Avalyn Pharma, Inc. Protocol v2.1
AP01-002 12 OCT 2020

CLINICAL STUDY PROTOCOL

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

Protocol Number:	AP01-002
Version:	Version 2.1 (12 OCT 2020)
Investigational Drug:	Pirfenidone Solution for Inhalation (AP01)

INVESTIGATOR'S SIGNATURE

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The Investigator will conduct this study as detailed herein, in compliance with current Good Clinical Practice (GCP) and the applicable regulatory requirements and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the Investigational Product relating to nonclinical and prior clinical experience, which was furnished by Avalyn Pharma, will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. The Investigator will discuss this material with them to assure that they are fully informed regarding the investigational product(s) and the conduct of the study.

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_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

Except where the Principal Investigator's signature is specifically required, it is understood that the term 'Investigator' as used in this Protocol and on the CRFs refers to the Principal Investigator or an appropriately qualified member of the staff that the Principal Investigator designates to perform specified duties of the Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

Avalyn Pharma, Inc.
AP01-002

Protocol v2.1
12 OCT 2020

SPONSOR'S SIGNATURE

Approved by:

Bruce Montgomery, MD (Print Name)

Chief Executive Officer

Signature

12 Oct 2020

Date

West A, *et al. Thorax* 2023;0:1–8. doi: 10.1136/thorax-2022-219391

SYNOPSIS

Protocol Title

A Randomized Open-Label, Phase 1b Study of the Safety of Pirfenidone Solution for Inhalation (AP01) in Patients with Idiopathic Pulmonary Fibrosis (ATLAS Study)

Protocol Number

AP01-002

Clinical Phase

Phase 1b

Product Sponsor

Avalyn Pharma, Inc.

Indication

Idiopathic Pulmonary Fibrosis (IPF)

Investigational Drug

Pirfenidone Solution for Inhalation (AP01)

Control

None (Open-label)

Objectives

To evaluate the safety and tolerability of AP01 given once or twice daily to patients with IPF.

To estimate the treatment effect of AP01 given 50 milligrams (mg) once daily and 100 mg twice daily on the absolute change in percent of predicted forced vital capacity (% FVC) in patients with IPF.

Safety Outcome Measures

- 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

Efficacy Outcome Measures

- Change from Baseline in % FVC
- Change from Baseline in diffusing capacity of the lungs for carbon monoxide (D_{LCO})
- Change from Baseline in Patient Reported Outcomes (PROs) scores
- Change from Baseline in cough frequency and intensity
- Change from Baseline in the extent of fibrosis and lung volumes as measured by High Resolution Computed Tomography (HRCT)

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)

Investigational Products

Investigational Drug Dosage

50 mg AP01, 100 mg AP01

Number of Patients

Approximately 100 patients will be treated; 50 each with 50 mg once daily or 100 mg twice daily

Study Duration

This study has two parts. In Part A, each patient will be screened and those enrolled will then receive 24 weeks treatment with AP01. Patients that complete Part A and in the opinion of the investigator are compliant with study procedures will be allowed to continue to Part B of the study for 48 weeks additional treatment.

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 Part B will return for a Follow-up visit 28 days after their End of Study visit (EOS/Visit 12) unless the patient has consented to enroll in the Rollover study, AP01-005.

The end of study for patients that plan to participate in the Rollover study (AP01-005) will be their last treatment visit (EOS/Visit 12) or an safety monitoring visit after Visit 12. The end of the study for patients not enrolling in AP01-005 will be the day of their last Follow-up or Early Termination visit.

Study Population

- Male and female patients at least 40 years of age

- 40% ≤ FVC ≤ 90% predicted; The first 20 patients randomized must have FVC ≥ 50% predicted. 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.
- FEV_1/FVC ratio ≥ 70%
- Not eligible for oral pirfenidone and nintedanib due to national formulary restrictions OR intolerant to or unwilling to start oral pirfenidone and nintedanib, if previously offered (Nintedanib use is allowed in Part B of the study)
- Confident diagnosis of IPF based on clinical, radiologic and pathologic data without evidence or suspicion of an alternative diagnosis that may contribute to their interstitial lung disease
- 30 ≤ % D_{LCO} ≤ 90%

Study Overview/Design

This is a randomized, open-label study of Pirfenidone Solution for Inhalation (AP01) 50 mg once daily or 100 mg twice daily. This study has 2 parts.

Part A (24 weeks): Patients will be randomized in a 1:1 ratio to one of two treatment arms: 50 mg once daily or 100 mg twice daily. On Day 1, the initial dose of the drug will be administered in the clinic to confirm airway tolerance. If in 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. The remainder of the doses will be administered by the patient outside of the clinic. Patients will have a telephone assessment at Week 1 and an in-clinic assessment at Weeks 4, 8, 12, 16, 20, and 24. Patients who do not continue to Part B or who are withdrawn from the study prior to completion should return for an Early Termination visit. Week 4 safety data from the first 20 patients will be reviewed by a Data and Safety Monitoring Board (DSMB), who may suggest changes to design or stopping of the study based on safety concerns.

Part B (48 weeks): Patients who, in the opinion of the investigator, are compliant with study treatment dosing and study procedures will be permitted to enter Part B. All patients continuing to Part B prior to the implementation of this amendment will continue to receive the treatment regimen (50 mg once daily or 100 mg twice daily) to which they were randomized in Part A. 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.

The DSMB for this study met on 12 OCT 2020 to review preliminary dose comparison data. It was determined that the 100 mg twice daily dose showed a trend for amelioration of FVC loss and recommended all patients in Part B be treated with the 100 mg twice daily dose. Therefore, all patients who participate in Part B after the implementation of this amendment will be treated with the 100 mg twice daily dose. Any patients already participating in Part B on the 50 mg once daily dose will be converted to the 100 mg twice daily dose regimen. Patients will have monthly telephone assessments and quarterly in-clinic assessments. All patients that complete the study visits through Part B will have the option to continue receiving AP01 by enrolling or planning to enroll in the AP01-005 study or to stop dosing after the EOS/Visit 12 and return for a Follow-up visit, 28 days after their End of Study visit.

Statistics

Power and Sample Size

This is an open-label study; no formal hypothesis testing is planned. 50 patients per arm will be adequate to assess the safety and tolerability of AP01 given once or twice daily, as well as provide estimation of changes in response endpoints over time.

Primary Analysis

Safety and tolerability will be assessed by treatment emergent AE rates, post-first dose spirometry, deaths, clinically significant laboratory findings and vital signs.

Secondary Analyses

Change from baseline in FVC % predicted, $D_{LCO,}$ PRO domain scores, cough frequency, extent of fibrosis and lung volumes over 24 and 72 weeks will be analyzed by treatment arm.

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LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

6MWT	6-Minute Walk Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ADL	Activities of Daily Living
AP01	Pirfenidone Solution for Inhalation
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Concentration-Time Curve
$AUC_{(0-x)}$	Area Under the Concentration-Time Curve from Time 0 to *x* Hours Post Dose
BAL	Bronchoalveolar Lavage
BFS	Blow-Fill-Seal
C_{max}	Maximum Concentration
CE	Conformité Européene
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular
CYP	Cytochome P450 Family
CYP1A2	Cytochome P450 Family Subfamily A Member 2
DSMB	Data and Safety Monitoring Board
D_{LCO}	Diffusion Capacity for Carbon Monoxide
EC	Ethics Committee
EC_{50}	Half Maximal Effective Concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eFlow	eFlow® Nebulizer System
ELF	Epithelial Lining Fluid
EOS	End of Study
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FOCBP	Female of Child-Bearing Potential
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSD	Geometric Standard Deviation
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
KBILD	The King's Brief Interstitial Lung Disease
Kg	Kilogram
L	Liters

LCM	Leicester Cough Monitor
LCQ	Leicester Cough Questionnaire
LDPE	Low Density Polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
µg	Micrograms
µg/mL	Micrograms per Milliliter
µg·h/mL	Micrograms per Hour per Milliliter
µm	Micrometer
mg	Milligram
mg/d	Milligrams per Day
mg/mL	Milligrams per Milliliter
mL	Milliliter
mM	Millimolar
MMAD	Mass Median Aerodynamic Diameter
NaCl	Sodium Chloride
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NOAEL	No Observed Adverse Effect Level
PE	Physical Exam
PP	Per-Protocol
PRO	Patient Reported Outcome
q.s.	quantum sufficit ("as much as is sufficient")
QSR	Quality Systems Regulations
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SaO_2	Saturated Oxygen
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
$T_{(0)}$	Time Zero
$T_{1/2}$	Half-life (lives)
UIP	Usual Interstitial Pneumonia
VAS	Visual Analogue Scale
VC	Vital Capacity
VS	Versus

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1. INTRODUCTION

1.1 Idiopathic Pulmonary Fibrosis (IPF) and Pirfenidone

Idiopathic pulmonary fibrosis is a fatal lung disease caused by both genetic and environmental factors resulting in progressive lung scarring and death due to respiratory failure and/or co-morbidities. Characterized by a dry cough, shortness of breath and decreased exercise capacity, this disease exhibits a post-diagnosis survival period of approximately 2-5 years and affects up to 200,000 Americans and 135,000 Europeans [1]. The true prevalence of IPF in Australia is unknown, however there are nearly 700 patients in the Australian IPF Registry[2].

Oral pirfenidone is marketed in the United States, Europe, Australia and Canada (Roche/Genentech Esbriet®) and Japan (Shionogi Pirespa®). Although Esbriet® has proven to slow IPF disease progression, it is a low potency drug that requires a very large oral dose to achieve efficacious lung levels. While the Esbriet® dose has been established near the upper safety threshold (3 X 267 milligram (mg) capsules/dose or 801 mg three times daily; 2403 mg/day (mg/d)), the distribution of drug is uniform resulting in lung levels that are below that required for optimal effect and systemic levels that are often poorly tolerated. Moreover, because oral-delivered blood levels exist at the upper-safety threshold, oral-dose escalation for additional efficacy is not practical. Complicating matters, dose-absorbing food, first-pass metabolism, and safety-driven dose-reduction and stoppage protocols further reduce pirfenidone lung dose and interrupt required maintenance therapy.[3-5]

Aerosol administration of multiple classes of drugs, including bronchodilators, corticosteroids, and antibiotics have been proven to improve both efficacy and safety by increasing delivery to lung tissue and decreasing systemic exposure[6]. Oral pirfenidone has been shown to provide amelioration of forced vital capacity (FVC) decline, as well as a positive impact on mortality in IPF patients, the latter by meta-analysis of Phase 3 studies.[3][7] However, systemic side effects and likely under-treatment of the alveoli suggest that an aerosolized formulation of pirfenidone has the potential to provide improved tolerability and efficacy profiles.

1.2 Summary of Nonclinical and Clinical Data

1.2.1 Nonclinical Summary

The systemic toxicities and target organs associated with the approved pirfenidone dosage forms have been well established. Nonclinical data revealed no special hazard for patients with IPF based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. These studies are detailed in the Investigator's Brochure (IB).

The nonclinical studies conducted for the eFlow® Nebulizer System (eFlow) evaluated and identified potential localized pulmonary and systemic toxicities associated with the inhalation delivery.

