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ADPT09

Clinical Trial Protocol CADPT09A12201 / NCT05497284

A participant- and investigator-blinded, randomized, placebo-controlled, multicenter, platform study to investigate efficacy, safety, and tolerability of various single treatments in participants with idiopathic pulmonary fibrosis

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List of abbreviations

6MWT	6 Minute Walk Test
AE	Adverse Event
ALAT	Latin American Thoracic Association
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BMI	Body Mass Index
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTT	Clinical Trial Team
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DLCO	Diffusing capacity for carbon monoxide
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DQF	Data Query Form
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
EFS	Event Free Survival
ELISA	Enzyme-linked immunosorbent assay
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
CCI	[redacted]
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
FVC%p	Forced Vital Capacity expressed in percent predicted
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase

h	Hour
HA	Health authority
HBcAb	Hepatitis B core anti-body
HBsAb	Hepatitis B surface anti-body
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IP	investigational product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
JRS	Japanese Respiratory Society
K-BILD	King's Brief Interstitial Lung Disease
L-IPF	Living with IPF
LCQ	Leicester Cough Questionnaire
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LPLV	Last Participant Last Visit
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
CCI	[redacted]
PAH	Pulmonary arterial hypertension
PCR	protein-creatinine ratio
PD	Pharmacodynamic(s)
PFT	Pulmonary function test
PK	Pharmacokinetic(s)

PoC	Proof of Concept
PRO	Patient Reported Outcomes
PT	prothrombin time
CCI	[redacted]
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R-Scale for PF	Raghu-Scale for Pulmonary Fibrosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SpO2	Oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
UIP	Usual interstitial pneumonia
ULN	upper limit of normal
UTI	Urinary Tract Infection
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of child-bearing potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.

Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal Product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial including a product with a marketing authorization when used or assembled (formulated or packaged) in a way difference from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved used.
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location

Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet, or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 05 (09-Oct-2023)

Amendment rationale

The primary purpose of this amendment serves to remove a protocol allowed contraception method introduced inadvertently via Amendment 04 that is not considered highly effective as per CTFG guidelines.

Changes to the protocol

- Section 17.1.4 Specific Exclusion Criteria: Removed barrier methods of contraception

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 04 (23-Aug-2023)

Amendment rationale

The primary purpose of this amendment serves to update for EU CTR submission and to add additional exclusionary considerations.

Changes to the protocol

- Section 4.6 Rationale for Public Health Emergency mitigation procedures: Updated to current Novartis language
- Section 5.2 Exclusion Criteria: Additional considerations to Exclusion criterion 19
- Section 6.3 Preparation and dispensation: Clarify drug accountability and reconciliation is recorded in IRT system
- Section 10.1.1 Adverse Events: Updated to current Novartis language
- Section 10.1.3 SAE reporting: Include European Clinical Trial Regulation 536/2014
- Section 13.1 Regulatory and ethical compliance: Include European Clinical Trial Regulation 536/2014
- Section 13.3 Publication of study protocol and results: Updated to current Novartis language and include CTIS public website
- Section 17.1.4 Specific Exclusion Criteria: Updated to current Novartis language

Other Changes

- To correct inconsistencies, errors and typos

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 03 (24-Feb-2023)

Amendment rationale

The primary purpose of this amendment serves to address German Health Authority feedback received by Novartis for the study protocol:

- Justification for the treatment period of 26 weeks on LTP001 or placebo in Cohort 1.

Changes to the protocol

- Section 4.2 Rationale for dose/regimen and duration of treatment: Justification added for 26 weeks of treatment

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 02 (18-Jan-2023)

Amendment rationale

The primary purpose of this amendment serves to address feedback received by Novartis for the study protocol:

- Participants with an ALT increase with bilirubin increase should discontinue study drug
- Participants with a Grade 4 (>10 x ULN) isolated total bilirubin elevation should discontinue study drug
- Sponsor should notify health authorities (HAs) and IRBs/ECs if the DMC recommendation to halt or terminate the study is not followed.

Changes to the protocol

- Table 8-1 (Assessment Schedule): Smoking History was added to Screening and Baseline. Footnote added to clarify ECG and DLCO will be performed on local site equipment.
- Section 8.2 Participant demographics/other baseline characteristics: Smoking history added.
- Section 10.3.1 Data Monitoring Committee: Clarify HAs and IRBs/ECs will be notified if recommendations are not followed.
- Table 16-2 Follow-up requirements for liver laboratory triggers – ALT, AST, TBL: Participants with an ALT increase with bilirubin increase should discontinue study drug.
- Table 16-3 Isolated total bilirubin elevation: Participants with a Grade 4 (>10 x ULN) isolated total bilirubin elevation should discontinue study drug.

Other Changes

- To correct inconsistencies, errors and typos

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 01 (04-Aug-2022)

Amendment rationale

The purpose of this CADPT09A12201 protocol amendment is to address:

i. The stratification of randomized participants by use of background therapy was outlined.

ii. The Diffusing Capacity (DLCO) at Baseline was missed in the Assessment Schedule. The timing of this assessment was however included at all other parts of the initial protocol.

iii. Clarification that additional participants may be enrolled if more than 15% of the planned, randomized participants have not completed the 26 weeks of treatment, following a DMC review for safety/ tolerability.

Changes to the protocol

- The Protocol summary was updated to reflect the modifications of the main document
- Section 3 (Study Design) and Section 6.4.2 (Treatment assignment, randomization)
  See rationale i. Stratification
- Section 8 (Assessment Schedule)
  See rationale ii. An X was added for the Diffusing Capacity (DLCO) Assessment at Baseline
- Section 12.8 (Sample size calculation)
  See rationale iii. Additional patient enrollment

Other changes

- Section 5.2 Criteria 26 was shortened as already included in Criteria 25
- Section 6.5 (Treatment Blinding) Clarification that unblinded interim reports are provided by an analysis team.
- Section 12.4 (Analysis supporting primary objectives)
- Standard of care was replaced by background therapy for better consistency and clarity.
- To correct inconsistencies, errors, or typos

