0.

6.2.6. First Dose Date of Part B

The first dose date of Part B is defined as first dose of study medication received after the Part A last dose date.

6.2.7. Treatment Duration

The overall treatment duration is defined as the last dose date – first dose date+1.

6.2.8. Dosing Switch Date

The dosing switch date is defined as the start date of the dosing change for those who switch from 50 mg once daily to 100 mg twice daily.

6.3. Missing Data

Missing values will not be imputed for data displayed in summary tables. For imputation of missing data used for the sensitivity analysis of the primary efficacy variable see Section 8.1.

Completely missing or partial dates will be presented in the listings as reported on CRFs.

If an AE has a completely missing onset date, then the AE will be considered a treatment emergent adverse event (TEAE). A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an adverse event or a medication has a partial missing start or stop date, the following rules will be used to impute the date; then the imputed date will be used to determine whether it is a TEAE for adverse event, or a prior or concomitant medication.

Table 6: Partial Date Derivation

Partial Missing Start or Stop Date	Derived Start Date	Derived Stop Date
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month derived as January or same as first dose month if the year is the same as the year of first dose	Missing month derived as December

6.4. Visit Windows

All data collected during study follow-up will be displayed and analyzed according to the actual visit data in the eCRF with the exception of early termination visits. Early termination visits will be mapped to the closest study visit, or analyzed according to the actual visit date, when possible.

The study assessments are summarized in Table 1 and Table 2 of the clinical study protocol. All information required by the protocol must be recorded on the source documents. The study schedule must be followed. However, under special conditions (e.g., holidays, weekends), a window of +/- 3 days is permissible for study procedures as long as the proper order of procedures and assessments is maintained. In Phase 2, a window of +/- 7 days is permissible. These windows are not applicable during the baseline period. Out-of-window data will be retained in the tables, listings, and figures. For the Part A interim analysis, Visit 8 will include data collected up to 36 weeks for HRCT and 28 weeks for all other variables.

6.5. Pooling of Centers

All centers will be pooled for summaries by treatment regimen. No by site analyses will be performed.

6.6. Subgroups

Subgroup analyses will be performed based on baseline groupings for FVC % predicted (FVC % predicted ≤ 65, 65 < FVC % predicted < 80, and FVC % predicted ≥ 80 at Baseline), region (Asia-Pacific and Europe), supplemental oxygen use (Y/N), age at screening categorized as >Median level vs. <=Median level, sex, D_{LCO} % predicted categorized as >Median level vs. <=Median level, and progression-related biomarkers (CXCL13, CCL18, MMP3) each categorized as >Median level vs. <=Median level provided each stratum contains at least 10 patients. Analyses of the primary efficacy endpoint will be performed by each subgroup in addition to by treatment group. In addition, a general

safety summary (overall AE summary, summary of respiratory [SOC respiratory, thoracic and mediastinal disorders] TEAEs by Preferred Term and summary of tolerability including cough due to drug administration and bronchospasm after in-clinic drug administration) will be performed by each subgroup in addition to by treatment group.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Patient Disposition and Withdrawals

The number of patients in each study population will be summarized by treatment group and overall. In addition, for each study part (Part A and Part B), patients' status with regard to study treatment and follow-up will also be summarized by treatment group and overall, along with the reasons for study discontinuations. The timing of the switch to 100 mg twice daily in Part B for 50 mg once daily patients and duration of time on 100 mg twice daily will be summarized.

All patient disposition data will be presented in a listing.

7.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics (age, sex, ethnicity, race and childbearing potential (and reason, if No)) will be summarized by treatment group and overall with descriptive statistics for Part A and Part B.

All demographic and baseline characteristics data will be presented in a listing.

7.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 21.1 or higher). Medical history will be listed by treatment group, patient number, start date and end date

7.4. Other Baseline Characteristics

Other baseline characteristics will be summarized by treatment group and overall with descriptive statistics for Part A and Part B including:

- IPF Diagnosis
    - Time since diagnosis
    - IPF-related cough (All the time, Most times during the day, Several times during the day, Sometimes during the day, Occasionally through the day, Rarely, Never)
- Smoking history:
    - Smoking Status (Current smoker, former smoker, never smoked)
    - For Current or Former Smokers Only:
        - Years smoked (Current Year – Year Started +1 for Current Smoker; Year Quit – Year Started +1 for Former Smoker)
        - Cigarette pack-years
        - Patients with ≥20 cigarette pack-years vs. patients with <20 cigarette pack-years.
- Region (Asia-Pacific and Europe)

- Disease Severity at Screening (40% predicted ≤ FVC < 50% predicted and FVC ≥ 50% predicted)
- Disease Severity at Baseline (FVC % predicted ≤ 65, 65 < FVC % predicted < 80, and FVC % predicted ≥ 80 at Baseline)
- FVC % predicted at Screening
- FVC (L) at Screening
- Progression related biomarkers at Baseline
    - CXCL13
    - CCL18
    - MMP3

All data for other baseline characteristics will be presented in a listing.

7.5. Drug Exposure

In this study, patients will be dosed in the clinic at Baseline to confirm tolerability for the first (and possibly second dose) and at home by the patient for all post-baseline doses. Drug exposure will be assessed as follows:

Baseline: In the Clinic

- The actual dose (mL) of AP01 for each patient will be the starting volume in the nebulizer minus the remaining volume in the nebulizer (if the full dose was not administered). If a second dose is given due to intolerance at the first dose, the actual dose will be derived in the same manner as the first dose. The number of patients who require a second dose in-clinic will be summarized and the total actual dose for each dose will be summarized by treatment group.
- The number of patients with physician-prescribed salbutamol taken prior to the dose will be summarized for each dose (first dose only if only 1 dose was received or for each dose if 2 doses are received) by treatment group with frequency counts and percentages. For patients who received salbutamol prior to dose, how many of those are because of prior toxicity for each dose and how many were added due to intolerance for the second dose will be summarized by treatment group with descriptive statistics.
- The number of patients with study drug inhalations interrupted will be summarized for each dose (first dose only if only 1 dose was received or for each dose if 2 doses are received) by treatment group with frequency counts and percentages.
- For patients with Inhalation interrupted during the second dose, the number of patients with salbutamol administered to continue dosing will be summarized by treatment group with frequency counts and percentages.
- For each patient, the time of nebulization for each dose will be derived as the study drug administration stop time minus the study drug administration start time and converted to minutes. If the study drug inhalation was interrupted, the time of interruption for each dose will be derived as the Inhalation Re-Start Time minus the Inhalation Interruption Time, converted to minutes and

then subtracted from the time of nebulization. Time of nebulization will then be summarized for each dose by treatment group with descriptive statistics. In addition, the Time of nebulation will be summarized for just those patients who took the full dose with no interruptions for each dose by treatment group with descriptive statistics.