To date, five Good Laboratory Practices (GLP) repeat dose inhalation toxicology studies have been conducted in rats and dogs using pirfenidone solution for inhalation. These inhalation studies included toxicokinetic determinations at the beginning and end of each study. In addition, a GLP cardiovascular safety pharmacology study was conducted in telemetered Beagle dogs and a respiratory safety pharmacology study was performed in association with the 28-day repeat dose inhalation toxicology study in rats. The studies completed to date are listed in Table 1. A 6-month repeat dose inhalation toxicology study in rats with a 3-month interim sacrifice showed no drug-related histological findings at any dose level at either the 3-month interim sacrifice or the 6-month terminal sacrifice.

Table 1: Completed GLP Nonclinical Inhalation Studies in support of Pirfenidone Solution for Inhalation (AP01)

Study Number	Study Title
CRL 7300392 GP-TX-001	Pirfenidone: A Maximum Tolerated Dose and 7-Day Repeat Dose Toxicity Study with Nebulized Aerosol Formulation in Rats
CRL 7300394 GP-TX-004	A 28 Day Study of Pirfenidone by Inhalation with a Nebulized Aerosol Formulation in Rats with a 28 Day Recovery Period
CRL 7300393 GP-TX-002	Pirfenidone: A Maximum Tolerated Dose and 7-Day Repeat Dose Toxicity Study with Nebulized Aerosol Formulation in Dogs
CRL 7300395 GP-TX-003	A 28 Day Study of Pirfenidone by Inhalation with a Nebulized Aerosol Formulation in Dogs with a 28 Day Recovery Period
CRL 6900865 GP-SP-001	A Pharmacological Assessment of the Effects of Pirfenidone on the Cardiovascular System of the Beagle Dog Using Telemetry
CRL 7300652 GP-TX-005	A 26 Week (with 13-Week Interim) Study of Pirfenidone by Inhalation with a Nebulized Aerosol Formulation in Rats with a 28 Day Recovery Period

The maximum tolerated dose level for each species tested was determined to be the maximum deliverable dose level using a clinically relevant formulation and the maximum duration of exposure allowed by the Contract Research Organization (CRO). Each study had 5 dose groups, including vehicle and air only control treatment groups and 3 pirfenidone treatment groups. In the 7-day rat study, the average achieved pulmonary dose for combined sexes over the 7-day treatment period were 2.78, 6.85 and 10.7 mg/kilogram (kg)/day. No pirfenidone treatment-related adverse effects were observed for any measured parameter. The No Observed Adverse Effect Level (NOAEL) was considered 10.7 mg/kg/day.

Administration of pirfenidone by inhalation for 28 days was well tolerated in rats. The average achieved pulmonary dose for combined sexes over the 28-day exposure period was 1.91, 3.94 and 6.05 mg/kg/day for the low, mid and high dose groups respectively. The determined mass median aerodynamic diameter (MMAD) ± geometric standard deviation (GSD) for pirfenidone ranged from 4.2 micrometers (μm) ± 1.6 to 4.4 μm ± 1.6. All animals survived until scheduled termination. There were no clinical signs or effects on body weights observed. Ocular and respiratory functions as well as blood parameters were unaffected by treatment. Minimal to mild, reversible, centrilobular hepatocellular hypertrophy was observed in males and females administered ≥ 3.94 mg/kg/day with associated increased liver weights in males at all dose levels and females at ≥ 3.94 mg/kg/day. No adverse effects were observed in a subset of rats from the high dose group allowed a 28-day treatment free recovery period. Based on the low severity and reversibility of the centrilobular hypertrophy observed in the liver, 6.05 mg/kg/day was considered the NOAEL, correlating to an average maximum concentration (C_{max}) values in males of 5.56 micrograms per milliliter (μg/mL) and in females of 6.89 μg/mL, and an average Area Under the Concentration-Time Curve (AUC) values in males of 21.0 micrograms per hour per milliliter (μg·h/mL) and in females of 26.5 μg·h/mL.

Results from the 7-Day dog study indicate that at the high pulmonary dose of 6.73 mg/kg/day in male and female Beagle dogs there were no adverse effects observed in clinical observations, food consumption, clinical pathology, necropsy, organ weights or histopathology that were considered related to treatment with pirfenidone.

Administration of pirfenidone by inhalation for 28 days was well tolerated in dogs. The average achieved pulmonary dose for combined sexes over the 28-day exposure period was 2.40, 4.90 and 10.2 mg/kg/day for the low, mid and high dose groups respectively. The determined MMAD ± GSD for pirfenidone ranged from 1.8 micrometers (μm) ± 1.6 to 1.9 μm ± 1.6. All animals survived until scheduled termination. There were no pirfenidone related changes in clinical signs, body weight, food consumption, ophthalmology, electrocardiogram (ECG), clinical pathology, necropsy, organ weights or histopathology following the 28-day treatment period. The NOAEL was considered 10.2 mg/kg/day. The average C_{max} and AUC values at day 28 were 10.3 (male) and 7.3 μg/mL (females) and 27.7 (males) and 19.3 μg·h/mL (females), respectively.

A Cardiovascular Safety Pharmacology Study was performed in telemetered Beagle dogs. Air and vehicle control and three pirfenidone dose levels were administered in an ascending manner to a group of 4 telemetered dogs with a minimum washout period of 4 days between each treatment. The highest achieved pulmonary dose given was 7.07 mg/kg. Measured cardiovascular parameters included mean arterial, systolic and diastolic blood pressure, pulse pressure, heart rate, body temperature, electrocardiographic waveform analysis including PR, QRS, QT and QT_c duration and intervals. No treatment-related abnormalities were observed in any measured parameter.

A Respiratory Safety Pharmacology study was conducted in association with the 28-day repeat inhalation dose study in rats. Baseline respiratory function measurements were conducted prior to treatment initiation, then in 5 animals/sex/group on Day 3 or 4 of treatment. Using plethysmography, respiratory parameters were measured including tidal volume, respiratory rate and derived minute volume. No treatment-related adverse effects were observed in any of the measured or derived parameters at the high dose level.

The average C_{max} and AUC values for the 28-day inhalation studies and for the anticipated clinical dose for the Phase 1b study (AP01-002) are listed in Table 2. Results from the nonclinical studies indicate that a margin of safety should range from 3.2 to 6.8 depending upon the comparison of exposure made. For comparison purposes, the C_{max} and AUC values for the approve oral dose is provided. The approved oral dose is 801 mg administered three times daily. Comparison between human routes of exposure indicates that the systemic exposure for inhalation is 4.6 (C_{max}) to 14.8 (AUC) fold lower than the oral dose.

Table 2: Safety Margins based on System Exposure (C_{max}, AUC) Comparisons to the Phase 1 Clinical Study (AP01-001)

Species	Achieved Pulmonary Dose (mg/kg/day)	C_{max} (µg/mL)	AUC (µg·h/mL)
Rat	6.05	5.56 to 6.89	21.0 to 26.5
Beagle dog	10.2	7.3 to 10.3	19.3 to 27.2
Human	100 mg*	1.7**	4.0
Human oral dose	801 mg	7.9	59.3
Margin of Safety	Not applicable	3.2 to 6.1	4.8 to 6.8

*The human dose is the total dose delivered (100 mg) but does not represent the expected pulmonary dose. The anticipated pulmonary exposure in humans is 40% of the total dose or 40 mg.**Data based on the average C_{max} of 6 patients from the Phase 1 study (AP01-001) back extrapolated to time zero ($T_{(0)}$) or immediate post dosing.

Based on the liver weight and liver histology findings in the rat, a 6-month repeat dose inhalation study with toxicokinetics in rats was performed. The treatment groups included an air only and vehicle control groups and 3 pirfenidone treatment groups at target pulmonary dose levels of 1, 2 and 4 mg/kg/day. The purpose of this study was to evaluate and chronic effects upon the respiratory system, as well as potential systemic effects following inhalation of pirfenidone solution. This study fulfilled the requirements of a single species chronic study, as indicated in the Food and Drug Administration guidance, "Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route", Guidance for Industry and Review Staff, (October 2015) Pharmacology/Toxicology. This study included a 90-day interim sacrifice. Plasma samples were taken on Day 1, at the 90-day time interval and at termination of the 6-month treatment period for toxicokinetics. In addition, a 28-day treatment-free recovery period for a subset of rats was included at the 90-day interval, as well as the end of the in-life phase of the 6-month study to evaluate any potential reversibility of adverse effects. The average achieved pulmonary dose levels for combined sexes determined over the 26-week treatment period was 1.09, 2.01 and 3.70 mg/kg/day for the low, mid and high dose levels of pirfenidone. No pirfenidone related adverse effects were observed in clinical observations, body weights, organ weights or ratios, clinical pathology investigations or histopathology at any dose level tested. Adverse effects observed included squamous metaplasia of the larynx in all treatment groups including controls that was reversible upon a 28 day treatment-free recovery period. These findings are commonly found in rat studies due in part to the oropharyngeal-laryngeal anatomy of this species. It is considered an adaptive response to a local irritant and has no human correlate[8],[9]. The NOAEL was considered the high dose level of 3.70 mg/kg/day corresponding to a sex averaged C_{max} of 2.975 µg/mL and an $AUC_{(0-t)}$ of 15.9 µg·h/mL as determined from plasma samples taken on Day 182.

In conclusion, the inhalation studies conducted to date demonstrate minimal, reversible adverse effects in the rat only and generally provide a better safety profile than similar studies conducted in support of the oral indication. The high dose levels in the inhalation studies were close to the maximum deliverable dose allowed by the CRO for reasons of animal welfare. While the systemic exposure of pirfenidone in rats and dogs provided a somewhat narrow safety margin compared to human inhalation exposure, the overall exposure for patients using this route of administration is significantly less that the oral indication.

1.2.2 Clinical Summary

Oral Pirfenidone

As of 2017, more than 3500 IPF patients have received oral pirfenidone in clinical studies and named patient programs at doses ranging from 801 mg/d to 4805 mg/d. The following clinical studies defined the safety profile, limits for gastrointestinal tolerability and dose-responsive human efficacy.[3, 5, 10-12]

- InterMune-sponsored PIPF-005 Phase 1 study (single- and multi-dose 801 to 4005 mg/d) – Demonstrated both pirfenidone and its primary metabolite, 5-carboxy-pirfenidone (inactive), have rapid elimination half-lives ($T_{1/2}$) of ~2.4 and ~2.0 hours, respectively. Single-dose plasma pharmacokinetic characteristics following an 801 mg dose in fed normal patients were C_{max} = 7.9 µg/mL and $AUC_{Time\ 0\text{-}infinity\ (0\text{-}\infty)}$ = 59.3 µg·h/mL. Significant multi-dose plasma accumulation was not observed. Initial dose-escalation over two weeks and food were necessary to reach a tolerated maintenance dose (up to 801 mg three times a day).

- InterMune-sponsored PIPF-010 Phase 1 study (drug-drug interaction study) – Demonstrated that pirfenidone clearance is reduced with co-administration of fluvoxamine, which inhibits Cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2) and several other Cytochrome P450 (CYP) isoforms. Further, pirfenidone clearance was significantly higher in cigarette smokers than non-smokers, presumably due to higher CYP1A2 enzyme activity in smokers. The human lung contains very low levels of CYP1A2.