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Protocol summary

Protocol number	CADPT09A12201
Full Title	A participant- and investigator-blinded, randomized, placebo-controlled, multicenter, platform study to investigate efficacy, safety, and tolerability of various single treatments in participants with idiopathic pulmonary fibrosis
Brief title	Study of efficacy and safety of various investigational products in participants with idiopathic pulmonary fibrosis
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of this proof-of-concept platform study is to determine whether selected systemic investigational products have an adequate clinical profile to support further clinical development in mild to moderate IPF. This platform design allows several investigational drugs to be tested in an adaptive way under the same conditions in one study.
Primary Objective(s)	The primary objective of this study is to assess the efficacy of the investigational products compared to placebo in participants with IPF measured by FVC expressed in percent predicted.
Secondary Objectives	• To assess the efficacy of the investigational products, compared to placebo in participants with IPF measured by FVC expressed in mL. • To assess the impact of the investigational products on “progression-free survival (PFS)” • To assess the incidence of absolute decline in FVC ≥10% predicted • To assess the impact of the investigational products on pulmonary physiology • To assess the impact of the investigational products on exercise capacity • To assess the impact of the investigational products on patient reported outcome • To assess the safety and tolerability of the investigational products in participants with mild to moderate IPF
Study design	This is a randomized, placebo-controlled, participant- and investigator-blinded platform study in participants with IPF. This study uses a platform type design to investigate multiple investigational products. Each investigational product and matching placebo entered into the trial at a given time will be considered a unique cohort. The decision to include future cohorts is not dependent on performance of prior products or cohorts. If multiple cohorts are open, participants will be allocated based on the cohort specific eligibility criteria. Should a participant be eligible for more than one cohort, they will be randomized to any suitable cohort. For each completed cohort, the data analysis will be performed upon final database lock for the cohort, and the results will be reported upon completion of each cohort in an end of cohort report. Each cohort in the study will undergo the same study evaluations and assessments. Each cohort will include a screening

	period (Day -42 to Day -1), a treatment period of 26 weeks (Day 1 to Day 183), and a post treatment safety follow-up that is cohort specific. Within each cohort, randomization will be stratified by background therapy with 2 levels: with background therapy (nintedanib or pirfenidone), or without background therapy.
Rationale	This study is designed to safely allow rapid and efficient screening of potentially efficacious investigational products in participants with IPF.
Study population	This study will be conducted in male and female participants with IPF who may or may not be receiving background therapy (either nintedanib or pirfenidone) and are at least 40 years of age.
Key Inclusion criteria	• Male and female participants at least 40 years of age • IPF diagnosed based on ATS/ERS/JRS/ALAT IPF 2018 modified guideline for diagnosis and management, within 5 years of screening • FVC ≥45% predicted at screening with no clinically significant deterioration between the screening visit and randomization, as determined by the investigator. • DLCO, corrected for hemoglobin, ≥25% predicted (inclusive) at screening with no clinically significant deterioration between the screening visit and randomization, as determined by the investigator. • Unlikely to die from cause other than IPF within the next 2 years, in the opinion of the investigator • Unlikely to undergo lung transplantation during this trial in the opinion of the investigator • If a participant is taking nintedanib or pirfenidone, they must be on a stable regimen for at least 8 weeks prior to randomization
Key Exclusion criteria	• Unable to perform PFTs, 6MWT or undergo HRCT procedure at time of screening • Peripheral capillary oxygen saturation (SpO2) <90% at rest (if on supplemental oxygen, must be ≤2 L/min at rest) • Airway obstruction (i.e., prebronchodilator FEV1/ FVC < 0.7) or evidence of a bronchodilator response at screening as defined by an absolute increase of ≥12% and an increase of ≥200ml in FEV1 or FVC, or both, after bronchodilator use, compared with the values before bronchodilator use at screening. • Emphysema >20% on screening HRCT as assessed visually by central reader. • Fibrosis <10% on screening HRCT as assessed visually by central reader. • Clinical diagnosis of any connective tissue disease (including but not limited to scleroderma, polymyositis/ dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis) or a diagnosis of interstitial pneumonia with autoimmune features as determined by the investigator applying the recent ERS/ ATS research statement • Other known causes of interstitial lung disease (e.g. domestic or occupational environmental exposures, drug toxicity) or another identifiable interstitial lung disease
Study treatment	A range of investigational products will be added to each cohort (placebo and active) that can enter the platform trial in a perpetual manner and at various unspecified time points.

Treatment of interest	The randomized treatment (the investigational product or the control treatment) with or without the allowed concomitant medication for IPF. The dose of the allowed concomitant medication for IPF must remain stable during the trial.
Efficacy assessments	• Spirometry • Diffusion capacity for carbon monoxide (DLCO) • Six-Minute Walk Test (6MWT) • High resolution computed tomography (HRCT) • Investigator determined IPF Exacerbation
Key safety assessments	• Adverse event monitoring • Physical examinations • Monitoring of laboratory markers in blood and urine • ECGs • Vital signs
Other assessments	• Exploratory biomarkers • Pharmacokinetics • Pharmacogenetics • PROs • CCI
Data analysis	For each completed cohort, the data analysis will be performed upon final database lock for the cohort, and the results will be reported upon completion of each cohort in an end of cohort report. Unless otherwise specified, placebo data from each previously completed cohort will be pooled with the current cohort placebo data. The treatment effect of the primary endpoint will be analyzed using a Bayesian random slope model to assess the difference in reduction rate (slope) between the treatment group and placebo group. The statistical model will include the intercept, time (as continuous variable), the interaction between treatment and time, the interaction of baseline FVC%p and time, and background therapy as fixed effect, and the intercept and slope of time for each participant as random effects. A robust weakly informative prior for the placebo time slope (based on 9 phase II and III studies after 2012 with total of 492 participants) will be used in the Bayesian analysis. The Robustified informative prior for the change from baseline in FVC%p is comprised of 3 components of normal distributed random variables specified in Table 12-1.
Key words	Idiopathic pulmonary fibrosis, FVC, DLCO, 6-minute walk test, patient reported outcome, HRCT

1 Introduction

1.1 Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease, associated with a median survival of 2-5 years from initial diagnosis (Raghu et al 2011). IPF affects approximately 1.5 million patients worldwide. IPF is a disease of aging typically affecting patients older than 60 and not affecting patients younger than 40. Recently, nintedanib and pirfenidone were shown to slow the rate of IPF progression by targeting fibroblasts (King et al 2014, Richeldi et al 2014). However, it was shown that nintedanib and pirfenidone cannot halt the progression of IPF disease. Furthermore, neither nintedanib nor pirfenidone was able to demonstrate a significant impact on IPF mortality. Therefore, a considerable unmet medical need remains.