- To assess tolerance, the number of patients with a ≥15% drop from pre-dose FEV_1 % predicted to post-dose FEV_1 % predicted will be summarized for each dose (first dose only if only 1 dose was received or for each dose if 2 doses are received) by treatment group with frequency counts and percentages (see more details in Section 10.6).

Post-Baseline: At Home

- For each patient, the treatment days will be derived cumulatively across all visits as the last dose date minus the first dose date + 1 and will be summarized by treatment group with descriptive statistics.
- For each patient, the actual total dosage (mg) of AP01 will be derived cumulatively across all visits across all patient doses as 50 times the total number of used ampoules returned, and will be summarized by treatment group with descriptive statistics.
- For each patient, the percent compliance will be derived cumulatively across all visits across all patient doses as 100 times (the total number of used ampoules returned divided by the total number of ampoules that would be used if they were fully dosing for the number of days between visits {slightly different from the number of ampoules dispensed}). If a subject discontinues early, the denominator will be the total number of ampoules, which would be used up to, and including the date of discontinuation. Percent compliance will be summarized by treatment group with descriptive statistics. The percent compliance will be categorized (≥80%, 60-<80%, 40-<60%, 20-<40% and <20%) and summarized by treatment group with frequency counts and percentages. The percent compliance will be calculated overall and separately for each dosing regimen for those patients who switch over from 50 mg once daily to 100 mg twice daily in Part B.
- For each patient, the percent compliance with the patient's care plan will be derived cumulatively across all visits across all patient doses as 100 times (the total number of used ampoules returned divided by the total number of ampoules that would be used if they were fully dosing for the number of days between visits minus the number of ampoules that would be missed if following instructions to reduce or interrupt dose). If a subject discontinues early, the denominator will be the total number of ampoules, which would be used up to, and including the date of discontinuation. Percent compliance will be summarized by treatment group with descriptive statistics. The percent compliance will be categorized (≥80%, 60-<80%, 40-<60%, 20-<40% and <20%) and summarized by treatment group with frequency counts and percentages. The percent compliance will be calculated overall and separately for each dosing regimen for those patients who switch over from 50 mg once daily to 100 mg twice daily in Part B.
- The number of patients who had any days where all doses were missed will be summarized cumulatively across all visits by treatment group with frequency counts and percentages. For those patients who had any days where all doses were missing, the maximum number of days between doses will be summarized cumulatively across all visits by treatment group with descriptive statistics.

All recorded information for study medication administration and accountability for AP01 will be listed.

All recorded information for Nebulizer Training, Nebulizer and Nebulizer handset accountability will be listed.

7.6. Prior and Concomitant Medications and Therapies

Medications and therapies that started and stopped prior to the first dose of AP01 are considered as prior medications. Medications and therapies that started prior to the first dose of AP01 and continued into the treatment period are considered as prior and concomitant medications. Medications or therapies with a start date from first dose of AP01 to 30 days after administration of the last dose of AP01 will be considered as concomitant medications.

Prior and concomitant medications will be coded according to World Health Organization (WHO) Drug Dictionary (March 2018 WHO DDE (Enhanced) B2 Format) for Concomitant Medication. The concomitant medications will be summarized for each treatment group and overall by Anatomical Therapeutic Chemical (ATC) level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) using the number and percentage of patients. Medications will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the overall total column. A patient will be counted only once within each level of summation if the patient has taken a medication more than once.

All prior and concomitant medications and therapies will be listed.

8. Efficacy

The following efficacy analyses will be performed:

- Change from baseline in absolute FVC % predicted
- Change from baseline in cough frequency as measured by LCM
- Change from baseline in the total KBILD score and in KBILD breathlessness and activity domains
- Change from baseline in the total LCQ score.
- Change from baseline in cough severity as measured by VAS
- Change from baseline in extent of fibrosis and lung volumes as assessed by HRCT
- Change from baseline in D_{LCO}

The primary endpoint of interest for efficacy is the absolute change from Baseline to Week 24 in FVC % predicted. Linear mixed-effects models will be used to estimate slopes representing the mean change from Baseline to Week 24 in each treatment group, and the difference between treatment groups will be examined. Baseline FVC % predicted, region, age at screening, sex, baseline D_{LCO} % predicted, and baseline progression-related biomarker (CXCL13**,** CCL18, MMP3) values each categorized as >Median level vs. ≤Median level will be included as covariates in the model. Similar modeling strategies will be employed for longer-term data obtained from Part B of the study.

No control group is included in this study; however, there is ample data in the literature showing a consistent rate of decline in IPF patients not receiving anti-fibrotic therapies. Historical data from the placebo groups of the three Phase III clinical trials of oral pirfenidone (ASCEND and CAPACITY trials) showed an average decline in FVC % predicted of ~4% at 6 months. These results will be used as a historical comparator. For each AP01 treatment group, a one sample Wald test will test H_0: mean change from Baseline to Week 24 in FVC % predicted ≤ -4% vs H_1: mean change from Baseline to Week 24 in FVC % predicted > -4%. For each AP01 treatment group, a 95% one-sided confidence interval will be derived for the difference (between A01 and historical reference) in the mean change from Baseline to Week 24 in FVC % predicted. Additionally, we will compare the change from baseline in FVC % predicted at Week 24 for each treatment group to the average decline in FVC % predicted at 24 weeks for patients with no documented antifibrotic treatment calculated from a set of (1) Pulmonary Fibrosis Foundation (PFF) Registry patients and (2) Australian IPF Registry patients, with matching baseline characteristics. For each treatment group and each registry, a two-sided Wald test will test: H_0: 24-week FVC decline$_{\text{AP01 group}}$= 24-week FVC decline$_{\text{registry}}$ vs. H_1: 24-week FVC decline$_{\text{AP01 group}}$ ≠ 24-week FVC decline$_{\text{registry}}$. For each of the 2 AP01 treatment groups and for each of the 2 registries, a 95% two-sided confidence interval will be derived for the difference (between AP01 and registry) in the mean change from Baseline to Week 24 in FVC % predicted.