- Shionogi-sponsored SP3 Phase 3 study – Data at 52 weeks demonstrated a significant benefit of oral pirfenidone compared with placebo where a reduced change in vital capacity (VC) from baseline was observed (-90 milliliters (mL) versus (vs.) -160 mL; a 44% relative difference; p = 0.042). As a secondary outcome, this study showed pirfenidone reduced disease progression by 55% relative to placebo (hazard ratio 0.45; 95% Confidence Interval (CI) 0.11-0.79; p = 0.028).

- InterMune-sponsored PIPF-004 (CAPACITY 2) Phase 3 study (2403 and 1197 mg/d vs. placebo) – Data at 72 weeks demonstrated a significant benefit of oral pirfenidone compared with placebo where a marked reduction in decline of percent predicted FVC from baseline was observed (2403 mg/d: mean decline from baseline of -8.0% vs. -12.4% for placebo, a 35% relative difference; p = 0.001). This study also demonstrated a dose response with 1197 mg/d showing a mean decline from baseline of -10% vs. -12.4% for placebo, a 19.4% relative difference (p-value not reported).

- InterMune-sponsored PIPF-006 (CAPACITY 1) Phase 3 study (2403 mg/d vs. placebo) – Data at 48 weeks demonstrated a significant benefit of oral pirfenidone compared with placebo where a marked reduction in decline of percent predicted FVC from baseline was observed (2403 mg/d: mean decline from baseline of -5.0% vs. -6.9% for placebo, a 27% relative difference; p = 0.005). However, at 72 weeks this effect was insignificant (p = 0.501). At 72 weeks, this study did not show that pirfenidone significantly reduced disease progression (hazard ratio 0.84; 95% CI 0.58-0.1.22; p = 0.355). Pirfenidone did show a significant reduced mean decline from baseline in 6MWT compared to placebo (-45.1 vs. -76.9 m; relative difference 41%; p < 0.001).

- Pooled analysis of InterMune-sponsored CAPACITY 2 and CAPACITY 1 (2403 mg/d vs. placebo) – At 72 weeks, categorical change in FVC ≥ 10%, progression-free survival and mean change in 6MWT were significant (p = 0.003, 0.025 and 0.0009, respectively).

- Meta-analysis of InterMune CAPACITY 2, CAPACITY 1, and Shionogi SP3 (high dose only) – Demonstrated a reduced disease progression with a hazard ratio of 0.70; 95% CI 0.56-0.88; p = 0.002 and clearly excluded no-effect from serial lung capacity treatment measurements.

- Adverse events (AEs) of InterMune CAPACITY 2 and CAPACITY 1 – The most commonly reported (≥ 10%) and important AEs during clinical study experience at a dose of 2403 mg/d compared to placebo, respectively, were nausea (32.8% vs. 13.3%), rash (28.7% vs. 8.6%), fatigue (22.3% vs. 13.3%), diarrhea (21.7% vs. 13.5%), dyspepsia (16.8% vs. 5.5%), photosensitivity reaction (12.2% vs. 1.7%) and elevated liver enzymes (>3X upper limit of normal aspartate aminotransferase/alanine aminotransferase (AST/ALT): 4.1% vs. 0.6%). Serious adverse events (SAEs) were recorded at similar frequencies between active and placebo groups. In the InterMune open-label Phase 3 extension AE and SAE observations out to 3 years treatment were similar in event and frequency.

- InterMune-sponsored ASCEND (2403 mg/d vs. placebo) – At 52 weeks, categorical change in FVC ≥ 10%, progression-free survival and categorical change in 6MWT were significant (p = 0.000001, 0.0001 and 0.036, respectively).

The recommended daily dose of Esbriet® for patients with IPF is three 267 mg capsules three times a day with food for a total of 2403 mg/d. Doses above 2403 mg/d are not recommended for any patient. Upon initiating treatment, it is recommended that the dose be titrated over a 14-day period.

During the InterMune CAPACITY studies[10], 48% of patients were dose-reduced or intermittently stopped due to AEs. Dose reductions were permitted to 50% before discontinuation. 6.2% more patients in the 2403 mg/d pirfenidone group discontinued treatment due to an AE than those on placebo (14.8% vs. 8.6%, respectively).

Inhaled Pirfenidone

Avalyn Pharma has sponsored a study (AP01-001) to investigate the safety/tolerability and pharmacokinetics of a single administration pirfenidone solution for inhalation (AP01) delivered by a high efficiency vibrating plate nebulizer in volunteers and patients with IPF. Forty-four adults in 6 cohorts were consented to receive single doses of AP01 to assess tolerability, effect on lung function, and pharmacokinetics. Cohorts 1, 2, and 3 (normal healthy volunteers) (n = 2 placebo; n = 6 active in each cohort) breathed a single ascending dose, of 25, 50, and 100 mg dose of AP01. Cohort 4 (normal healthy volunteers (n = 6 active, no placebo) were administered 100 mg of AP01 and underwent bronchoalveolar lavage (BAL) to measure epithelial lining pirfenidone concentrations. Cohort 5 (prior or current smokers) (n = 2 placebo; n = 6 active), and Cohort 6 (IPF patients) (n = 6 active, no placebo), were administered 100 mg of AP01. All treatments were administered with an eFlow; PARI Pharma GMBH, Starnberg, Germany. Serial measures of urine and plasma pirfenidone were collected during the 24-hour post administration in all subjects. The same formulation of AP01 used in the AP01-001 study will be used in this study (AP01-002). See Table 8 for drug product composition.

Table 3: AP01-001 Adverse Events

	Cohort 1 NHV	Cohort 2 NHV	Cohort 3 NHV	Cohort 4 BAL in NHV	Cohort 5 Smokers	Cohort 6 IPF
Status	Completed	Completed	Completed	Completed	Completed	Completed
Active Placebo	6 2	6 2	6 2	6 0	6 2	6 0
Dose	25 mg 2 mL	50 mg 4 mL	100 mg 8 mL	100 mg 8 mL	100 mg 8 mL	100 mg 8 mL
Treatment Time Range	3 – 4 min	4 – 8 min	11 – 15 min	12– 15 min	9 – 14 min	11 - 15 min
Subject with AEs	4	3	4	2	3	5
<u>Possibly/Probably Related</u>						
Cough	1 mild	1 mild	3 mild	1 mild	1 mild	1 mild
↑ upper airway secretion	2 mild	0	0	0	0	0
Dizziness	0	1 mild	0	0	0	1 mild
Headache	0	1 mild	0	0	0	1 moderate
Dysphonia	0	0	0	0	0	1 mild
<u>Not/Unlikely Related</u>						
Nasal Congestion	0	0	1 mild*	0	0	0
Anxiety	1 mild	0	0	0	0	0
Headache	1 moderate	0	0	1 moderate	2 mild 1 moderate	0
Toothache	0	1 moderate*	0	0	0	0
Nausea	0	0	0	1 mild	0	0
Abdominal distension	0	0	0	0	0	1 mild
Oropharyngeal pain	0	0	0	0	0	1 mild
Fatigue	0	0	0	0	0	1 mild
Soft tissue injury	0	0	0	0	0	1 moderate

*Placebo patients

Following the 100 mg dose, mean peak concentrations extrapolated back to time zero (T_0) in the six volunteers that underwent BAL in plasma were 1.7 µg/mL, and in epithelial lining fluid (ELF) concentrations, 135.9 µg/mL. To place context on the aerosol pirfenidone pharmacokinetics, the approved dose of oral pirfenidone is 801 mg[4] administered 3 times daily. Following the 801 mg oral dose, the peak plasma mean concentration is 7.9 µg/mL and the $AUC_{0\text{-}18hr}$ is 60.9 µg·hr/mL. Following a 100 mg inhalation, the $AUC_{0\text{-}18hr}$ is 4 µg·hr/mL. Therefore, the 100 mg nebulizer dose leads to on average 1/15th the systemic exposure of the oral dose. (Data on file, Avalyn Pharma.)

The CAPACITY 004 phase 3 study of oral pirfenidone established that 400 mg three times daily compared to 801 mg three times daily had a better AE profile, but had about half the efficacy, as measured by amelioration of the rate of FVC decline[10]. This study demonstrated that AEs were

dose related, not idiosyncratic, suggesting that a much lower systemic dose achieved with the 100 mg AP01 nebulized dose may have a superior safety profile. The dose response seen in the CAPACITY 004 study suggests that higher local concentrations after aerosol administration may also result in improved efficacy.

1.2.3 Known and Potential Risks and Benefits

Pirfenidone has well established animal and human toxicity profiles after oral administration which are dose dependent, including gastrointestinal side effects, photosensitivity, and hepatic dysfunction.

Total systemic absorption anticipated after inhaled administration will be on average 15-fold less than standard 801 mg oral dose, therefore, the known systemic side effects are not expected to present in this study. Liver function tests (AST/ALT) will be monitored throughout the study as an extra precaution, however liver toxicity is not expected due to the low systemic exposure. In the case of an AST or ALT value greater than 5 times the upper limit of normal, an alert will be sent to the site and to the medical monitor informing them of the value and providing further instructions regarding eligibility and assessment for potential adverse events. An AST or ALT value of greater than 5 times the upper limit of normal is exclusionary for enrollment.

In the AP01-001 single ascending dose study, the drug was well tolerated in both normal volunteers and IPF patients. The most commonly reported event was cough, which was noted in 7/38 volunteers and 1/6 IPF patients in the Phase 1 study. Cough was mild, self-limited, and did not prevent the full administration of aerosol dose in any subject. Refer to Table 3 for the full summary of AEs observed in the single aerosol dose AP01-001 Phase 1 study.

Forced expiratory volume in one second (FEV_1) values were obtained 10 minutes post-dosing to detect whether the inhaled dose would lead to bronchospasm. One volunteer had a 17% asymptomatic reduction of FEV_1 after a 100 mg nebulizer dose, with a post dose FEV_1 of 3.9 liters (L). No other subject had a decline greater than 15%.

1.2.4 Rationale for Study Design

Oral pirfenidone has been shown to provide improvements in FVC as well as a positive impact on mortality in IPF patients. However, systemic side effects and likely under-treatment of the airways indicate an inhaled formulation has the potential to provide improved tolerability and efficacy profiles. AP01-001, demonstrated that a single dose up to 100 mg/mL was safe and well-tolerated while achieving greatly improved pirfenidone ELF concentrations and reduced systemic levels. AP01-002 is designed to demonstrate AP01 multiple dose safety and tolerability in IPF patients, as well as provide estimates of the variability and effect of AP01 on important efficacy outcomes. The results of AP01-002 will assist in the design of future studies. The preliminary 6 month results from AP01-002 allowed the DSMB to select the optimal dosing regimen of 100 mg twice daily for future AP01 studies.

2. OBJECTIVES

- To evaluate the safety and tolerability of treatment with AP01 when given either once or twice daily to patients with IPF
- To estimate the treatment effect of AP01 given 50 mg once daily and 100 mg twice daily on absolute change in percent predicted 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 percent 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. STUDY ENDPOINTS

3.1. Safety Outcome Measures

- Treatment-emergent 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

3.2. Efficacy Outcome Measures

- Change from Baseline in FVC % predicted
- Change from Baseline in D_{LCO}
- Change from Baseline in Patient Reported Outcomes (PRO)
- Change from Baseline in cough frequency and intensity
- Change from Baseline in extent of fibrosis and lung volumes

3.3. Exploratory Outcome Measures

- 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. INVESTIGATIONAL PLAN

4.1. Study Design

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 arms: 50 mg day once daily or 100 mg twice daily. The primary objective is to evaluate safety and tolerability of treatment with AP01 by monitoring AEs and post-dose spirometry. This study will also evaluate the effect of AP01 on various efficacy measures as detailed in Section 2.