Globally, North America and Europe have the highest incidence and prevalence of IPF (Hutchinson et al 2015). The incidence has been increasing steadily worldwide, in part due to an aging population. The annual incidence of IPF is currently between 3 and 9 per 100,000 persons in Europe and North America. In a review of studies published between 1990 and 2011, the prevalence of IPF ranged from 14.0 to 27.9 per 100,000 persons in the United States and from 1.25 to 23.4 per 100,000 persons in Europe (Nalysnyk et al 2012). Recent estimates from South Korea suggest the incidence and prevalence of IPF in Asia may be comparable to that of North America and Europe (Lee et al 2016).

Clinical features of IPF include progressive cough, dyspnea, restrictive ventilatory defect, and progressive fibrosis and destruction of the lung parenchyma (Lynch et al 2016). The diagnosis is made in patients with the appropriate clinical features and the histologic pattern of usual interstitial pneumonia (UIP) (based on lung biopsy or high-resolution computed tomography (HRCT)). Challenging factors for clinical management include older age, comorbid conditions, and acute unpredictable exacerbations. Acute exacerbations of IPF are defined as sudden (typically less than 30 days onset) unexplained worsening of underlying disease, including new radiological infiltrates (based on HRCT) or UIP pattern. The progressive deterioration of lung function results in respiratory failure. The prognosis following acute exacerbation and deterioration of lung function is poor, with 1-year and 5-year survival rates of 56.2% and 18.4% following acute exacerbation, which is considerably shorter than in IPF patients without acute exacerbation (Song et al 2011).

The underlying pathophysiology of IPF remains unknown and likely involves a complex interplay of several key factors including environmental exposures, cellular susceptibilities and aberrant repair process. It is believed that recurrent micro injuries to the alveolar epithelium over time leads to a maladaptive repair process, which is characterized by epithelial cell death, senescence and inappropriate re-epithelization. In this setting, epithelial signaling leads to recruitment and activation of fibroblasts into myofibroblasts and recruitment of inflammatory cells. Additionally, failure of re-endothelization may lead to a dysfunctional alveolar-capillary barrier, inducing an additional pro-fibrotic response (du Bois 2010, Sgalla et al 2018). The ultimate proliferation and activation of fibroblasts and myofibroblasts and profibrotic immune cells leads to secretion of connective tissue matrix molecules, such as collagen, to replace the damaged tissue but also displaces healthy tissue leading to scarring and ultimately organ failure (du Bois 2010).

1.2 Purpose

The purpose of this proof-of-concept platform study is to determine whether selected systemic investigational products have an adequate clinical profile to support further clinical development in mild to moderate IPF. This proof-of-concept study is designed as a platform study. This platform design allows several investigational drugs to be tested in an adaptive way under the same conditions in one study.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of the investigational products compared to placebo in participants with IPF	• Change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in percent predicted
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the efficacy of the investigational products, compared to placebo in participants with IPF	• Change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in mL

• To assess the impact of the investigational products on "progression-free survival (PFS)"	• Time to progression as defined by a composite endpoint including any of the following events:
	  • Absolute reduction from baseline of ≥10% predicted in FVC
	  • Nonelective hospitalization for respiratory events
	  • Lung Transplant
	  • Death

• To assess the incidence of absolute decline in FVC ≥10% predicted	• Number of participants with absolute decline of ≥10% predicted in FVC
• To assess the impact of the investigational products on pulmonary physiology	• Change from baseline to the end of treatment epoch (26 weeks of treatment) in DLCO absolute and percent predicted
• To assess the impact of the investigational products on exercise capacity	• Change from baseline to the end of treatment epoch (26 weeks of treatment) in 6-minute walk distance
• To assess the impact of the investigational products on patient reported outcome	• Change from baseline to the end of treatment epoch (26 weeks of treatment) in scores from the L-IPF (Impacts and Symptoms Modules), K-BILD, Leicester cough, and R-Scale for PF questionnaires
• To assess the safety and tolerability of the investigational products in participants with mild to moderate IPF	• Adverse Events, physical examinations, labs, ECGs, vital signs

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To assess the impact of the investigational products on disease exacerbation.	• IPF exacerbations or suspected exacerbations as determined by investigator and by using modified diagnostic criteria derived from Collard et al 2016 and exacerbations as determined by the investigator as AEs/SAEs

• To assess the impact of the investigational products on additional "progression-free survival (PFS)" analysis	• Time to progression as defined by a composite endpoint including any of the following events:
	  • Absolute reduction from baseline of ≥5% predicted in FVC
	  • Non-elective hospitalization for respiratory events
	  • Lung Transplant
	  • Death

• To evaluate change in extent of pulmonary fibrosis quantified by HRCT scan	• Change in fibrosis from baseline to the end of treatment epoch (26 weeks of treatment) in quantitative high-resolution computed tomography (qHRCT)
• To explore the impact of the investigational products on peripheral blood biomarkers	• Change from baseline in soluble pharmacodynamic, target engagement and disease markers (may include but are not limited to: CCI [redacted], and additional protein profiling) in the peripheral blood.
• The pharmacokinetics of the investigational products after multiple doses will be assessed.	• Appropriate PK parameters will be calculated where possible using non-compartmental analysis. These may include Tmax, Cmax, AUCs. Population PK modelling may also be used for parameter estimation.
• To explore the pharmacogenetics for the potential disease association or participant stratification	• DNA analysis at baseline
• [redacted]	CCI [redacted]

2.1 Primary estimands

Not applicable

2.2 Secondary estimands

Not applicable

3 Study design

This is a randomized, placebo-controlled, participant- and investigator-blinded platform study in participants with IPF.