The primary population used for efficacy analyses will be the PP with the FAS used for specified sensitivity analyses.

8.1. Primary Efficacy Endpoint and Analysis

Spirometry will be conducted at approximately the same time each visit (within 60 minutes of Day 1 spirometry measurement) with the patient in seated position. The test will be performed to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[3]. On days of clinic visits (including the screening visit), patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing (PFT). FVC % predicted will be calculated using the ERS Global Lung Function Initiative 2012 equations[2] as outlined in the clinical study manual.

PFTs will be collected at Screening, Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) as described in Section 6.1.

The primary efficacy endpoint is the change from baseline in absolute FVC % predicted from Baseline to Week 24. The population used for efficacy analyses of the primary variable will be the PP with the FAS used for the first sensitivity analyses.

A linear mixed-effects model (PROC MIXED) will be used and differences between treatment groups between slopes estimating the change from baseline in absolute FVC % predicted from Baseline to Week 24 will be examined. Baseline FVC % predicted, region, age at screening, sex, baseline D_{LCO} % predicted, and baseline progression-related biomarker (CXCL13**,** CCL18, MMP3) values each categorized as >Median level vs. ≤Median level will be included as covariates in the model. This analysis requires at least three post-baseline FVC % predicted values in addition to baseline be available for a patient to be included in the analysis so that the slope estimated is identifiable. Similar modeling strategies will be employed for longer-term data obtained from Part B of the study. Spirometry data collected after patients switched dosing regimen from 50 mg once daily to 100 mg twice daily will be omitted for this analysis.

For the sensitivity analyses of the primary efficacy endpoint, two different imputation strategies will be used to address missing in-clinic spirometry data used in the calculation of the change in absolute FVC % predicted from Baseline to Week 24. In both imputation strategies, missing data for early terminations other than deaths will be imputed for all visits following termination by assuming the average change at each visit calculated for all patients on the same cohort with FVC % predicted data available at that visit. For patients with missing data due to death, the remaining FVC % predicted values will be imputed as 30%.

For the second imputation strategy, in addition to imputing missing data due to early termination, home spirometry data will be used to replace missing in-clinic data using the following algorithm:

- Flag any biologically implausible home spirometry records for exclusion from analysis defined to be PFT measurements where the corresponding FVC % predicted value is <10 or >136.
- If home spirometry is available within the first two weeks following first dose of study drug, use it to calculate changes from baseline for home spirometry data.
- If home spirometry is not available within the first two weeks following first dose of study drug, use the patient's home spirometry data to fit a linear regression and the estimated intercept as a baseline for home spirometry data.

- Calculate all changes from baseline possible for a patient based on home spirometry data.
- Using any home spirometry data collected within the mapping window for a scheduled visit, create a pseudo office observation as the average of these home spirometry changes from baseline.
- Insert pseudo office observations for missed visits, setting the weeks of the observation to be the target weeks for that visit.

The primary variable will also be summarized by treatment group with descriptive statistics for the following subgroups: FVC (FVC % predicted ≤ 65, 65 < FVC % predicted <80, and FVC % predicted ≥ 80 at Baseline); region (Asia-Pacific and Europe); age at screening (>Median level vs. <=Median level); sex (Male and Female); baseline D_{LCO} % predicted (> Median level vs. <=Median level) and baseline progression-related biomarkers (CXCL13, CCL18, MMP3) each categorized as >Median level vs. <=Median level.

The following statistics for in-clinic FVC and FVC % Predicted will be calculated and summarized by treatment group and displayed in a table:

- Summary statistics of in-clinic FVC and FVC % Predicted at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of in-clinic FVC and FVC % Predicted reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for in-clinic FVC and FVC % Predicted:

- Mean FVC (or FVC % Predicted) Change from Baseline (±SD) vs. Visit Week (Week 4, Week 8, Week 12, etc.) with lines for each treatment group.

Linear mixed-effects models (PROC MIXED) will be used for the analyses. The model will include the change from baseline in in-clinic FVC (or FVC % Predicted) (measured at any time in the study) as the dependent variable and will include patient and time (continuous) as random effects, fixed effect of time and time-varying effects for treatment group and treatment-by-time interaction to account for those patients who switched dosing regimens from 50 mg once daily to 100 mg twice daily in Part B. Longitudinal plots at selected timepoints displaying the model adjusted, least square means and 95% confidence intervals will be produced.

All in-clinic pulmonary function data will be presented in a listing.

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Change from baseline in cough frequency as measured by LCM

The LCM[4] is an audio-based cough detection device that allows sounds to be reconstructed and measured as cough events. Patients that pass all of the screening criteria and will be randomized in the study will be provided with a cough monitor to wear for a 24-hour period prior to coming in for their Baseline visit. This will be used as their baseline reading. The LCM and mailing materials will also be dispensed at Visits 5 and 8. Patients will wear for a 24-hour period, fill out the cough monitor paper diary

and when complete, mail the LCM and diary back using the mailing materials provided. Further details regarding LCM dispensation and return will be outlined in the clinical study manual.

The following statistics for cough frequency (coughs/hour) as measured by LCM will be calculated and summarized separately for 24 hours and for awake time by treatment group and displayed in a table:

- Summary statistics of the cough frequency (coughs/hour) as measured by LCM at Baseline and at Visits 5 and 8 (Week 12 and 24)
- Summary statistics of the cough frequency (coughs/hour) as measured by LCM reflecting the absolute change from Baseline to Visit 5 and 8 (Week 12 and 24).

The following plot will be produced for cough frequency (coughs/hour) as measured by LCM:

- Mean Cough Frequency (coughs/hour) as measured by LCM Change from Baseline (±SD) vs. Visit Week (Week 12, Week 24) with lines for each treatment group.

A linear mixed-effect model (PROC MIXED) will be used and differences between treatment groups between the change from Baseline in coughs/hour as measured by LCM to Weeks 12 and 24 will be examined. Baseline cough frequency (coughs/hour), region, age at screening, sex, baseline D_{LCO} % predicted, and baseline progression-related biomarker (CXCL13**,** CCL18, MMP3) values each categorized as >Median level vs. <=Median level will be included as covariates in the model. The model will include a random effect for patient and fixed effects for treatment, visit (Week 12 or Week 24), and the interaction between treatment and visit. To account for correlated repeated measures within patients a compound symmetric variance-covariance matrix will be used.