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

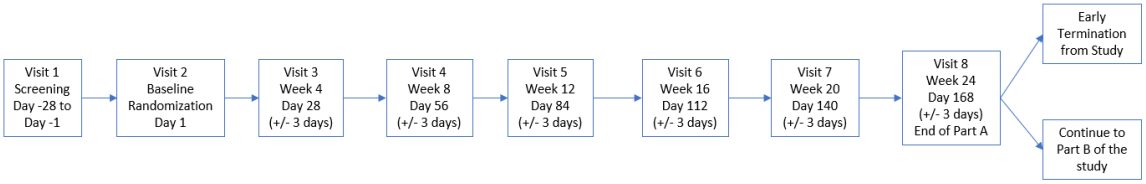
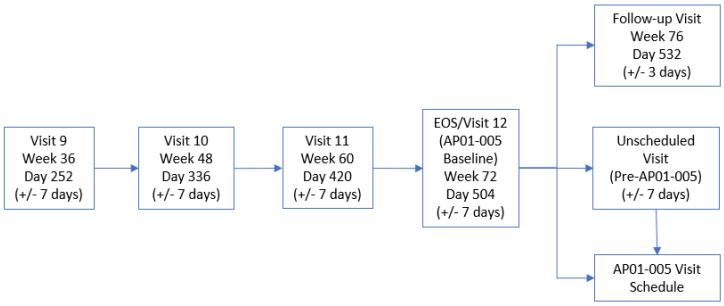


Figure 2: Part B Study Schema

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, $40 \leq$ %FVC ≤ 90, FEV_1/FVC ratio $\geq 70\%$ and $30 \leq \% D_{LCO} \leq 90$ 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 micrograms (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 percent 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 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 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. The DSMB for this study met on 12 OCT 2020 to review preliminary dose comparison data. It was determined that the 100 mg twice daily dose showed a trend for amelioration of FVC loss and recommended all patients in Part B be treated with the 100 mg twice daily dose. Therefore, all patients who participate in Part B after the implementation of this amendment will be treated with the 100 mg twice daily dose. Patients participating in the AP01-005 study will continue treatment that they are receiving at Visit 12 on this study and then transition to the Rollover study upon approval of AP01-005 at their site.

Study duration is up to 80 weeks for patients that complete both Part A and Part B of the study and up to 92 weeks for patients that plan to continue AP01 on the AP01-005 Rollover 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 unless the patient plans to participate in AP01-005. Patients planning to enroll in AP01-005 will continue administering AP01 using EOS/Visit 12 as their Baseline visit for AP01-005. If Regulatory approval for AP01-005 has not been achieved by the time a patient is ready to enroll in AP01-005, the patient will continue treatment that they are receiving at Visit 12 on this study and then transition to the Rollover study upon approval of AP01-005 at their site. Patients will have a visit to assess safety and compliance at least every 3 months while awaiting approval of AP01-005 at their site. The end of the study for all patients will be the day of their last Follow-up or Early Termination visit or their last treatment visit for those enrolling in AP01-005.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible to be randomized in the clinical study:

Population

1. Male and female patients, at least 40 years of age at Screening
2. Not eligible for oral pirfenidone and nintedanib due to national formulary restrictions OR intolerant to or unwilling to start oral pirfenidone and nintedanib, if previously offered

Diagnosis of IPF

3. Clinical symptoms consistent with IPF of ≥ 12 months duration (with or without IPF diagnosis)
4. Diagnosis of IPF, defined as the first instance in which a patient was informed of having IPF, no more than 60 months before randomization.
    - Patients that have had an IPF diagnosis ≥ 1 year, the following criteria must be met:
        - HRCT and/or Surgical Lung Biopsy findings consistent with UIP. If honeycombing is not present on the HRCT, then one or both of the following criteria must be present:
            - Disease progression since diagnosis by HRCT and/or
            - An absolute loss of FVC ≥ 5% percent predicted over the past 12 months
    - Patients that have had IPF diagnosis within the last year, the following criteria must be met:
        - Diagnosis of Usual Interstitial Pneumonia (UIP) or IPF by HRCT (HRCT must be performed within 12 months prior to Screening) and/or Surgical Lung Biopsy as outlined in Table 4:

Table 4: Diagnosis of UIP or IPF by HRCT and Surgical Lung Biopsy

CT pattern as determined by Fleischner Society White Paper[13]	Surgical Lung Biopsy Not Available	Pathology Panel: Definite UIP	Pathology Panel: Probable UIP	Pathology Panel: Possible UIP	Pathology Panel: Inconsistent with UIP or Not Classifiable
Typical UIP Pattern	Eligible	Eligible	Eligible	Eligible	NOT Eligible
Probable UIP Pattern	Eligible	Eligible	Eligible	Eligible	NOT Eligible
Indeterminate or most consistent with non-IPF diagnosis	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible

5. Extent of fibrotic changes (honeycombing, reticular changes) greater than the extent of emphysema on HRCT scan
6. No features supporting an alternative diagnosis on transbronchial biopsy, BAL, or surgical lung biopsy, if performed

IPF Disease Severity and Progression

7. 40% ≤ FVC ≤ 90 % predicted at Screening based on Global Lung Initiative[14] equations. The first 20 patients randomized must have FVC ≥ 50% predicted. After the first 20 patients have 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
8. Change in FVC (measured in liters) between Screening and Day 1 (pre-dose measurement) must be a < 10% relative difference, calculated as:

$$\frac{\text{Screening FVC (L)} - \text{Day 1 FVC (L)}}{\text{Screening FVC (L)}} \times 100\%$$

9. $30 \leq \%\ D_{LCO} \leq 90\%$ at Screening
10. In the investigator's opinion, no evidence of improvement in measure of IPF disease severity over the preceding year
11. $FEV_1/FVC \geq 70\%$

Informed Consent and Protocol Adherence

12. Able to understand and sign a written informed consent form
13. Able to understand the importance of adherence to study treatment and the study protocol and willing to follow all study requirements, including the concomitant medication restrictions, throughout the study

5.2. Patient Exclusion Criteria

The presence of any of the following exclusion criteria excludes a patient from study enrollment:

Disease-Related Exclusions

1. Significant clinical worsening of IPF between Screening and Day 1, in the opinion of the investigator
2. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator
3. History of acute IPF exacerbation requiring hospitalization in the last 3 months
4. History of clinically significant environmental exposure known to cause pulmonary fibrosis, including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds
5. Known explanation for interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus, viral hepatitis, and cancer
6. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis
7. Current diagnosis of asthma or chronic obstructive pulmonary disease
8. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis

Medical Exclusions

9. Females with a positive pregnancy test at Screening or are currently breastfeeding
10. Any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next 6 months. This does not include minor surgical procedures for localized cancer (e.g., basal cell carcinoma)
11. Any condition other than IPF that, in the opinion of the investigator, is likely to result in the death of the patient within the next 6 months
12. History of severe hepatic impairment or end-stage liver disease or ALT or AST greater than 5 times the upper limit of normal at Screening
13. History of end-stage renal disease requiring dialysis
14. Participation in a clinical study with administration of an investigational drug product within the previous 30 days, or five half-lives of the previously administered investigational product

5.3. Study Restrictions

Patients are not to receive pirfenidone or nintedanib within 3 days prior to randomization to the study and during participation in Part A of the study. Nintedanib, but not oral pirfenidone, use is allowed if deemed necessary by the investigator during Part B of the study. In the event of an acute exacerbation, any treatment deemed necessary by the investigator is acceptable until the resolution of the event. 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. Oxygen use is allowed during the study.

5.4. Screening Rules and Rescreening

Patients who do not meet all the inclusion criteria or who meet at least one of the exclusion criteria will be considered screen failures. Patients may be rescreened after failing screening in the event of changes in responses to the eligibility criteria.

5.5. Randomization Criteria

Randomization will occur at Baseline/Study Visit 2. Patients must continue to meet all of the inclusion and none of the exclusion criteria to be randomized.

5.6. Patient Withdrawal Criteria

Patient participation in the study is purely voluntary; patients can withdraw consent at any time for any reason without effect on subsequent care. This is an open-label study in which the investigator is aware of the patient's treatment assignment. The investigator, in consultation with the Medical Monitor, or the Medical Monitor may exercise his or her medical judgment to terminate a patient's participation in the study due to clinically significant changes in any clinical or laboratory parameter. If in the opinion of the investigator, the patient is failing the study drug for lack of efficacy, as evidenced by an excessive decline of FVC, during Part A of the study, the patient can be withdrawn and placed on alternative therapies. During Part B of the study, the investigator may choose to add nintedanib, but not oral pirfenidone, to the patient's treatment regimen.

Any randomized patient desiring to discontinue prior to study completion should be encouraged to discuss his or her reasons and concerns with the investigator. If, after discussion, the patient still chooses to discontinue participation in the study, the patient should be encouraged to attend an Early Termination visit. (Patients that discontinue during the screening process will be considered screen failures.) Patients who are discontinued during a scheduled visit will be encouraged to complete all unique assessments for both that study visit and the End of Treatment visit at the time of discontinuation. If a patient is still participating in Part A and has had a HRCT scan within the past month, the HRCT from the End of Treatment visit will not be performed.

An End of Study case report form (CRF) page will be completed for every patient who receives study medication whether or not the patient completes the study. The reason for any early discontinuation from the study will be indicated on this form. The primary reason for any early termination will be selected from the following standard categories:

- Adverse Event: Clinical or laboratory events occurred that in the medical judgment of the investigator, in consultation with the Medical Monitor and Avalyn Pharma, represents an unacceptable risk to the patient if he/she continues in the study. This includes serious and non-serious AEs regardless of relationship to study medication. The investigator must follow the patient until the AE resolves or satisfactorily stabilizes
- Withdrawal of Consent: The patient desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the investigator. If the patient gives a reason for this desire, this will be recorded on the CRF
- Pregnancy
- Lack of tolerability to drug or device
- Lost to Follow-up: The patient fails to complete the study and site personnel are unable to contact the patient within 30 days post-dose
- Death

5.7. Stopping Rules

This study may be discontinued at any time if, in the opinion of the DSMB, investigator, or Avalyn Pharma, continuation of the study represents a significant medical risk to participating patients. The DSMB will perform a safety data review after 20 patients have completed Week 4 and will make a recommendation at that time as to whether the study should continue or be modified. Avalyn Pharma also reserves the right to terminate the study at any time for any reason.

6. STUDY SCHEDULE AND PROCEDURES

6.1. Study Schedule

The study schedule can be found in Tables 5 and 6. At-home patient assessments are outlined in Table 7. Detailed information on study assessments is provided in Section 7.

6.2. 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.