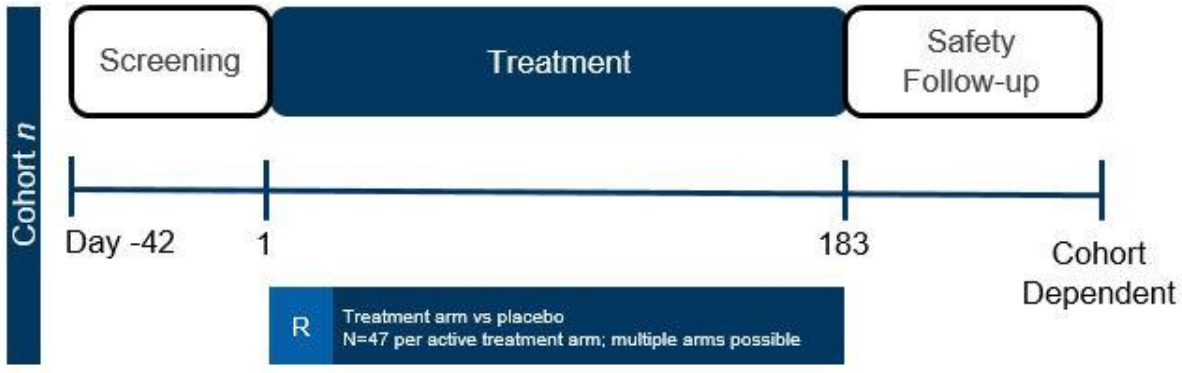
This study uses a platform type design to investigate "multiple targeted therapies in the context of a single disease in a perpetual manner" (Woodcock and LaVange 2017). Each investigational product and matching placebo entered the trial at a given time will be considered a unique cohort. The decision to include future cohorts is not dependent on performance of prior investigational products or cohorts. Each time a new cohort is introduced, investigational product specific information will be added to the protocol (Section 17) as a substantial amendment and submitted to Health Authorities and Ethical Committees, as required by local regulations.

If multiple cohorts are open, participants will be allocated based on the cohort-specific eligibility criteria. Should a participant be eligible for more than one cohort, they will be randomized to any suitable cohort.

Within each cohort, randomization will be stratified by background therapy with 2 levels: with background therapy (nintedanib or pirfenidone), or without background therapy.

For each completed cohort, the data analysis will be performed upon final database lock for the cohort, and the results will be reported upon completion of each cohort in an end of cohort report. Each cohort in the study will undergo the same study evaluations and assessments. Each cohort will include a screening period (Day -42 to Day -1), a treatment period of 26 weeks (Day 1 to Day 183), and a post treatment safety follow-up that is cohort specific per Section 17.

Figure 3-1 Study design



R = Randomization

3.1 End of Study Definition

Participant Completion

A participant will be considered to have completed an intervention cohort if he or she has completed assessments through the final follow-up visit for that intervention cohort or discontinued earlier.

Intervention Cohort Completion

The end of the intervention cohort is defined as the date of the last visit for the last participant in that intervention cohort.

Platform Study Completion

The end of the platform study is defined as the date of the last visit of the last participant in the last cohort.

4 Rationale

This study is designed to safely allow rapid and efficient screening of potentially efficacious investigational products in participants with IPF. The rationale for key aspects of the design is provided below.

4.1 Rationale for study design

Novartis has several investigational products in its portfolio that are well situated to be studied in IPF. By applying a platform study protocol, Novartis can potentially assess multiple investigational products in a single trial. This is considered an efficient way to screen for investigational products that suggest high efficacy (Woodcock and LaVange 2017).

Platform designs allow for the removal of investigational products based on emerging data and facilitates introduction of new investigational products by protocol amendment. Moreover, platform designs may allow for a reduced number of placebo participants as well as the potential to compare between cohorts and/or investigational products tested. Master protocol designs also offer potential advantages to participants in that they have the ability to use fewer participant resources, provide greater opportunity to be on active investigational product, and reach conclusions more quickly than traditional clinical trials. In this study, continuity of sites, including sites performing spirometry, a central imaging reader, and central labs across all cohorts and investigational products will specifically contribute to this master protocol advantage. In oncology, where master protocols are more frequently utilized, a review article suggested that master protocols also decrease heterogeneity of the study population, allowing for a more targeted approach to disease subtypes (Bitterman et al 2020). All these aspects of master protocol design, as well as an enriched ability to learn from parallel or prior cohorts within these trials, provide a strong rationale to apply this novel trial design to an area of high unmet need, such as IPF.

Addition of new cohorts to the platform study occurs through protocol amendments. The core part of this platform protocol (Section 1 through Section 16) is not expected to significantly

change over time. New investigational product-specific information is added to Section 17 using self-contained, cohort-specific modules in the form of amendments. This modular approach is expected to provide a consistent, reliable approach to adding new treatment cohorts.

The cohort-specific modules (Section 17) will contain the mechanism of action, non-clinical information, proposed dose and dosing regimen, and rationale for each investigational product including anticipated safety, potential investigational product-investigational product interactions, unique inclusion or exclusion criteria, unique stopping rules or dose reduction criteria and other treatment specific information.

4.1.1 Rationale for choice of background therapy

A current dose of ≤5 mg/day of prednisone or its equivalent is acceptable prior to randomization, and it is anticipated that the dose will remain stable throughout the participant's enrollment.

During a participant's enrollment, pirfenidone or nintedanib may be taken as background therapy for IPF. The participant must be on a stable dose of either drug for at least 8 weeks prior to randomization. **Both drugs are not to be used simultaneously.** Participants should not initiate background therapy during the study. In cases where the investigator feels that background therapy is clinically indicated, this therapy can be started, but the initiation of background therapy will be considered a protocol deviation and possibly an outcome, such as an IPF exacerbation. Note, that a participant may continue in the study on their assigned treatment if background therapy is initiated, adjusted, or discontinued.