In order to assess the impact of treatment on cough in those patients for whom coughing is of greatest concern, additional analyses of cough frequency will be performed on the subset of patients with baseline cough severity VAS ≥ 40 millimeters and in patients with baseline cough frequency ≥10 awake time coughs/hour. When examining these subgroups, the outcome will be % change from baseline.

All data for LCM will be presented in a listing.

8.2.2. Change from baseline in the total KBILD score and in the KBILD breathlessness and activity domain score

The KBILD Questionnaire[8] is a disease specific questionnaire consisting of 15 items that measures three specific domains: breathlessness and activities (questions 1, 4, 11 and 13), psychological (questions 3, 5, 6, 8, 10, 12 and 14) and chest symptoms (questions 2, 7 and 9). All items are scored on a seven-point response scale (1, 2, 3, 4, 5, 6, 7). The KBILD domain and total score ranges are 0–100; 100 represents the best health status A KBILD total score can be derived from the 3 domain scores with the addition of question #15. The algorithm for scoring the KBILD Questionnaire is logit-based and described in Sinha et al. 2019[9].

The KBILD Questionnaire will be completed at Baseline, all subsequent visits and the Follow-up visit. This is a paper-based questionnaire that will be completed by the patient at the relevant visits. The results of the KBILD will be entered into the appropriate eCRF. Appendix Section 14.2 presents the KBILD Questionnaire.

The following statistics for each KBILD questionnaire data domain and total score will be calculated and summarized by treatment group and displayed in a table:

- Number and percentage of patients in each treatment group that completed each survey at Baseline and at each post-Baseline time point.
- Summary statistics of the total KBILD score and each KBILD domain score at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of the total KBILD score and each KBILD domain score reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for each KBILD domain score and the KBILD total score:

- Mean KBILD domain (or Total) score Change from Baseline (±SD) vs. Visit Week (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) with lines for each treatment group.

All KBILD Questionnaire data will be presented in a listing.

8.2.3. Change from baseline in the total LCQ score.

The LCQ Questionnaire[10] is a disease specific questionnaire consisting of 19 items that measures three specific domains: physical (questions 1, 2, 3, 9, 10, 11, 14 and 15), psychological (questions 4, 5, 6, 12, 13, 16 and 17) and social (questions 7, 8, 18 and 19). All items are scored on a seven-point response scale (1, 2, 3, 4, 5, 6, 7). Domain scores are calculated as the total score from items in the domain divided by the number of items in the domain (range 1–7). The total score is the addition of all domain scores (range 3–21). For all domains, the higher the score the better the quality of life (QOL). If there are missing items, domain scores can be prorated by averaging the number of items actually answered. When there are missing data, prorating by domain in this way is acceptable as long as at least 50% of the items were answered (e.g., a minimum of 2 of 4 items).

The LCQ will be completed at Baseline, all subsequent visits and the Follow-up visit. This is a paper-based questionnaire that will be completed by the patient at the relevant visits. The results of the LCQ will be entered into the appropriate eCRF. Appendix 14.3 presents the LCQ.

The following statistics for each LCQ questionnaire domain and total score will be calculated and summarized by treatment group and presented in a table:

- Number and percentage of patients in each treatment group that completed each survey at Baseline and at each post-Baseline time point.
- Summary statistics of the total LCQ score and each LCQ domain score at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of the total LCQ score and each LCQ domain scores reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for each LCQ domain score and the LCQ total score:

- Mean LCQ domain (or total) score Change from Baseline (±SD) vs. Visit Week (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) with lines for each treatment group.

All LCQ Questionnaire data will be presented in a listing.

8.2.4. Change from baseline in cough severity as measured by VAS

The European Respiratory Society Cough Severity VAS[6] will be completed at Baseline, all subsequent visits and the Follow-up visit. This is a paper-based scale that will be completed by the patient at the relevant visits. The scale will range on a vertical line from 'No Cough' at the bottom to 'Worst Cough Ever' at the top. The patient will put a cross on the line to indicate the severity of their cough in the last 2 weeks. The results of the scale will be measured in millimeters from the bottom of the scale to the marked cross and entered into the appropriate eCRF. Appendix Section 14.1 presents an example of the Cough Severity VAS.

The following statistics for Cough VAS will be calculated and summarized by treatment group and presented in a table:

- Summary statistics of the Cough Severity VAS score at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of the Cough Severity VAS score reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for the Cough Severity VAS:

- Mean Cough Severity VAS Change from Baseline (±SD) vs. Visit Week (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) with lines for each treatment group.

All Cough Severity VAS score data will be presented in a listing.

8.2.5. Change from baseline in extent of fibrosis and lung volumes as assessed by HRCT

HRCT scans will be obtained to measure the extent of fibrosis and lung volumes at the Baseline visit and the Week 24 visit, or at an early termination visit if the patient does not complete Part A. These scans will be read and interpreted by a central reader.

The following statistics from the HRCT scans will be calculated and summarized by lung region and treatment group and displayed in a table:

- Summary statistics of the extent of fibrosis and lung volumes as assessed by HRCT at Baseline and the Week 24 post-Baseline time point, or separately for early terminations at the post-Baseline time point available.
- Summary statistics of the extent of fibrosis and lung volumes as assessed by HRCT reflecting the absolute change from Baseline to the Week 24 time point, or separately for early terminations at post-Baseline time point available.

The following plot will be produced for extent of fibrosis and lung volumes as assessment by HCRT:

- Mean Extent of Fibrosis (or Lung Volume) Change from Baseline (±SD) vs. Weeks from Baseline (calculated based on visit date) for each lung region with lines for each treatment group.

A linear model will be used and differences between treatment groups between the change from baseline in whole lung extent of fibrosis and whole lung volume from Baseline to post-Baseline will be examined. Change from baseline will be the dependent variable and baseline whole lung extent of fibrosis (or whole lung volume), region, age at screening, sex, baseline D_{LCO} % predicted and baseline progression-related biomarker (CXCL13**,** CCL18, MMP3) values each categorized as >Median level vs. ≤Median level, and time of HRCT (relative to baseline) will be included as covariates in the model.

All HRCT scan data will be presented in a listing including early termination and unscheduled visits.