6.2.1. Visit 1 – Screening (Day -30 to Day -1)

- Informed Consent
- Demography
- Medical history and concomitant medications including past 3 months
- Complete physical exam (PE) and vital signs, including height and weight
- Standard 12-lead ECG
- Saturated Oxygen (SaO_2)
- Spirometry and D_{LCO}
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology)
- Urinalysis
- Urinary pregnancy test for females of childbearing potential (FOCBP) only
- Confirmation of IPF diagnosis as described in Section 5
- Inclusion/Exclusion Review

Leicester Cough Monitor (LCM) training. Patients that pass all of the screening criteria and are deemed eligible for the study will be provided with a LCM between the Screening and Baseline visit to wear for 24 hours. Patients will bring the LCM with them to the site at the Baseline visit. Optionally, patients may return to the clinic one day prior to the Baseline visit to receive their LCM and perform the 24-hour Baseline LCM reading; returning the LCM to the clinic the following day.

6.2.2. Visit 2 - Baseline (Day 1)

The following procedures will be conducted on Day 1 in chronological order:

- Cough Visual Analogue Scale (VAS), King's Brief Interstitial Lung Disease (KBILD) Questionnaire and Leicester Cough Questionnaire (LCQ)
- Concomitant medications since previous visit
- Record any AEs after signing informed consent
- Complete PE and vital signs

- HRCT (If not performed at Screening or Screening HRCT was performed more than 1 month prior to Baseline. For scheduling purposes, the Baseline HRCT may be performed up to 1 month prior to or 1 week after the Baseline visit.)
- Pre-dose Spirometry and D_{LCO}
- Pre-dose SaO_2; Patients with $SaO_2 < 90\%$ will be administered supplemental oxygen until the SaO_2 reaches 93% prior to dosing
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology, Biomarkers (CXCL13**,** CCL18, MMP3, CA19-9 and CA-125)
- Urinalysis
- Urinary pregnancy test (FOCBP only)
- Confirm Inclusion/Exclusion criteria
- Randomization
- Study material training and first study drug administration; patients experiencing excessive cough or bronchospasm will be administered 1 – 2 puffs (90 - 100 µg) of salbutamol prior to subsequent doses or during initial dosing
- Post-dose Spirometry to be performed ≤ 10 minutes after completion of AP01 dose (Patients with a ≥ 15% drop from pre-dose spirometry who are symptomatic will be treated as described in section 8.6.)
- Post-dose SaO_2
- Study material dispensation, including salbutamol and instructions for use of salbutamol (if needed as described in Sections 8.6 and 8.7.)
- Home spirometry training and dispensation

6.2.3. Weekly Home Spirometry

Patients will perform home spirometry weekly during both Part A and Part B of the study. Home spirometry readings will be transferred electronically to the vendor.

6.2.4. Visit 2A

One week after the Baseline visit, the site will conduct a follow-up call to the patient to assess tolerability, study drug compliance, AEs, concomitant medications, status of the LCM return and use of the home spirometer.

6.2.5. Visits 3, 4, 5, 6, and 7 (Day 28, 56, 84, 112, 140 +/- 3 days, respectively)

The following procedures will be conducted at the listed visits in chronological order:

- Cough VAS, KBILD Questionnaire and LCQ
- AEs and concomitant medications since previous visit
- Modified PE (Lungs and Cardiovascular (CV) body systems only)
- Weight (Visit 5 only)

- Vital signs
- SaO_2
- Spirometry and D_{LCO}
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology, Biomarkers (CA19-9 and CA-125 only))
- Urinalysis
- Urinary pregnancy test (FOCBP only)
- LCM dispensation (Visit 5 only)
- Study material dispensation

6.2.6. Visit 8 - End of Part A (Day 168 +/- 3 days)

The following procedures will be conducted at the listed visits in chronological order:

- Cough VAS, KBILD Questionnaire and LCQ
- AEs and concomitant medications since previous visit
- Modified PE (Lungs and CV body systems only)
- Weight
- Vital signs
- SaO_2
- Spirometry and D_{LCO}
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology, Biomarkers (CA19-9 and CA-125 only))
- Urinalysis
- Urinary pregnancy test (FOCBP only)
- HRCT
- LCM dispensation
- End of Treatment form for Part A completion
- Study material dispensation (3-month supply for patients participating in Part B only)

6.2.7. Monthly Calls to Patient

During Part B, the site will conduct a monthly call to the patient between visits to assess tolerability, study drug compliance, AEs, concomitant medications, status of the LCM return (when applicable) and use of the home spirometer.

6.2.8. Visits 9, 10, and 11 – Part B (Day 252, 336, and 420 +/- 7 days, respectively)

The following procedures will be conducted at the listed visits in chronological order:

- Cough VAS, KBILD Questionnaire and LCQ

- AEs and concomitant medications since previous visit
- Modified PE (Lungs and CV body systems only)
- Weight (Visit 10 only)
- Vital signs
- SaO_2
- Spirometry and D_{LCO}
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology, Biomarkers (CA19-9 and CA-125 only))
- Urinalysis
- Urinary pregnancy test (FOCBP only)
- Study material dispensation (3-month supply)

6.2.9. Visit 12 - End of Study (Day 504 +/- 7 days)

The following procedures will be conducted at the listed visits in chronological order:

- Cough VAS, KBILD Questionnaire and LCQ
- AEs and concomitant medications since previous visit
- Modified PE (Lungs and CV body systems only)
- Weight
- Vital signs
- SaO_2
- Spirometry and D_{LCO}
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology, Biomarkers (CA19-9 and CA-125 only))
- Urinalysis
- Urinary pregnancy test (FOCBP only)
- End of Treatment for Part B form completion
- Informed Consent for continued treatment until enrollment in the AP01-005 Rollover study (Patients waiting approval of AP01-005 at their site only.)

6.2.10 Safety Monitoring Visits for Patients Awaiting Site Approval to Enroll in AP01-005 Only (Day 588 +/- 7 days)

- Spirometry
- AST and ALT
- Saturated Oxygen (SaO_2)
- Urinary pregnancy test for females of childbearing potential (FOCBP) only

- Abnormalities on chest and skin exam
- Vitals
- AEs and concomitant medications since previous visit

6.2.11 Follow-up Visit for Patients NOT Enrolling in AP01-005 (28 days +/- 7 days after the Visit 12 - End of Study visit)

Follow-up visits will occur 28 days after the End of Study visit for Part B. The following procedures will be conducted in chronological order:

- Cough VAS, KBILD Questionnaire and LCQ
- AEs and concomitant medications since previous visit
- Modified PE (Lungs and CV body systems only)
- Vital signs
- SaO_2
- Spirometry and D_{LCO}
- Blood samples for laboratory tests (Chemistry including AST and ALT, Hematology, Biomarkers (CA19-9 and CA-125 only))
- Urinalysis
- End of Study form completion

Patients may experience AEs that necessitate an unscheduled visit. There may also be situations in which the investigator asks a patient to report for an unscheduled visit following the report of an AE or a significant decrease in FVC during home spirometry readings. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of patients during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

Table 5: 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 6: Study Schedule for Part B

	Study Phase – Part B					
	Treatment					
Visit	9	10	11	12[9]	Follow-up[10]	Safety Visit[11]
Day	252	336	420	504 End of Study	28 days after End of Study	588
Window (Days)	+/- 7	+/- 7	+/- 7	+/- 7	+/- 7	+/- 7
Cough VAS, KBILD and LCQ	X	X	X	X	X	
Physical Exam[2]	X	X	X	X	X	X
Weight		X		X		
Vital Signs	X	X	X	X	X	X
Laboratory Tests[4]	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	
Urinary Pregnancy Test[5]	X	X	X	X		X
Spirometry and D_{LCO}	X	X	X	X	X	X[12]
Saturated Oxygen	X	X	X	X	X	X
Study Material Dispensation	X	X	X	X[13]		X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
End of Treatment/Study Form				X	X	
Informed Consent to continue AP01 until enrollment in AP01-005[11]				X		

Notes for Tables 5 and 6:

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. For Safety Visits, only chest and skin exam are required.
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.) For Safety Visits, only AST and ALT are required.
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.
9. Patients will be assessed for eligibility to participate in AP01-005 at EOS/Visit 12. Those enrolling in AP01-005 will use EOS/Visit 12 as their AP01-005 Baseline visit.
10. Patients enrolling in AP01-005 will not participate in the Follow-up visit.
11. Patients awaiting site approval of AP01-005 only.

12. For Safety Visits, D_{LCO} not required.
13. Study Material Dispensation only for patients continuing AP01 at Visit 12.

Table 7: 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) during Part A and Part B of the study

7. ASSESSMENTS

7.1. Background Assessments

7.1.1. Demographic/Medical History

Information relating to the patient's sex, age, race, height, and weight will be recorded at Screening on the appropriate eCRF page. Medical history of each patient will be collected at Screening and recorded on the appropriate eCRF page.

7.2. Efficacy Assessments

7.2.1. FVC

Pre and post-dose spirometry will be conducted the day of first dose. The post-dose spirometry reading should be performed ≤ 10 minutes after completion of the AP01 dose. Spirometry will be conducted at approximately the same time each visit (within 60 minutes of Day 1 pre-dose spirometry measurement) with the patient in seated position. The test will be performed to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[15]. On days of clinic visits (including the screening visit), patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. FVC % predicted will be calculated using the ERS Global Lung Function Initiative 2012 equations[14] as outlined in the clinical study manual.

7.2.2. Leicester Cough Monitor[16]

The LCM 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.

7.2.3. 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[17] on D_{LCO} measurements and the prediction formula appropriate for that method[18]. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

7.2.4. Cough Visual Analogue Scale (VAS)[19]

The Cough VAS 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 results of the scale will be measured in millimeters and entered into the appropriate eCRF. Appendix 17.1 presents an example of the Cough VAS.

7.2.5. The King's Brief Interstitial Lung Disease (KBILD) [20]

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 17.2 presents the KBILD Questionnaire.

7.2.6. Leicester Cough Questionnaire (LCQ)[21]

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 17.3 presents the LCQ.

7.3. Additional Endpoint(s) Assessments

7.3.1. Weekly home spirometry measurements

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.

7.3.2. 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 Baseline and the Week 24 visits. These scans will be read and interpreted by a central reader.

7.4. Safety Assessments

All patients who enter the study will be assessed for safety. Safety will be monitored by observation of and direct inquiry regarding AEs at each visit after the first dose of study drug.

7.4.1. Adverse Events

All AEs will be collected from informed consent through the Follow-up visit. Details regarding AE definitions, collection, recording, and reporting are found in Section 10.1.

7.4.2. 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.

Body height will be measured at Screening only. Weight will also be measured at the Screening and Week 24 and 48 visits.

7.4.3. Vital Signs

Blood pressure and pulse will be assessed at each visit. Patients should be comfortably seated for 5 minutes prior to blood pressure readings. Study staff will take care to select the appropriate cuff size for each patient. Respiratory rate and temperature will be measured at each visit.

7.4.4. Concomitant Medications/Therapies

All concomitant medications/therapies collected throughout the study must be recorded on the Concomitant Medications and Therapies eCRF. The prohibited and allowed concomitant medications/therapies for the study are discussed in Section 8.9.1.

7.4.5. Electrocardiography (ECG)

A 12-lead ECG will be recorded at Screening by the investigator or other designated, qualified individual from the study research team. ECGs will be assessed for clinical relevance including rhythm and repolarization.