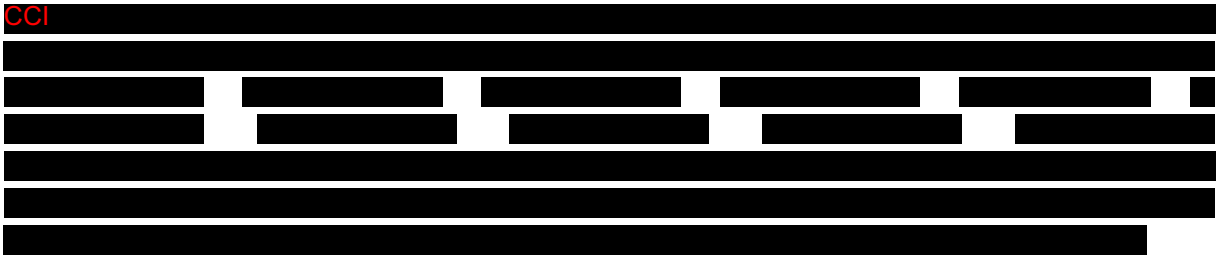
While participating in the study, every effort should be made to maintain the participant on a stable dose of background therapy. However, background therapy dosing may be adjusted or discontinued by the physician responsible for the participant's pulmonary care, with no dose to exceed the labeled maximum doses.

In the event of an IPF exacerbation as determined by the investigator, if the investigator feels that additional therapy (other than pirfenidone or nintedanib) is clinically indicated, this therapy may be started and the medications, doses, and duration of treatment must be documented as concomitant medications. The participant may continue in the study.

Participants should be instructed to continue the medications that they were receiving at enrollment and to avoid starting any new medications or herbal preparations during the study, since these may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Participants should inform the investigator of any changes in the medications they are taking.

4.2 Rationale for dose/regimen and duration of treatment

CCI [redacted]



Please refer to Section 17 (cohort-specific information) for a detailed rationale of each investigational product.

In general, the dose of the investigational product to be studied will be chosen based on an evaluation of all available preclinical and/or clinical data to ensure target or pathway modulation and acceptable safety and tolerability and will be detailed in the corresponding Section 17.

4.3 Rationale for choice of control drugs (comparator/placebo)

Matching placebo will be used in a blinded fashion within each cohort. The use of a placebo control is considered essential to ensure study validity and allow for appropriate assessments of safety and tolerability data as well as efficacy data (see Section 17 for investigational product specific treatment vs placebo randomization allocation). No active comparator is used in this study but use of background therapy is allowed (as noted above).

4.4 Purpose and timing of interim analyses

For each investigational product, one or more interim analyses may be conducted, as appropriate, to support decision making concerning the sponsor's clinical development projects in general, or in case of any safety concerns. The first interim analysis will ideally occur when approximately half of the participants complete dosing per cohort. Additional modifications may be made per Section 17. Additional information is presented in Section 12.7.

4.5 Risks and benefits

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Refer to the Investigator's Brochure of each respective investigational product as identified per cohort.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria.

Detailed descriptions of the expected safety and tolerability characteristics of each IP can be found in Section 17.

The key risks associated with participation in CADPT09A12201, and their mitigation include:

1. Two HRCTs will be performed in this study. Published dosimetry for HRCT shows a total maximal amount of radiation exposure per participant in the study will be approximately 10 mSv (1000 mrem), less than the annual limits allowed in the EU and US, 20 and 50 mSv, respectively. This amount of radiation is equivalent to approximately 3-5 years of exposure to background radiation (9 to 15 mSv, average yearly background dose is approximately 3 mSv in the US). For effective radiation doses between 3 mSv (300 mrem) and 50 mSv (5000 mrem), the risk is considered to be minimal. The radiation exposure in this study is aligned with other IRB approved respiratory trials, involves minimal risk, and is necessary to obtain the desired research information.
2. Although this study excludes participants who are <40 years of age, there is a potential for enrolling women of childbearing potential and the treatments may involve unknown risks to the fetus if pregnancy were to occur during the study. This risk is mitigated by requiring proof the participant is not pregnant prior to start of treatment and requiring appropriate contraception during and for a suitable interval after treatment, as defined for each IP. See Section 17 for further details on each IP.

Based on the above risk considerations, additional safety measures employed in CADPT09A12201 include, but are not limited to:

- The study employs safety management measures, which are considered relevant and appropriate for this participant population and protocol to facilitate safe conduct of the study.
- The study will only be conducted by investigators who have broad experience with participants who have IPF and concomitant medications.
- Participants with severe IPF and high-expected mortality will not be enrolled.
- Specific exclusion criteria prohibited medications and dietary restrictions will be put in place that are pertinent to each IP being tested.
- This protocol pre-specifies both liver and renal events requiring intervention (Section 16.1 and Section 16.2, respectively).
- The study will also be monitored by an unblinded Data Monitoring Committee (DMC), which will provide an additional layer of oversight for safety events. For further details, please refer to Section 10.3.1.

The key potential benefits expected to be associated with participation in the CADPT09A12201 protocol include:

1. Study participants may receive a potentially efficacious treatment; where currently, limited treatment options are available.
2. Study participants will contribute to the potential identification of efficacious therapies for treatment of IPF, which has a high unmet medical need and increasing prevalence.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 32 weeks including screening and treatment periods and an additional variable safety follow-up period defined in Section 17, from each participant as part of the study. The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1) and Section 17.

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See the Section 8.5.3.2 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health Emergency as declared by Local or Regional authorities e.g., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures..

5 Study Population

This study will be conducted in participants with IPF who may or may not be receiving background therapy (either nintedanib or pirfenidone).

The diagnostic criteria for IPF used in this protocol are derived from evidence-based guidelines developed by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) joint task force for the diagnosis and management of IPF (Raghu et al 2018a).

The diagnosis of IPF requires radiographic and/or histopathologic evidence of UIP and exclusion of other causes of idiopathic interstitial pneumonia and interstitial lung diseases (e.g. occupational, or environmental exposures, drug toxicities, collagen vascular diseases).

The ATS/ERS/JRS/ALAT joint task force concludes that, in the appropriate clinical setting, the diagnosis of IPF may be ascertained by HRCT alone if the HRCT image fulfills the criteria for "UIP pattern" or, in participants > 60 years old, a "probable UIP pattern" (i.e., surgical lung biopsy/cryobiopsy is not required). However, if the HRCT does not show a definitive UIP pattern or a probable UIP pattern in participants > 60 years old, then a surgical lung biopsy/cryobiopsy is necessary and specific combinations of the HRCT and histopathological criteria are used to determine the diagnosis of IPF (see Table 5-1).