8.2.6. Change from baseline in D_{LCO}

D_{LCO} will be collected at each visit. For predicted normal values, different sites may use different prediction formulas, based on the method used to measure D_{LCO}. In any case, the method used must be in compliance with the ATS/ERS guidelines[5] on D_{LCO} measurements and the prediction formula appropriate for that method[7]. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

PFTs will be collected at Screening, Baseline (pre-dose and post-dose) and at each Post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) as described in Section 6.1.

The following statistics for D_{LCO} and D_{LCO} % Predicted will be calculated and summarized by treatment group and displayed in a table:

- Summary statistics of D_{LCO} and D_{LCO} % Predicted at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of D_{LCO} and D_{LCO} % Predicted reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for D_{LCO} and D_{LCO} % Predicted:

- Mean D_{LCO} (or D_{LCO} % Predicted) Change from Baseline (±SD) vs. Visit Week (Week 4, Week 8, Week 12, etc.) with lines for each treatment group.

A linear mixed-effects model (PROC MIXED) will be used for the analysis. The model will include the change from baseline in D_{LCO} (or D_{LCO} % Predicted) (measured at any time in the study) as the dependent variable and will include patient as a random effect, fixed effect of time and time-varying effects for treatment group and treatment-by-time interaction to account for those patients who switched dosing regimens from 50 mg once daily to 100 mg twice daily in Part B. To account for correlated repeated measures within patients a spatial power matrix will be used. Longitudinal plots at selected timepoints displaying the model adjusted, least square means and 95% confidence intervals will be produced.

All D_{LCO} data will be presented in a listing.

9. Exploratory

9.1. Correlation between weekly home spirometry measurements and in-clinic spirometry

Patients will obtain spirometry readings at home on the same day and at approximately the same time each week (+/- 2 hours). Home spirometers will be dispensed at the Baseline visit; patients will be trained on the use of home spirometers prior to their departure from the Baseline visit. Home spirometer training and accountability data will be presented in a listing.

The home spirometry measurements (FVC, FVC % predicted) will be summarized by treatment group and visit including change from the baseline in-clinic pre-dose spirometry value using descriptive statistics. For the tabular summary and graphical summary, biologically implausible values and outliers will be removed as described previously in Section 8.1. The remaining spirometry measurements (FVC, FVC % predicted) within the mapping window for a scheduled visit will be averaged. All home spirometry data will be included in a listing.

Bland-Altman plots will be produced to describe the agreement between the home and in-clinic spirometry measurements at each visit. In these plots, the average of home spirometry measurements within the mapping window for a scheduled visit will be compared with the in-clinic spirometry at each visit.

A linear mixed-effects model (PROC MIXED) approach[12] will be used to determine the repeated-measures correlation coefficient estimates for in-clinic FVC measurements with averages of home FVC measurements across visits for each treatment group. A normal approximation will be used to determine the estimate for the correlation coefficient (ρ_{hat}), the 95% confidence intervals for the correlation coefficient estimate and p-value. This analysis for Part B will only use measurements in the 50 mg once daily group taken prior to the switch to the 100 mg twice daily group if the patient switched dosing regimens.

9.2. Change in absolute FVC % predicted from home spirometry Baseline visit to Week 24 and Week 72

A linear mixed-effects model (PROC MIXED) will be used for analysis. The model will include FVC % predicted (measured at home) as the dependent variable and will include patient and time of spirometry reading (study day) as random effects, and fixed effects of treatment group, time of spirometry reading (study day), along with a treatment-by-time interaction. Longitudinal plots at selected timepoints displaying the model adjusted, least square means and 95% confidence intervals will be produced. Spirometry data collected after patients switched dosing regimens from 50 mg once daily to 100 mg twice daily will be omitted for this analysis.

9.3. Correlation of extent of fibrosis and lung volume as measured by HRCT at Baseline and Week 24 to other measures of clinical status

The following HRCT measurements will be correlated with the following In-Clinic Spirometry Measurements (FVC) at Baseline and Week 24 or early termination:

- Extent of Fibrosis as Measured by HRCT with FVC

- Lung Volume as Measured by HRCT with FVC.
- Change in Extent of Fibrosis as Measured by HRCT with Change in FVC
- Change in Lung Volume as Measured by HRCT with Change in FVC

A linear mixed-effects model (PROC MIXED) will be used for the analyses of the absolute measures. The models will include the Extent of Fibrosis (or Lung Volume) (measured at Baseline and Week 24 or early termination) as the dependent variable and will include patient as a random effect, and fixed effects of treatment group, FVC (Baseline, Week 24 or early termination), visit, timing of HRCT in weeks from Baseline, and a treatment-by-visit interaction. To account for correlated repeated measures within patients a compound symmetric variance-covariance matrix will be used. Longitudinal plots at selected timepoints displaying the model adjusted, least square means and 95% confidence intervals will be produced. A linear model will be used for the change in Extent of Fibrosis (or Lung Volume). The model will include the change from baseline in Extent of Fibrosis (or Lung Volume) (measured at Week 24 or early termination) as the dependent variable and will include fixed effects of change from baseline in FVC, treatment group, baseline Extent of Fibrosis (or Lung Volume), and timing of HRCT in weeks from Baseline. The model adjusted, least squares mean and 95% confidence interval at Week 24 will be produced.

A linear mixed-effects model will be used to determine the repeated-measures correlation coefficient estimate for Extent of Fibrosis (or Lung Volume) with FVC across visits (Baseline, Week 24) for each treatment group. A normal approximation will be used to determine the estimate for the correlation coefficient (ρ_{hat}), the 95% confidence intervals for the correlation coefficient estimate and p-value. A partial correlation coefficient will be used to determine the correlation coefficient estimates for change in Extent of Fibrosis (or Lung Volume) with change in FVC for each treatment group. The corresponding 95% confidence intervals and p-values for the correlation coefficient estimates also will be reported.

9.4. Change from baseline in serum biomarkers of alveolar epithelial injury (CA19-9 and CA-125)

The serum biomarkers of alveolar epithelial injury (CA19-9 and CA-125)[11] will be collected at Baseline, all subsequent visits and the Follow-up visit. The following statistics for CA19-9 and CA-125 will be calculated and summarized by treatment group and displayed in a table:

- Summary statistics of CA19-9 and CA-125 at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of CA19-9 and CA-125 reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for CA19-9 and CA-125:

- Mean CA19-9 (or CA-125) Change from Baseline (±SD) vs. Visit Week (Week 4, Week 8, Week 12, etc.) with lines for each treatment group.