7.4.6. Laboratory Assessments for Hematology, Serum Chemistry, Biomarkers and Urinalysis

At each visit, clinical laboratory tests will be conducted at the study's central laboratory with the exception of biomarkers, which may be sent to a specialty lab. 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[22, 23]: CXCL13**,** CCL18, MMP3 (progression-related) will be tested at Baseline only. CA19-9 and CA-125 (predictive of alveolar epithelial damage) will be collected at all visits except for the Screening visit.)

7.4.7. Pregnancy Testing

At all visits except the Follow-up visit, a urinary pregnancy test will be performed for all FOCBP.

Contraceptive Requirements

Patients must be willing to comply with the contraceptive requirements of the study.

To prevent pregnancy in a FOCBP, FOCBP patients must agree to use one of the following contraceptive methods during the study and for 30 days after the last dose of IP:

- Abstinence from heterosexual intercourse OR
- Use a highly-effective form of contraception (e.g. hormonal contraception, or

  an intrauterine device) AND

  use of a barrier method by the female or her sexual partner.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7.5. Pharmacokinetic Assessments

This study will have no pharmacokinetic parameters assessed.

8. INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

8.1. Investigational Drug Dose Regimen

Two dose levels/regimen combinations will be tested in this study:

- Pirfenidone 50 mg in 4 mL aqueous solution delivered once daily
- Pirfenidone 100 mg in 8 mL aqueous solution delivered twice daily

8.2. Dose Rationale

In addition to demonstrating safety and tolerability of AP01 multiple dosing in IPF patients, a key goal of the Phase 1b study is to select an optimal dosing regimen for further development of AP01. The initial dosing regimen was selected by formulation considerations, time and frequency of administration and local lung pharmacokinetics. Results from this study will help to elucidate whether therapeutic effect is dependent on peak dose, frequency of administration after a peak dose, or AUC in the lung.

Aqueous solubility limits the stability of the AP01 pirfenidone formulation concentration to 12.5 mg/mL. Time and frequency of administration are also important considerations; improved compliance is expected with fewer dose administrations per day and shorter administration times.

The 801 mg oral pirfenidone plasma pharmacokinetics have been well described. From this, one can estimate drug levels in the ELF and lung tissue from plasma concentrations. Assuming 50% of the drug is tightly protein-bound with the rest freely capable of local diffusion and with a known plasma $T_{1/2}$ (2.4 hours), we may estimate AUC in both the ELF and lung tissue. Following an 801 mg oral dose, a measured plasma C_{max} is 7.9 μg/mL[11], with the estimated ELF and lung tissue C_{max} of 3.9 μg/mL. The $AUC_{0-\infty}$ is 59.3 μg·hr/mL in plasma and estimated as 29.7 μg·hr/mL in ELF and lung tissue.

One can also estimate inhaled pirfenidone ELF pharmacokinetics from a single collected BAL fluid sample from healthy volunteers. Due to the time to administer anesthesia and perform the procedure, BAL collection is typically 30 - 50 minutes post-drug administration, which is several $T_{1/2}$ from the true C_{max} seen at the end of inhaled administration. Therefore, because the ELF clearance $T_{1/2}$ is unknown, one can only estimate the ELF pirfenidone C_{max} and local lung AUC. To strengthen this estimation, a large animal sheep pharmacokinetic study was performed. Sheep were administered inhaled pirfenidone and both serial BAL and plasma samples collected. Analysis of this data provided a pirfenidone plasma/ELF pharmacokinetic relationship curve, which was used to extrapolate the single human ELF data point back to C_{max} and estimate AUC. In normal human volunteers, the 100 mg dose provided an average ELF C_{max} of 135.9 μg/mL and an $AUC_{0\text{-}last}$ of 54.5 μg·hr/mL. With these data, one can also then confirm adequate pirfenidone ELF delivery in the IPF population in the absence of BAL fluid sampling by correlating obtained plasma levels and 24-hour urine collections between normal volunteers and IPF patients.

The 24-hour urine collection in the normal human volunteers BAL cohort compared to the IPF cohort was similar on average but with less variability (40.2 ± 20.5 mg vs. 42.2 ± 14 mg). Since the IPF cohort has less lung surface area but the same absorption, this suggests that the IPF cohort had higher C_{max} ELF levels. The C_{max} plasma levels in the IPF cohort were lower than the volunteer cohorts, but absorption was prolonged, also suggesting the ELF AUCs were similar or superior to the BAL cohort.

There are other preclinical and clinical observations that provide considerations for potential dose regimens. The first is that the inhaled C_{max} with the 100 mg dose exceeds the pirfenidone half maximal inhibitory concentration (~25 µg/mL) from in vitro models and nears the observed half maximal effective concentration (EC_{50}) (~100 µg/mL) in animal models of bleomycin injury[24]. As noted before, the C_{max} in the ELF of the 801 mg oral dose is 3.9 µg/mL and does not approach the required concentrations from in vitro and in vivo models of lung injury. These observations suggest that a higher C_{max} may improve efficacy. Second, as noted above, preclinical models of IPF using bleomycin suggest that efficacy is correlated with C_{max} rather than AUC, this finding would be ideal for an aerosol dose with high ELF concentrations and fast clearance. Although these same animal models suggest that once a day dosing can be effective, the duration of action after a peak dose in IPF patients is not known.

The high dose chosen for the Phase 1b study is 100 mg administered twice daily. The 100 mg dose based on the modeling noted above would provide an average C_{max} in the ELF of 135.9 µg/mL and an $AUC_{0\text{-}18\ hr}$ of 54.5 µg·hr/mL. The C_{max} is approximately 35-fold higher than what is achieved with the oral 801 mg dose, with the total $AUC_{0\text{-}18\ hr}$ 2-fold higher. IPF's pathogenesis is postulated to pivotally depend upon alveolar epithelial cell damage. This dose would provide dramatically higher ELF C_{max} and a daily cumulative AUC with the twice daily aerosol dose 1.5-fold higher compared to a three times daily 801 mg oral dose. The 100 mg aerosol dose requires a 9 - 15 minutes administration time.

The second dose chosen for the Phase 1b study is 50 mg administered once daily. In the Phase 1 dose escalation study, the plasma pharmacokinetics were proportional to the dose. Assuming proportionality, the 50 mg once daily dose would have a C_{max} 17-fold higher than the oral 801 mg dose, and a total 24-hour AUC in the ELF that would be 2/3 of the 801 oral three times daily regimen. The administration time of the 50 mg dose is expected to be 5 - 7 minutes and a shorter regimen would likely lead to more compliance, better patient acceptance and perhaps fewer adverse respiratory effects.

Both of these doses will have substantially less systemic pirfenidone exposure compared to the 801 mg oral dose. Following an 801 mg oral dose, the peak plasma mean concentration is 7.9 µg/mL and the $AUC_{0\text{-}18hr}$ is 60.9 µg·hr/mL.[11] Following a 100 mg inhalation, the peak plasma mean concentration is 1.7 µg/mL and the AUC $_{0\text{-}18hr}$ is 4 µg·hr/mL. Therefore, the 100 mg nebulizer dose leads to less than 1/15, and the 50 mg dose 1/30, the systemic exposure of the oral dose.

No clinical study has examined fewer than three oral pirfenidone doses per day. Since oral pirfenidone is taken at meals, the time between dinner and breakfast is usually twelve hours, suggesting the duration of action is at least that long. Like inhalation, the three times daily oral regimen delivers a short-duration peak with very low trough levels. Testing a 100 mg twice daily regimen would mimic the duration between evening and morning dose and would also increase the AUC in the ELF over a 24-hour period by 1.5-fold compared to the 801 mg three times daily oral dose. If efficacy is driven by C_{max} rather than AUC, the 100 mg twice daily and 50 mg once daily doses would provide a 34-fold and 17-fold higher peak concentration, respectively, than is achieved from an 801 mg oral dose. The 50 mg once daily regimen would provide a 17-fold higher peak concentration than is achieved from an 801 mg oral dose. The 50 mg once daily regimen was chosen to test the hypothesis that only once daily dosing is adequate and efficacy is driven by C_{max} in the ELF. The 100 mg twice daily regimen was chosen to test whether efficacy is also dependent on total ELF AUC or multiple daily peaks.

8.3. Investigational Drug Manufacturing, Packaging and Labeling

Investigational drug used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International

Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), guidelines for Quality System Regulations (QSR), and applicable regulations.

8.3.1. Drug Substance

The manufacturer of cGMP pirfenidone drug substance for this study is Procos S.p.A, Italy.

8.3.2. Drug Product

AP01 is a sterile, aqueous solution formulation consisting of pirfenidone (active ingredient) dissolved in a 5 mM citrate buffer containing sodium chloride (for osmolality and tolerability improvement) and sodium saccharin (to improve taste and tolerability). AP01 is formulated with an osmolality ~380 milliosmoles/kg with a final pH ~6.0. All excipients have good history of use in pharmaceutical products and have been used in United States Food and Drug Administration (US FDA), European and Australian-approved inhalation solutions. AP01 IP has been tested in a Phase 1 study with the composition presented in Table 8. All excipients have good history of use in pharmaceutical products and have been used in US FDA, European and Australian-approved inhalation solutions.

Table 8: Drug Product Composition

Ingredient	Function	Concentration
Pirfenidone	Active pharmaceutical ingredient	12.5 mg/mL
Sodium citrate dihydrate	Buffering agent	4.5 mM
Citric acid monohydrate	Buffering agent	0.5 mM
NaCl	Osmolality adjustment/Tolerability improvement	150 mM
Sodium saccharin dihydrate	Taste/Tolerability improvement	0.75 mM
Sterile Water for Injection	Vehicle	q.s.

8.3.3. Manufacture of Drug Product

AP01 IP is manufactured by Holopack GmbH in Sulzbach-Laufen, Germany. The manufacturing process is comprised of formulation compounding, aseptic filling into low density polyethylene (LDPE) ampoules by the blow-fill-seal (BFS) operation, and secondary packaging filled ampoules in foil laminate overwrap. Release and stability testing is conducted at Pharmaceutical Product Development, Inc., located in Middleton, Wisconsin, United States of America.

8.3.4. Nebulization Device

The nebulizer is a re-usable device intended for single patient use. AP01 will be delivered to the lung by oral inhalation using the PARI (Germany) eFlow® Nebulizer System. The eFlow is a high-efficiency, 510(k)-cleared, Conformité Européene (CE)-marked device that is marketed with other products for other disease indications.

With the AP01 formulation, the eFlow nebulizer (model with large holding chamber and with 35 membrane head) produces an aerosol with a narrow particle size distribution with a mass median diameter of 2.9 – 3.9 μm and a GSD < 1.8, which is well suited to lower airway and alveolar drug deposition.

8.3.5. Packaging and Labeling of AP01 and Nebulizer Kits

AP01 IP Supply

Overwrapped AP01 IP ampoules will be packaged and labelled as required by regional regulation by PPD Development, L.P. in Athlone, Ireland. Each IP carton will contain 18 AP01 overwrapped pouches, each pouch containing two ampoules. Each ampoule will contain 4 mL AP01 12.5 mg/mL formulation, which is a 50 mg dose. The 50 mg once daily inhaled dose cohort will use one IP carton every 4 weeks (1/2 pouch per day; 1 ampoule per once daily dose). The 100 mg twice daily inhaled dose cohort will use four IP cartons every 4 weeks (2 pouches per day; 2 ampoules per twice daily dose). Details of IP distribution will be outlined in the clinical study manual.