Table 5-1 CCI

CCI

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female participants at least 40 years of age
3. IPF diagnosed based on ATS/ERS/JRS/ALAT IPF 2018 modified guideline for diagnosis and management, within 5 years of screening (Modified Raghu et al 2018a, Table 5-1) (HRCT and surgical lung biopsy or cryobiopsy (if available) will be read by a central reader) (see text and Table 5-1 for more information on how such diagnoses will be made)
4. FVC ≥45% predicted at screening with no clinically significant deterioration, as determined by investigator between the screening visit and randomization, as determined by the investigator.
5. DLCO, corrected for hemoglobin, ≥25% predicted (inclusive) at screening with no clinically significant deterioration, as determined by investigator between the screening visit and randomization, as determined by the investigator.
6. Unlikely to die from cause other than IPF within the next 2 years, in the opinion of the investigator
7. Unlikely to undergo lung transplantation during this trial in the opinion of the investigator
8. If a participant is taking nintedanib or pirfenidone, they must be on a stable regimen for at least 8 weeks prior to randomization
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Unable to perform PFTs, 6MWT or undergo HRCT procedure at time of screening
2. Inability to comply with study requirements.
3. Peripheral capillary oxygen saturation (SpO2) <90% at rest (if on supplemental oxygen, must be ≤2 L/min at rest)
4. Airway obstruction (i.e., prebronchodilator FEV1/ FVC < 0.7) or evidence of a bronchodilator response at screening as defined by an absolute increase of ≥12% and an increase of ≥ 200ml in FEV1 or FVC, or both, after bronchodilator use, compared with the values before bronchodilator use at screening.
5. Emphysema >20% on screening HRCT as assessed visually by central reader.
6. Fibrosis <10% on screening HRCT as assessed visually by central reader.
7. Clinical diagnosis of any connective tissue disease (including but not limited to scleroderma, polymyositis/ dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis) or a diagnosis of interstitial pneumonia with autoimmune features as determined by the investigator applying the recent ERS/ ATS research statement (Fischer et al 2015). Note: serological testing is not needed if not clinically indicated.
8. Other known causes of interstitial lung disease (e.g. domestic or occupational environmental exposures, drug toxicity) or another identifiable interstitial lung disease
9. Clinically diagnosed acute exacerbation of IPF (AE-IPF) or other significant clinical worsening within 3 months of randomization
10. History of major organ, hematopoietic stem cell or bone marrow transplant
11. History of hypersensitivity to the study drug or to drugs of similar chemical classes in the cohort the participant is to be randomized
12. Serious local infection (e.g. cellulitis, abscess) or systemic infection that required hospitalization or was clinically significant in the opinion of the investigator, within 3 months prior to screening.
13. Fever (body temperature >38 degrees Celsius) or symptomatic viral or bacterial infection within 2 weeks prior to screening or randomization
    - A known or suspected symptomatic Covid diagnosis within 3 months of screening visit or prior to randomization
14. History of primary or secondary immunodeficiency, including a positive human immunodeficiency virus (HIV) (enzyme-linked immunosorbent assay [ELISA] and western blot) test result
15. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV ribonucleic acid [RNA]). Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] or positive anti-HBc with a negative anti-HBs). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

16. History of malignancy of any organ system (other than completely excised, localized carcinoma of the skin such as basal cell or squamous cell carcinoma or in situ cervical cancer), treated or untreated, within the past 5 years of screening, regardless of whether there is evidence of local recurrence or metastases
17. Significant cardiac disease (e.g. New York Heart Association Class 3 or 4; myocardial infarction within the past 6 months of screening; unstable angina; coronary angioplasty or coronary artery bypass graft within the past 6 months of screening; uncontrolled atrial or ventricular cardiac arrhythmias).
18. Pulmonary hypertension requiring pharmacologic treatment.
19. Any surgical, medical (e.g. uncontrolled hypertension, diabetes), psychiatric or additional physical condition that the investigator feels may jeopardize the participant in case of participation in this study. The investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory evidence of any of the following:
    - Moderate or severe hepatic failure (Child-Pugh classification stage B or C)
    - Significant renal impairment with an estimated glomerular filtration rate (eGFR) < 30 mL/min as calculated by the CKD-EPI formula
21. Other unspecified reason that in the opinion of the investigator in consultation with the sponsor makes the participant unsuitable for enrollment
22. Active drug or alcohol abuse (as defined by the investigator) within 3 months prior to screening.
23. Use of any inhaled substance, including but not limited to tobacco or marijuana products and/ or the use of any electronic cigarette or vaping device, within 12 weeks prior to screening (note that respiratory inhalers or nebulizers for delivery of prescribed medication for pulmonary disease are allowed).
24. Any one of the following screening values of complete blood count laboratory values:
    - Hemoglobin levels < 10.0 g/dL
    - Total leukocyte count < 3,000/μL
    - Neutrophils <1.5 x 10^3 /μL
    - Platelets <100.0 x 10^3 /μL
    - Total Bilirubin > 1.5 mg/dL (in the absence of known Gilbert's syndrome)
    - Aspartate transaminase (AST) or alanine transaminase (ALT) > 2X upper limit of normal
25. Currently receiving high-dose corticosteroid, cytotoxic therapy (e.g. chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g. bosentan), unapproved (e.g. IFN-γ, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine [may vary by country]) and/or investigational therapy or device for IPF or administration of such therapeutics within 5 half-lives of the IP prior to initial screening in this study. A current dose of ≤5 mg/day of prednisone or its equivalent is acceptable if the dose is expected to remain stable during the study. (Note: N-Acetylcysteine used to treat cough is permissible).
26. Plan to enroll in another interventional trial while in this study

27. Blood donation of 1 unit (approximately 473mL) or more within 1 month prior to screening.
28. Male or female planning a pregnancy during the duration of this study. A serum pregnancy test will be performed on all female participants of childbearing potential.
29. Pregnant or nursing (lactating) women
30. Elective surgery planned to take place during this trial (excluding diagnostic procedures such as colonoscopy, etc.)
31. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using appropriate methods of contraception for 3 months prior to screening, during dosing, and for a period after stopping of investigational medication (any treatment specific contraception requirements and changes to duration or if WOCBP cannot be enrolled at all are outlined in Section 17).