Change from baseline in CA19-9 and CA-125 will be correlated with change from baseline in FVC at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, and 72. Linear mixed-effects models (PROC MIXED) will be used for the analyses. The model will include the change from baseline in CA19-9 (or CA-125) (measured at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, and 72) as the dependent variable and will include patient as a

random effect, fixed effects of time, change from baseline in FVC (measured at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60 and 72), baseline CA19-9 (or CA-125), visit and time-varying effects for treatment group and treatment-by-time interaction to account for those patients who switched dosing regiments from 50 mg once daily to 100 mg twice daily in Part B. To account for correlated repeated measures within patients a spatial power variance-covariance matrix will be used. Longitudinal plots at selected timepoints displaying the model adjusted, least square means and 95% confidence intervals will be produced.

A linear-mixed effects model (PROC MIXED) approach will be used to determine the repeated-measures correlation coefficient estimates for change from baseline in CA-19 (or CA-125) with change from baseline in FVC for each treatment group using change from baseline at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60 and 72. A normal approximation will be used to determine the estimate for the correlation coefficient (ρ_{hat}), the 95% confidence intervals for the correlation coefficient estimate and p-value. Spirometry data collected after patients switched dosing regimens from 50 mg once daily to 100 mg twice daily will be omitted from this analysis.

10. Safety

The population used for safety analyses will be the SAF. Safety will be assessed on the basis of AE or adverse drug reactions (ADR) reports, clinical laboratory data, ECG parameters, physical examinations, vital signs and change from pre-dose to post-dose FEV_1 after initial dose.

Treatment-emergent AEs (any AEs recorded during or following the first study drug administration) will be summarized by treatment group and categorized by severity and relationship to the study procedures and to the investigational product (IP). If a patient has more than 1 occurrence of the same AE, he/she will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures and IP, will be indicated in cases of multiple occurrences of the same AE. SAEs will be summarized separately.

All AE data will be presented in a listing. Additionally, listings of SAEs and AEs leading to discontinuation will be generated. All SAEs will be evaluated to determine whether they are SUSARs or Unexpected Adverse Device Effects.

10.1. Adverse Events / Adverse Drug Reactions

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in this clinical study. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 21.1 or higher) terminology and the severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v5.0, where applicable. An adverse drug reaction (ADR) means any AE caused by a drug or biologic.

Treatment-Emergent Adverse Events (TEAEs) are those adverse events/adverse drug reactions that are recorded during or following the initiation of AP01 medication administration, and do not necessarily have a causal relationship to the use of the study medication. Treatment-Emergent Adverse Events (simply referred to as adverse events in summary tables) will be summarized.

The following adverse event summary tables will be summarized by treatment group and combined over both treatment groups:

1) An overall summary with the number and percentage of patients reporting AEs, serious AEs, grade 3 or higher AEs, treatment-related AEs, AEs leading to study treatment (AP01) discontinuation and AEs with outcome of deaths. In addition, this overall summary will be performed for each subgroup listed in Section 6.6.

2) AEs overall and by system organ class and preferred term. In this summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class. In addition, this summary will be performed for each subgroup listed in Section 6.6.

3) A separate summary of respiratory [SOC respiratory, thoracic and mediastinal disorders] TEAEs by Preferred Term and summary of tolerability including cough due to drug administration and bronchospasm after in-clinic drug administration) will be performed by each subgroup listed in Section 6.6.

4) AEs overall and by system organ class, preferred term and highest CTCAE grade.

In this summary, a patient is counted once at the highest grade for which the event occurred in the system organ class and the highest grade for each unique preferred term within that system organ class. Therefore, patients may only contribute once to each preferred term and once to each system organ class. The missing severity grade will be reported in a separate category.

5) Study-treatment-related AEs overall and by system organ class and preferred term.

All those AEs with relationship to AP01 marked as “Possibly Related” or “Probably Related” or missing will be reported in the table.

6) Study-treatment related AEs by system organ class, preferred term and Highest CTCAE grade

7) AEs leading to study treatment termination by system organ class and preferred term

8) AEs leading to study treatment termination by system organ class, preferred term and highest CTCAE grade

9) CTCAE Grade 3 or higher AEs, overall and by system organ class and preferred term

A Serious Adverse Event (SAE) is an AE that falls into one or more of the following categories:

a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability or incapacity
e. Is a congenital anomaly/birth defect
f. Is any other important medical event

Serious adverse events will be summarized by treatment group and combined over both treatment groups.

1) SAEs overall and by system organ class and preferred term.

In this summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class.

2) SAEs overall and by system organ class, preferred term and highest CTCAE grade.

10.2. Laboratory Evaluations

At each visit, clinical laboratory tests will be conducted at the study’s central laboratory. Clinical laboratory tests will include:

- Hematology: complete blood count with differential, platelet count

- Serum Biochemistry: bilirubin, alkaline phosphatase, sodium, potassium, chloride, bicarbonate, urea, creatinine, total protein, albumin, glucose, ALT, AST
- Urinalysis: pH, specific gravity, presence/absence of protein, glucose, blood
- Biomarkers: MMP3, CCL18, CXCL13, CA19-9, CA-125

Clinical laboratory results will be summarized using Standard International System of Units (SI) units. Laboratory measurements will be summarized for all protocol scheduled time points. Descriptive statistics (n, mean, SD, median, min and max) will be presented for all clinical chemistry, hematology, urinalysis (continuous) and biomarker (CA19-9 and CA125) laboratory parameters at each scheduled visit. Change from baseline at each scheduled post-Baseline visit will also be presented.

Patient counts and percentages of patient for each category of each urinalysis (categorical) parameters will be summarized at each scheduled visit.

Shift tables (i.e., low-normal-high at Baseline versus low-normal-high at each post-Baseline visit in a 3-by-3 contingency table) will be provided for hematology, clinical chemistry, urinalysis and biomarker to assess changes from baseline in laboratory values by visit.

A listing for all laboratory results for each laboratory category (hematology, serum biochemistry, urinalysis and biomarkers) and a listing of treatment-emergent abnormal values will be presented.