Nebulizer Starter Kits and Replacement Handsets

Randomized patients will receive an eFlow nebulizer starter kit with their initial AP01 IP cartons at the Baseline visit. At subsequent visits, patients will receive an eFlow replacement handset to exchange with their used handset every 4 weeks or as needed. Nebulizer starter kits will be packaged separately from IP cartons. Nebulizer starter kits will comprise of a single box with a study-specific label as required by regional regulation. Replacement handsets will be packaged separately from eFlow starter kits and IP cartons. Each eFlow replacement handset will be packaged with a study-specific label as required by regional regulation. Details of device distribution will be outlined in the clinical study manual.

8.4. Investigational Drug and Device Storage

Manufactured IP and nebulizer supplies must be kept in a secure, limited access storage area maintained under room temperature (15° - 25° Celsius).

8.5. Investigational Drug Preparation

The IP is to be kept in the aluminum foil pouch until the point of use.

The patient should be instructed not to use this IP with any other nebulizers, and not to use this eFlow with any other drug products. Details regarding drug preparation will be outlined in the clinical study manual.

8.6. Investigational Drug Administration

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 percent 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.

8.7. Missed Doses and Dose Modifications

Doses that are missed can be taken in a 24-hour period, as long as doses are 4 hours apart.

In the event of excessive coughing while drug administration at home, the patient will contact the site to determine how to proceed. Salbutamol may be prescribed to be administered prior to dosing, as described in section 8.6, if deemed necessary by the investigator.

If AP01 is stopped during treatment due to intolerance, restart dosing when the patient has improved. The initial dose after restarting should be observed for tolerance.

It is recommended to reduce the 100 mg twice daily dose to 50 mg twice daily if the patient cannot tolerate the 100 mg dose. If the 50 mg twice daily dose cannot be tolerated, the patient may have their dose reduced to 50 mg once daily.

8.8. Investigational Drug Accountability, Handling and Disposal

8.8.1. Investigational Drug Handling and Disposal

Administration of the first dose of IP will be observed by the investigator or designee; time of administration and confirmation of full dose being administered will be noted on the eCRFs.

The investigator or designee is responsible for IP and accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, designated research or pharmacy staff at each study site must maintain IP accountability records for study drug throughout the course of the study.

Patients will be instructed to bring back the box(es) of unused ampoules at each study visit for drug accountability purposes. Patients will be instructed to dispose of all used ampoules. Details regarding drug accountability procedures will be captured in the clinical study manual.

8.8.2. Salbutamol Handling and Disposal

Patients requiring salbutamol as described in Sections 8.6 and 8.7 will be provided with salbutamol at the study visits or as needed. Patients will dispose of the salbutamol at the end of the study.

8.8.3. Device Handling, Cleaning and Disposal

The eFlow instructions for use provide detailed instructions for the patient to follow regarding cleaning and maintenance of the handsets for this study.

In the event of a nebulizer (base unit, handset or both) malfunction, the patient will contact the site immediately for a replacement unit. The patient will return the malfunctioning nebulizer to the site. The site will return the malfunctioning nebulizer to the manufacturer (via the clinical packager) for a root cause analysis. Further details regarding the handling of malfunctioning devices will be outline in the clinical study manual.

In accordance with all applicable regulatory requirements, designated research or pharmacy staff at each study site must maintain accountability records for the nebulizer system (base units and handsets) throughout the course of the study. Details regarding device accountability procedures will be captured in the clinical study manual.

8.9. Treatment of Patients

8.9.1. Concomitant Medications and/or Treatments

Patients are prohibited from receiving pirfenidone or nintedanib within 3 days prior to randomization to the study and during participation in Part A of the study. Other than brief periods of medically appropriate treatment for acute IPF exacerbation, patients will not receive any other therapy for the treatment of IPF in Part A of the study. 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. Nintedanib, but not oral pirfenidone, use is allowed if deemed necessary by the investigator during Part B of the study. If AP01 is stopped during treatment of an exacerbation due to a patient's intolerance, it should be restarted when the patient has improved, however the first dose should be observed for tolerance. Oxygen use is allowed during the study.

Due to the low systemic levels expected with delivery by inhalation, drug-drug interactions are unlikely and unexpected.

Patients who are experience excessive coughing during study drug administration will be required to inhale 1 - 2 puffs (90 - 100 µg) of salbutamol within 10 minutes prior to subsequent study drug dosing. Pre-treatment with salbutamol will be documented on the Concomitant Medications eCRF page.

8.9.2. Treatment Compliance

Administration of the first dose of IP will be observed by the investigator or designee; time of administration and confirmation of full dose being administered will be noted in the eCRF. Patients will bring all unused ampoules to each visit for drug accountability and compliance assessment. At the discretion of the investigator, patients that are not in compliance with study dosing and procedures will be discontinued from the study.

9 RANDOMIZATION AND BLINDING PROCEDURES

9.1 Randomization

Patients will be randomized in a 1:1 ratio to receive 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.

9.2 Blinding

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

10 ADVERSE EVENTS

10.1 Adverse and Serious Adverse Events

Adverse Events (AEs) will be recorded after the patient signs informed consent and throughout the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to Avalyn Pharma or its designated representative.

10.1.1 Definitions of AEs

10.1.1.1 Adverse Event

An AE is defined as any untoward or unfavorable medical occurrence associated with the patient's participation in the research, whether or not considered related to the patient's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the patient is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

AEs are defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which do not necessarily have to have a causal relationship with this treatment.

Clinical Abnormalities

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant, and thus constitutes an AE.

10.1.1.2 Serious Adverse Event

An AE is considered "serious" if, in the view of either the investigator or Avalyn Pharma, it results in any of the following outcomes (21 Code of Federal Regulations (nacl) 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to Avalyn Pharma whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the investigator or Avalyn Pharma, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of IP dependency or abuse.
- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to Avalyn Pharma as described in Section 10.1.5.

AEs reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any hospitalization except observational admissions of less than 24 hours meets these criteria. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard of care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- < 24-hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g. for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

10.1.1.3 Adverse Drug Reaction and Suspected Adverse Reaction

An adverse drug reaction (ADR) means any AE caused by a drug or biologic.

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug or biologic caused the AE. For the purposes of safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug or biologic and the AE. An SAR implies a lesser degree of certainty about causality than an ADR (21 CFR 312.32(a)).

10.1.1.4 Unexpected Adverse Reaction

Avalyn Pharma is responsible for assessing AEs for expectedness. With regards to reporting to the Health Authority, an AE is considered “unexpected” when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the protocol or IB for AP01. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular

drug under investigation (21 CFR 312.32(a)). In addition, clinical events that commonly occur in IPF patients, such as pulmonary exacerbations, may be unexpected in a specific patient, but are likely to occur during the course of the study. These events should be classified as 'expected' rather than 'unexpected' as they are part of the natural history of the disease.

10.1.2 Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 5.0.* This document (referred to herein as the "NCI-CTCAE manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of AEs. Please refer to the NCI-CTCAE manual for the desired event and specific grading for that event.

If the event is not listed in the NCI-CTCAE manual, please refer to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = moderate minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 = life-threatening consequences; urgent intervention indicated.
- Grade 5 = death related to AE.

For additional information and a printable version of the NCI-CTCAE manual, go to
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 10.1.1.2 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/adverse outcome. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a patient is hospitalized should be reported as an SAE.

10.1.3 Relationship to Investigational Drug Treatment

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

Avalyn Pharma's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table 9:

Table 9: Relationship of the AEs to the Study Drug

Relationship	Description
Not Related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study patient's medical record OR, the time of occurrence of AE is not reasonably related to administration of the study medication.
Unlikely Related	The event is unlikely to be related to the investigational study drug and likely to be related to other factors.
Possibly Related	There is an association between the event and the administration of study drug and there is a plausible mechanism for the even to be related to study drug, but there may also be alternative etiology, such as characteristics of the patient' clinical state or underlying disease.
Probably Related	There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related and causes other than the study drug have been ruled out, and/or the event reappeared on re-exposure to the study drug.

The investigator is obligated to assess the relationship between IP and the occurrence of each AE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the administration of IP will be considered and investigated. The investigator will also consult the IB and/or product information in the determination of his/her assessment.

The causal relationship of the AE to the IP, study devices or procedures should be assessed by the investigator (or medically qualified delegate) using the classifications provided in Table 9.

10.1.4 Collecting and Recording AEs

10.1.4.1 Period of Collection

All AEs will be collected from the time of informed consent through the final study visit. All AEs and SAEs should be treated as medically appropriate and followed until event resolution.

10.1.4.2 Methods of Collection

AEs may be collected as follows:

- Observing the patient
- Questioning the patient in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the patient

An abnormal value or result from a clinical evaluation, laboratory value, etc. can also indicate an AE if it is determined by the investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE/SAE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the patient’s safety is not at risk.

10.1.4.3 Recording Method

10.1.4.3.1 AEs

All AEs occurring during this clinical study after informed consent is signed will be recorded by the investigator on the appropriate eCRF in precise medical terms, along with the date of onset and the date of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to study drug, therefore if the AE occurs on the date of first dose, whether it occurred prior to the dose or after the dose will be also be recorded.

The severity of the AE and its relationship to the study drug will be assessed by the investigator. The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the Concomitant Medications and Therapies eCRF as a concomitant medication administered. The action taken and the outcome must also be recorded. The investigator will follow a non-serious AE until resolution, stabilization of the event up to the Follow-up visit. The investigator will follow an SAE (regardless of relationship to study drug until the event resolves, stabilizes, or becomes non-serious. The terms of AE resolution (i.e., recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown) should also be recorded.

10.1.4.3.2 SAEs

SAEs will be recorded both on the AE eCRF and on the SAE form. Health authorities will be notified as outlined in Section 10.1.5.2.

10.1.5 Reporting AEs

10.1.5.1 Reporting SAEs to Avalyn Pharma

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Reporter
- Patient Identifier
- Study product or intervention
- Serious AE term
- Relationship to study medication(s)
- Reason why the event is serious

Supplemental eCRF pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, study drug administration, and death as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE report form should be updated and re-submitted.

For additional information regarding SAE reporting, please refer to the clinical study manual. Safety monitoring will be handled by Syneos Health.

10.1.5.2 Reporting SAEs to Health Authorities

Avalyn Pharma or designee is responsible for reporting SAEs to the health authorities in accordance with the regulations for each country.

After the SAE has been reported by the site investigator and assessed by Avalyn Pharma, there are 2 options to report an event to the appropriate health authorities:

Standard reporting is required. This option applies if the AE is classified as one of the following:

- Serious, SAR per the definitions section (Section 10.1.1)
- Serious and not an SAR per the definitions section (Section 10.1.1)

Expedited reporting is required. This option applies if the AE/safety finding is classified as one of the following:

1. Serious and unexpected suspected adverse reaction (SUSAR) per the definitions section (Section 10.1.1)

    - Avalyn Pharma must report any SAR that is both serious and unexpected. Avalyn Pharma must report AE as an SAR only if there is evidence to suggest a causal relationship between the study product and the AE, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with the product treatment (e.g. relevant associated events, e.g. angioedema, hepatic injury, or Stevens-Johnson Syndrome);
    - One or more occurrences of an event that is not commonly associated with product treatment but is otherwise uncommon in the population exposed to the product (e.g. relevant associated events, e.g. tendon rupture);
    - An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of IP therapy) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group.