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatment are outlined in Section 17.

Refer to Section 17 for details of dosing and food intake, if relevant.

6.1.1 Investigational and control drugs

Refer to cohort-specific information in Section 17.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Refer to cohort-specific information in Section 17

6.2 Other treatment(s)

Refer to Section 17 for guidance for other treatments based on the specific IP/cohort.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy, blood transfusions, oxygen) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

IP-specific permitted concomitant therapy is listed in Section 17 where applicable for each IP.

6.2.2 Prohibited medication

Treatment-specific prohibited medications are provided in Section 17 for the individual IPs/cohorts. Any medications prohibited in the core protocol are listed in the core inclusion (Section 5.1) and exclusion (Section 5.2) criteria. Simultaneous use of pirfenidone and nintedanib is prohibited.

Please refer to the respective cohort-specific information in Section 17 for additional restrictions, as applicable.

6.2.3 Rescue medication

Treatment for an acute exacerbation is at the discretion of the investigator and medications (such as prednisone) can be freely initiated or increased at the investigator's discretion.

6.2.4 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined in the IP-specific Section 17 and within Section 6.

6.2.4.1 Dietary restrictions and smoking

Participants must abstain from smoking or vaping any substances.

Refer to cohort-specific information in Section 17 for any IP specific dietary restrictions.

6.2.4.2 Other restrictions

No other restrictions apply.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs Section 6.1.1.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT system and obtaining the medication number(s). Drug accountability and reconciliation data is recorded in the IRT system.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the investigator. Refer to Section 17 for details.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

It should be checked at each visit that other concomitant IPF specific therapy has been kept stable as specified in the study eligibility criteria (Section 5) and in Section 6.2.1.

6.3.2 Instruction for prescribing and taking study treatment

Refer to cohort-specific information in Section 17.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number, that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new informed consent form will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No. The original Participant No must be added in the respective eCRF to link the two subjects for reporting and validation purposes.

Participants may join subsequent cohorts. Participants will sign a new informed consent form and will screen per protocol. Participants will be assigned to the next sequential Participant No. available. The original Participant No must be added in the respective eCRF to link the two subjects for reporting and validation purposes.

6.4.2 Treatment assignment, randomization

The following methods have been used to minimize bias in the assignment.

Participants will be randomized in two-stages. Participants will be randomized to a cohort first and then randomized to a treatment arm (i.e. investigational drug or placebo) within a cohort. Participants eligible for only one cohort will be assigned directly to that cohort.

Randomization to any cohort will follow dynamic allocation ratio which allows flexibility to allocate participants based on weighted probabilities assigned to the cohorts. Allocation to treatment arms within a cohort will initiate with a pre-specified ratio for that particular cohort (e.g. 1:1, 2:1, 3:1) that could vary at any time during the study. Any changes in randomization ratio will be updated in the ICF. This randomization scheme allows the Sponsor to maintain at least 1:1 ratio for placebo vs. treatment for any given cohort after sharing placebo subjects across cohorts.

Randomization will be stratified by background therapy with 2 levels: with background therapy (nintedanib or pirfenidone), or without background therapy. Note that nintedanib and pirfenidone are the only IPF treatments permitted outside of study treatment assignment.

The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

For any prematurely terminated cohort not due to safety, all ongoing participants in the treatment arms in this cohort may be discontinued and not replaced. For any prematurely terminated cohort due to safety, all ongoing participants in the treatment arms in this cohort will be discontinued and not be replaced. Enrollment into any prematurely terminated cohort will be stopped.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Details of the randomization requirements will be documented in randomization requirement specification document. The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.5 Treatment blinding

Participants and the investigator staff (except as outlined below) will remain blind to the identity of the treatment from the time of randomization until cohort database lock. However, both participant and investigator will know to which cohort the participant has been assigned.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

The following methods will be used to maintain the blind:

(1) Randomization data will be kept strictly confidential until the time of cohort database lock and will not be accessible by anyone else involved in the study with the following exceptions:

- an independent analysis team who needs to prepare the safety interim analysis reports for the DMC
- the bioanalyst for PK analysis (to avoid the unnecessary analysis of placebo samples)

(2) data with unblinding potential, (such as applicable PK concentrations and biomarkers) collected after the randomization visit, will be kept blind until the time of cohort database lock.

At the time of safety review/interim analysis, the DMC will review unblinded interim reports created by an analysis team. More details will be provided in the DMC charter.

At the time of interim analysis for efficacy, the Novartis Clinical Trial Team will create and review unblinded interim reports.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-1. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following cohort database lock for each investigational product, all sponsor roles may be considered unblinded.

Table 6-1 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis/ dose escalation/ safety review
Subjects/Patients	B	B	UI	B
Site Staff	B	B	UI	B
Unblinded site staff, e.g. pharmacy staff	B	UI	UI	UI
Randomization Office	UI	UI	UI	UI
Unblinded Sponsor staff, e.g. for study treatment re-supply, unblinded monitor(s), sample analyst(s)	B	UI	UI	UI
Independent Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	B	UI	UI
All other Sponsor staff not identified above (i.e. project team, management & decision boards, support functions)	B	B	UI	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	B	B	UI	UI

B Complete blinded
UI Unblinded to individual participant treatment codes

6.6 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are only permitted as described in Section 17.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants, as detailed in Section 17.

6.7.2 Recommended treatment of adverse events

Adverse events should be treated as per standard of care. Medication used to treat AEs must be recorded on the appropriate CRF.

6.7.2.1 Acute Exacerbations of IPF

A participant who experiences a worsening of respiratory status at any time during the study should immediately contact their treating physician. The participant should also notify the investigator (if different than the treating physician) to schedule the IPF Exacerbation Visit as soon as possible so that the investigator may assess and confirm the IPF exacerbation. Should the participant be unable to come to the clinic for the IPF Exacerbation Visit, the investigator should attempt to complete the investigator's determination of IPF exacerbation (see Section 6.7.2.2) as soon as possible.