10.3. Vital Signs

Vital sign measurements including systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and body temperature at each scheduled time and changes from baseline in vital sign measurements will be summarized with descriptive statistics at each scheduled time point by treatment group. Temperature will be displayed in Celsius.

Body height will be measured at Screening only and will be summarized by treatment group. Weight will be measured at Screening and Week 12, 24, 48 and 72 visits and, along with changes from baseline, will be summarized with descriptive statistics at each scheduled time point by treatment group. Weight will be displayed in kilograms; height will be displayed in centimeters.

Body mass index (BMI) will be derived from the weight (at Week 12, 24, 48 and 72) and height (at Screening) along with changes from baseline, will be summarized with descriptive statistics at each schedule timepoint by treatment group. BMI will be displayed in kilograms per meter squared.

All vital signs data will be presented in a listing.

10.4. Physical Examination

A complete PE will be performed at the Screening and Baseline visits. This will include physical examination of the following body areas and systems: examination of general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system.

A modified PE of the lungs and CV body systems will be performed at each subsequent visit.

A complete or modified physical exam is optional at unscheduled visits, per the investigator's discretion.

The physical examination data will be presented in a listing.

10.5. Saturated Oxygen (SaO_2) Assessment

Saturated Oxygen (SaO_2) assessments will be performed at Screening, Baseline (Pre-Dose and Post-Dose) and at all post-Baseline Visits (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up). The SaO_2 % result will be captured and an indication will be noted if a patient received supplemental oxygen and, if so, the number of liters per minute. For Pre-Dose at Baseline, patients with SaO_2 < 90% will be administered supplemental oxygen until the SaO_2 reaches 93% prior to dosing.

The following statistics for SaO_2 will be calculated and summarized by treatment group and displayed in a table:

- Number and percentage of patients in each treatment group that had a SaO_2 result at screening, Baseline (pre-dose) and at each post-Baseline time point.
- Summary statistics of SaO_2 at screening, Baseline (pre-dose) and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of SaO_2 reflecting the absolute change from Baseline (pre-dose) to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for SaO_2:

- Mean SaO_2 Change from pre-dose Baseline (±SD) vs. Visit Week (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) with lines for each treatment group.

All SaO_2 data will be presented in a listing.

10.6. Pre and Post-Dose Spirometry at Baseline

At the Baseline visit, the first dose of study drug will be administered at the clinic; post-dose Spirometry will be performed and the post-dose spirometry FEV_1 results will be compared with the pre-dose FEV_1 results. Patients that have a ≥ 15% drop in FEV_1 % predicted in their pre-dose to post-dose readings and who are symptomatic will be required to use 1 - 2 puffs (90 - 100 µg) of salbutamol prior to dosing throughout the study unless these patients are currently taking a long-acting beta-2-agonist therapy.

If based on the investigator's opinion, the patient had tolerability issues during the first dose administration, a second dose, at least 4 hours later, will also be observed at the Baseline visit. For the second dose, a second pre-dose spirometry and post-dose spirometry will be performed. In addition, pre- and post-dose SaO_2 will also be recorded for the second dose.

For the first dose, the following statistics for pre- and post-dose FEV_1 results will be calculated and summarized by treatment group and displayed in a table:

- Number and percentage of patients in each treatment group that had an FEV_1 result at Baseline (pre-dose) and post-dose at Baseline
- Summary statistics of FEV_1 at Baseline (pre-dose) and at Baseline (post-Baseline)
- Summary statistics of FEV_1 reflecting the absolute change from Baseline (pre-dose) to Baseline (post-dose).

- Number and percent of patients who had a ≥ 15% drop in FEV_1 % predicted in their pre-dose and post-dose reading at Baseline.
    - For those with this drop, the number and percent that were symptomatic:
        - For those who were symptomatic, the number and percent that were discontinued due to intolerance or were given salbutamol and re-dosed at clinic,
            - For those who were re-dosed, summary statistics of their FEV_1 % predicted drop after that second dose and the number and percent who discontinued study.

All Baseline Pre- and Post-dose (first dose and second dose, if needed) spirometry data will be presented in a listing.

10.7. FEV_1/FVC Ratio

The following statistics for FEV_1/FVC ratio (as described in Section 6.1) will be calculated and summarized by treatment group and displayed in a table:

- Number and percentage of patients in each treatment group that had a FEV_1/FVC ratio result at Baseline and at each post-Baseline time point.
- Summary statistics of FEV_1/FVC ratio at Baseline and at each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up)
- Summary statistics of FEV_1/FVC ratio reflecting the absolute change from Baseline to each post-Baseline time point (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up).

The following plot will be produced for FEV_1/FVC ratio:

- Mean FEV_1/FVC ratio Change from Baseline (±SD) vs. Visit Week (Week 4, 8, 12, 16, 20, 24, 36, 48, 60, 72 and Follow-Up) with lines for each treatment group.

10.8. Urine Pregnancy Test

At all visits except the Follow-up visit, a urinary pregnancy test will be performed for all FOCBP and the results from these tests will be presented in a listing.

10.9. 12-Lead ECG

A 12-lead ECG will be performed at the Screening visit. The following results will be collected:

- Pulse rate (bpm)
- QRS duration (msec)
- QT interval (msec)
- QTcF interval (msec)
- QTcB interval (msec)
- ECG evaluation (Normal; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant).

The FAS will be used. An ECG is optional at unscheduled visits, per the investigator's discretion. All ECG data will be presented in a listing.

11. Interim Analyses

The DSMB will perform a review of safety data from the first 20 patients after Week 4 to confirm the safety of multiple dose administration. A decision to stop, continue or modify the study will be made based on this review. Throughout the course of the study, all SAEs will be sent to the DSMB for review.

At the completion of Part, A, all endpoints will be analyzed and a full set of tables, listings and figures will be generated. At the end of Part B, all analyses will be produced including data from both Parts A and B of the study.

12. Changes from Analysis Planned in Protocol

The FAS will be added and will be used for disposition and baseline analyses and as supporting sensitivity analyses for efficacy analyses. The FAS population is considered a standard analysis population used in most studies.