2. Any safety findings from other studies: Avalyn Pharma must report any findings from other epidemiological studies, pooled analysis of multiple studies, or clinical or nonclinical studies that suggest a significant risk in humans exposed to the IP that would result in a safety-related change in the protocol, informed consent, IB, or other aspects of the overall conduct of the study.

These events must be reported by Avalyn Pharma to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days.

10.1.5.3 Reporting SAEs to IRBs or ECs

It is the responsibility of the investigators to promptly notify their respective Institutional Review Board(s) (IRBs) or Ethics Committees (ECs) of safety reports or other matters involving risk to patients as mandated by the IRBs/ECs.

10.1.5.4 Reporting SAEs to the Data Safety Monitoring Board

Avalyn Pharma will provide the DSMB with data of all SAEs on an ongoing basis.

10.1.5.5 Reporting Pregnancy

During the study, all patients should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the patient will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information on the Pregnancy form within 24 hours of becoming aware of the event, although pregnancy itself if not considered an AE. The investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 10.1.5. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the investigator suspects is related to the in-utero exposure to the study treatment should also be reported.

11 STATISTICS

11.1 Power and Sample Size Determination

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 arm, we have a 92% chance of detecting an AE with a true population rate of 5%, as displayed in Table 10:

Table 10: 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)[12] 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 arm, a two-sided 95% CI for mean change from baseline in % of predicted FVC will extend 1.25 from the observed mean. The ASCEND[12] study showed a decrease of 1.5 and 3.9 in % of predicted FVC at Week 26 in the pirfenidone and placebo arms, respectively. Table 11 shows results of the ASCEND[12] active and placebo arms 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 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 arms. With this sample size we can be confident on selecting dosing regimen(s) for future trials.

Table 11: Observed and potential change in FVC

	ASCEND[12] Placebo (n = 262)	**ASCEND[12] 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)

11.2 General Considerations

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 individual patient data will be displayed in listings. For comparisons to baseline, data from Visit 2 prior to the first dose of study drug will be used as baseline. Subgroup analyses will be performed based on baseline groupings for FVC, region 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. Data listings will include a variable to denote the regimen switch and flag the time of the switch for affected patients.

Patients will be analyzed according to randomized treatment.

Details of data handling and summaries will be further defined in the Statistical Analysis Plan (SAP).

11.2.1 Significance Levels

No formal hypothesis tests are planned.

11.2.2 Multiple Comparisons

No formal hypothesis tests are planned.

11.2.3 Missing Data

Due to the COVID-19 pandemic, which occurred while the study was actively enrolling, additional strategies are included for handling missing data. Missing values will not be imputed for data displayed in summary tables. For patients with missing data due to death, remaining FVC values will be imputed as a sensitivity analysis using a lower value of FVC than the patient's last observed value. Because home spirometry data collection continues when COVID-19 prevented in-clinic visits, home spirometry FVC will be used to inform missing office spirometry data handling for reasons other than early terminations. Full details of imputation methods will be included in the SAP.

11.2.4 Visit Windows

All data collected during study follow-up will be displayed according to the actual visit in the eCRF. Assessments taken outside of windows described in the protocol will be displayed and analyzed as outlined in the SAP.

11.3 Analysis Populations

The analysis populations are defined as follows:

- The safety population is defined as all randomized patients who receive the study drug.
- The per-protocol (PP) population will include all patients 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. The details of major protocol deviations that exclude patients from the PP population will be defined in the SAP.

Safety analyses will be performed on the safety population.

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

11.4 Background and Demographic Characteristics

Demographic and baseline characteristics will be summarized by treatment arm and overall.

11.5 Efficacy and Safety Analyses

11.5.1 Efficacy Analyses

The following 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 modeling will be used and differences between treatment arms will be examined. Baseline FVC, region and progression-related biomarker (CXCL13**,** CCL18, MMP3) values will be considered as covariates in the model. Further details on the assumptions and planned analyses will be provided in the SAP. 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 exploratory analyses will be conducted using registry and historical data as comparators. Details of all analyses will be provided in the SAP.

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 coughs/hour during awake hours.

11.5.2 Safety Analyses

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 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 AEs 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.

11.6 Pharmacokinetic Analyses

This study will have no pharmacokinetic parameters assessed.

11.7 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 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1 Study Monitoring

According to ICH GCP guidelines, Avalyn Pharma is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The CRO is responsible for assigning the study monitor(s) to this study. The study monitor's duties are to aid the investigator in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB(s) or EC(s) review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an investigational drug and nebulizer, as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the patients; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the clinical monitoring plan.

12.2 Source Documents

Avalyn Pharma requires that the investigator prepare and maintain adequate and accurate records for each patient treated with the investigational drug. Source documents such as any hospital, clinic, or office charts and the signed informed consent forms are to be included in the investigator's files with the patient's study records.

Study data will be captured electronically; study site personnel will record eCRF data from source documents. Patients will record selected study assessments directly into the eCRF. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

12.3 Data Collection and Management

This study will be conducted in compliance with the ICH document "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)," dated March 2018. This study will also be conducted in accordance with the Declaration of Helsinki (2013).

This study will use electronic data collection techniques to collect data directly from the investigational site using eCRFs. The data will be stored centrally in a fully validated clinical database. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan.

Data management will be coordinated by the CRO in accordance with their SOPs and a formal study data management plan.

AEs will be coded with MedDRA. Concomitant medications will be coded using World Health Organization – Drug Reference List.

Data from outside sources (e.g. HRCT results, home spirometry results, LCM results, lab results, etc.) will be integrated into the clinical database.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from Avalyn Pharma, the CRO or its designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

14 ETHICS

14.1 Ethics Review

The investigator will not start this study, nor will devices be shipped to the investigator's site, before providing Avalyn Pharma and/or the CRO with evidence of IRB(s) or EC(s) approval. The investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to patients. The investigator will not make any changes in the research without IRB(s) or EC(s) approval, except where necessary to eliminate apparent immediate hazards to the patients. The investigator will provide progress reports to the IRB(s) or EC(s) as required by the IRB(s) or EC(s). The investigator will provide a final report to the IRB(s) or EC(s) after completion of participation in the study.

14.2 Ethical Conduct of the Study

The investigator should conduct the study in accordance with this protocol, the Declaration of Helsinki, and ICH GCP guidelines. The investigator and Avalyn Pharma and/or the CRO will sign the protocol and study contract to confirm agreement. The investigator will not implement any amendment (deviation or changes of the protocol) without agreement by Avalyn Pharma and/or the CRO and the IRB(s) or EC(s) approval/information, except where necessary to eliminate immediate hazards to study patients or when changes involve only logistical or administrative aspects of the study.

14.3 Written Informed Consent

14.3.1 Patient Information and Informed Consent

The informed consent document will be approved by the IRB(s) or EC(s) that is appropriate for each study site. The investigator is responsible for ensuring that the patient fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible. No patient should be obliged to participate in the study. Patients, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the patient's subsequent care. Patients must be allowed sufficient time to decide whether they wish to participate. Patients will provide consent after they have read the Informed Consent Form and the investigator or designee has answered any questions they may have about the study.

The patient must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB(s) or EC(s), and regulatory authorities. The patient should be informed that such access will not violate patient confidentiality or any applicable regulations. The patient should also be informed that he/she is authorizing such access by signing the informed consent form.

Each patient will be given a signed copy of the informed consent form to keep for his/her records.

Patient's choosing to participate in the Rollover study (AP01-005) may be asked to provide consent to continue the treatment that they are receiving at Visit 12 on this study and then transition to the Rollover study upon approval of AP01-005 at their site.

14.3.2 Provision of New and Important Information Influencing Patient's Consent

When any new and important information that may be relevant to the patient's consent is obtained, the investigator and Avalyn Pharma, the CRO, and/or their designee(s) will consult with each other on how to deal with the information. When Avalyn Pharma, the CRO, and/or their designee(s), and a responsible investigator judge it necessary, the investigator must immediately provide the patients with such information, revise the written information and other explanatory documents based on the new information, and obtain approval from the IRB(s) or EC(s). In this instance, the investigator should also immediately inform patients currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision.

14.4 Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the patient's physician or to other appropriate medical personnel responsible for the patient's well-being. Each patient will be asked to complete a form allowing the investigator to notify the patient's primary health care provider of his/her participation in this study.

15 ADMINISTRATIVE PROCEDURES

15.1 Publications of the Clinical Study

The clinical study plan and the results of the study will be published on the World Health Organization's International Clinical Trials Registry Platform. The results of and data from this study belong to Avalyn Pharma Inc.

15.2 Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the investigator, Avalyn Pharma and/or the CRO after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator, Avalyn Pharma and/or the CRO. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and Avalyn Pharma and/or the CRO. IRB or EC approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) or EC(s) will be promptly notified.

No waivers to inclusion/exclusion criteria will be granted; patients need to meet all criteria, exactly as specified, to be enrolled. No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a patient in an emergency. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a patient in an emergency. Deviations that occur unintentionally or are the result of action by the patient must be documented and reported to Avalyn Pharma and to the IRB(s) or EC(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

15.3 Data and Safety Monitoring Board

An independent DSMB will review accumulated individual safety data for the first 20 patients after their first four weeks of treatment. The data to be reviewed will be unblinded since this is an open-label study. Based on this review, the DSMB will make a recommendation to continue, modify or stop the study. Enrollment will continue during the DSMB review unless 5 or more of the first 20 patients are discontinued due to intolerance.

At any time during the study, should any untoward safety issue be observed, the DSMB Chair may schedule an immediate meeting to review the relevant safety data.

16 DATA HANDLING AND RECORD KEEPING

16.1 Inspection of Records

Avalyn Pharma and/or the CRO, their designee(s), the IRB(s) or EC(s), or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow Avalyn Pharma and/or the CRO, their designee(s), the IRB(s) or EC(s), or regulatory authorities to inspect the investigational drug and device storage area, investigational drug and device stocks, investigational drug and device records, patient charts and study source documents, and other records relative to study conduct.

16.2 Retention of Records

The principal investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

16.3 Sample Retention

Samples may be used for purposes related to this research. The samples may be stored until the study team has determined that specimens are no longer needed and the decision has been made that there are no samples to be re-assayed. In addition, identifiable samples can be destroyed at any time at the request of the patient.

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17 APPENDICES

17.1 ERS Cough Visual Analogue Scale for Cough (Example)

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

17.3 Leicester Cough Questionnaire

17.4 Protocol Amendments

Appendix 17.1 Cough Visual Analogue Scale (Example)

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

WORST COUGH EVER

NO COUGH

17.2 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

17.3 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.

17.4 Protocol Amendments

Version 2.1 dated 12 OCT 2020

Date	Section	Change from	Change to	Justification
12OCT2020	Synopsis, Sections 1..2.4, 4.1, 8.2	Previous verbiage	Various revisions and additions of verbiage to document the DSMB change in dose for 50 mg daily dose during Part B of the study	DSMB meeting on 12 OCT 2020 advised for all patients in Part B to receive the 100 mg twice daily dose
12OCT2020	Synopsis	Unscheduled treatment visit	Monitoring safety visit	Clarification of visit name