13. Reference List

1. King Jr. MD Talmedge E, Bradford M.D., Ph.D Williamson Z., Castro-Bernardini M.D. Socorro, Fagan M.D. Elizabeth A., Glaspole M.B., B.S., Ph. D. Ian, Glassberg M.D. Marilyn K., Hopkins M.D. Peter M., Kardatzke Ph.D. David, Lancaster M.S. Lisa, Lederer M.D. David J., Nathan M.D., Steven D. et al., for the ASCEND Study Group; A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med 2014; 370:2083-2092. https://www.nejm.org/doi/10.1056/NEJMoa1402582

2. Quanjer Philip H, Stanojevic Sanja, Cole Tim J, Baur Xever, Hall Graham L, Culver Bruce, Enright Paul L, Hankinson John L, Ip Mary SM, Zheng Jinpin, Stocks Janet. European Respiratory Journal 2012; Multi-ethnic reference values for spirometry for the 3 – 95 year age range: the global lung function 2012 equations. https://www.ncbi.nlm.nih.gov/pubmed/22743675

3. M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P.M. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi and J. Wanger. Standardisation of spirometry. Eur Respir J 2005; 26: 319–338 DOI: 10.1183/09031936.05.00034805.
https://www.thoracic.org/statements/resources/pfet/PFT2.pdf

4. S. S. Birring, T. Fleming, S. Matos, A. A. Raj, D. H. Evans, I. D. Pavord**.** The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. European Respiratory Journal 2008 31: 1013-1018; http://erj.ersjournals.com/content/31/5/1013

5. Brian L. Graham, Vito Brusasco, Felip Burgos, Brendan G. Cooper, Robert Jensen, Adrian Kendrick, Neil R. MacIntyre, Bruce R. Thompson and Jack Wanger; 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. https://www.thoracic.org/statements/resources/pft/DLCO.pdf

6. A.H. Morice, G.A. Fontana, M.G. Belvisi, S.S. Birring, K.F. Chung, P.V. Dicpinigaitis, J.A. Kastelik, L.P. McGarveye, J.A. Smith, M. Tatar and J. Widdicombe ERS guidelines on the assessment of cough. Eur Respir J 2007; 29: 1256–1276 DOI: 10.1183/09031936.00101006 https://www.lid.lt/wp-content/uploads/2013/07/Cough-assessment.pdf

7. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J 2017; 50: 1700010 [https://doi.org/10.1183/13993003.00010-2017] http://www.ers-education.org/guidelines/global-lung-function-initiative/tl,co-tools.aspx

8. Patel Amit S., Siegert Richard J, Brignall Katherine, Gordon Patrick, Steer Sophia, Desai Sujal J, Maher Toby M, Renzoni Elisabetta A, Wells Athol U, Higginson Irene J, Birring Surinder S; The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. https://thorax.bmj.com/content/thoraxjnl/early/2012/05/02/thoraxjnl-2012-201581.full.pdf

9. Sinha A, Patel AS, Siegert RJ, *et al*. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. *BMJ Open Resp Res* 2019;**6**:e000363. doi:10.1136/bmjresp-2018-000363.

10. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003; 58:339-343. https://thorax.bmj.com/content/58/4/339

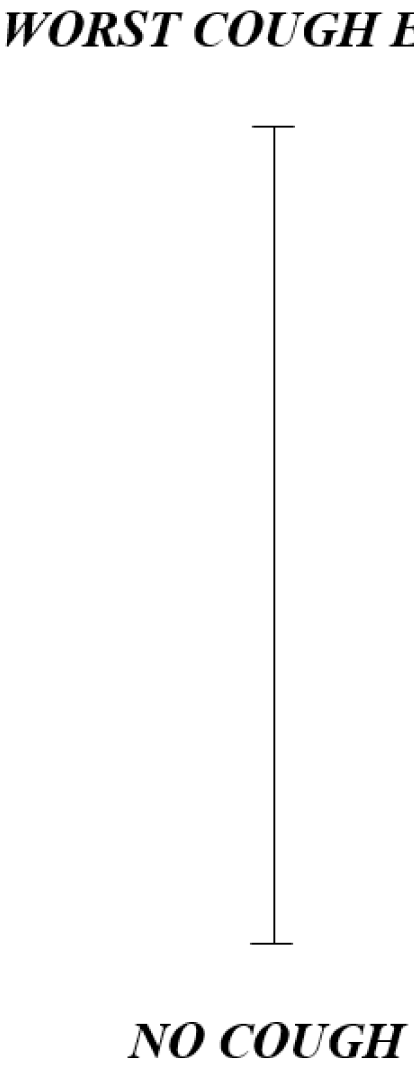
11. Maher TM, Oballa E, Simpson JK, Porte J, Habgood A, Fahy WA, Flynn A, Molyneaux PL, Braybrooke R, Divyateja H, Parfrey H, Rassl D, Russell AM, Saini G, Renzoni EA, Duggan AM, Hubbard R, Wells AU, Lukey PT, Marshall RP, Jenkins RG. An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. Lancet Respir Med. 2017 Dec;5(12):946-955. doi: 10.1016/S2213-2600(17)30430-7. Epub 2017 Nov 14. https://www.ncbi.nlm.nih.gov/pubmed/29150411

12. Hamlett A, Ryan L, Wolfinger R. On the use of PROC MIXED to Estimate Correlation in the Presence of Repeated Measures. 2004 SUGI 29 Proceedings.

14. Appendices

14.1. Cough Visual Analogue Scale (Example)

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



14.2. The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)

The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)©2011

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Please circle the response that best applies to you for each question

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.						
1. Every time	2. Most times	3. Several Times	4. Some times	5. Occasionally	6. Rarely	7. Never
2. In the last 2 weeks, because of my lung condition, my chest has felt tight.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
3. In the last 2 weeks have you worried about the seriousness of your lung complaint?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
4. In the last 2 weeks have you avoided doing things that make you breathless?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
5. In the last 2 weeks have you felt in control of your lung condition?						
1. None of the time	2. Hardly any of the time	3. A little of the time	4. Some of the time	5. A good bit of the time	6. Most of the time	7. All of the time
6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
8. In the last 2 weeks, my lung condition has made me feel anxious.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
10. In the last 2 weeks, how much of the time have you felt your lung disease is getting worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
12. In the last 2 weeks have you expected your lung complaint to get worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
14. In the last 2 weeks, has your lung condition made you think more about the end of your life?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
15. Are you financially worse off because of your lung condition?						
1. A significant amount	2. A large amount	3. A considerable amount	4.A reasonable amount	5. A small amount	6. Hardly at all	7. Not at all

14.3. 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.