The IPF Exacerbation Visit should include the following per Table 8-1:

- Physical examination
- Vital signs
- Oxygen saturation
- Spirometry
- DLCO
- Imaging studies (chest X-ray or HRCT) if not performed at another facility
- Investigator's determination of IPF exacerbation (see Section 6.7.2.2)

This visit may also include the following at the investigator's discretion:

- ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Other tests or evaluations at the discretion of the investigator

Note: If an IPF exacerbation is suspected at the time of a scheduled visit or is to be evaluated at a scheduled visit, the IPF exacerbation assessments listed above must be performed at the scheduled visit if not already included.

A participant who is evaluated, treated, or hospitalized at a facility other than the study site should contact the study site following that visit to determine if the participant should come in for a stand-alone IPF Exacerbation Visit or have additional IPF exacerbation assessments during a routine, scheduled study visit. In addition, if a participant was hospitalized or had IPF exacerbation assessments at another facility, study site personnel should make every effort to obtain sufficient medical records to determine the following:

- Possible triggers or causes of the event.
- The results of relevant tests and assessments, including but not limited to:
  - Detailed radiography reports and copies of images of all radiographic
  - examinations (e.g. chest X-ray or HRCT scan) for submission to the central imaging vendor.
  - Spirometry, body plethysmography (lung volume), and/or DLCO testing reports.
- Descriptions of the severity and duration of the event.

- Details of the medical treatment provided, including relevant medications and other major elements of the clinical management.

The participant's response to the treatment and clinical status at the time of discharge.

6.7.2.2 Determination of IPF Exacerbation

Based on the results obtained from evaluations at the IPF Exacerbation Visit and/or the records obtained from a visit to another facility (if applicable), the investigator will determine whether an IPF exacerbation or suspected IPF exacerbation has occurred. The investigator will assess the occurrence of IPF exacerbation using the revised diagnostic criteria for IPF exacerbation and suspected IPF exacerbation of the international working group report in 2016 (Collard et al 2016), as follows:

- Acute worsening or development of dyspnea typically <1 month duration.
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern.
- Deterioration not fully explained by cardiac failure or fluid overload.

Note: Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all diagnostic criteria owing to missing computed tomography data should be termed "suspected acute exacerbations."

The investigator's determination of IPF exacerbation based on the 2016 definition should be documented on the appropriate CRF.

As noted, treatment for an acute exacerbation is at the discretion of the investigator and medications (such as prednisone) can be freely initiated or increased at the investigator's discretion.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

After an emergency break, the participant will not be allowed to continue treatment in their current cohort. The participant should still be followed for safety.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational product can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Optional Genetics Consent to provide a DNA sample for exploratory DNA studies

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

The study includes an optional DNA component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA) will in no way affect the participant's ability to join the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue study treatment must return for an End of Treatment visit as soon as possible, but within 4 weeks after discontinuation of treatment, as outlined in Section 9.1.1.

If a participant is discontinued from the study, an End of Treatment visit will be scheduled or performed as soon as possible but within 4 weeks, as outlined in Section 9.1.2. If a participant withdraws their consent/opposes the use of their data/biological samples, an End of Treatment visit may be scheduled or performed as soon as possible but within 4 weeks, if the participant agrees.

At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

When the following assessments are scheduled to be performed at the same time point, the order of priority will be as follows:

The 6MWT must be performed after all ECGs, PFTs and PROs have been completed.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic, or natural disaster) that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening	Treatment							IPF Exacerbation	Post-Treatment Follow-Up
Visit Name	Screening	Baseline/Treatment	Treatment					EOT[1]	Exacerbation	Follow-Up
Days	-42 to -1	1	29 ±3	57 ±3	85 ±3	113 ±3	141 ±3	183 ±5	1 to EOS	See Section 17
Informed consent	X									
Genetic consent	X									
Inclusion / Exclusion criteria	X									
Demography	X									
Medical history/current medical conditions	X	X[2]								
Smoking history	X	X[2]								
Hepatitis screen	S									
HIV screen	S									
Pregnancy and assessments of fertility[3]	S	S	S	S	S	S	S	S		S
Body Height	X							X		
Body Weight[4]	X							X		
Physical Examination	S	S						S	S	
Limited Physical Examination[5]			S	S	S	S	S			S
Body Temperature	X								X	
Blood Pressure, Oxygen Saturation and Pulse Rate	X	X	X	X	X	X	X	X	X	
Electrocardiogram (ECG)[6]	X	X			X			X	X	

Period	Screening	Treatment						IPF Exacerbation	Post-Treatment Follow-Up
Visit Name	Screening	Baseline/Treatment	Treatment				EOT[1]	Exacerbation	Follow-Up
Days	-42 to -1	1	29 ±3	57 ±3	85 ±3	113 ±3	141 ±3	183 ±5	1 to EOS	See Section 17
Spirometry[7]	X	X	X	X	X	X	X	X	X	X
Diffusing Capacity (DLCO)[6]	X	X			X			X	X	
CCI										
High Resolution CT of Chest	X							X	X	
6-Minute Walk Test[8]		X			X			X		
Urinalysis	X	X								
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X	X
Cohort Specific Assessments	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
PK/PD/Biomarkers[10]		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]		
Exploratory DNA Sampling (optional)[12]		X								
Drug dispensation		X[13]	X[13]	X[13]	X[13]	X[13]	X[13]			
Drug administration record			X	X	X	X	X	X		
L-IPF[14]		X			X			X		
R-Scale for PF		X			X			X		
K-BILD		X			X			X		
Leicester Cough		X			X			X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Period	Screening	Treatment							IPF Exacerbation	Post-Treatment Follow-Up
Visit Name	Screening	Baseline/Treatment	Treatment					EOT[1]	Exacerbation	Follow-Up
Days	-42 to -1	1	29 ±3	57 ±3	85 ±3	113 ±3	141 ±3	183 ±5	1 to EOS	See Section 17
Study completion information										X
Adverse Events/Serious Adverse Events	As Required	As Required	As Required	As Required	As Required	As Required	As Required	As Required	As required	As required

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] If study treatment is permanently discontinued prior to the end of the Treatment Period, an Early EoT visit will occur as soon as possible, but within 4 weeks. All assessments planned for the Day 183 visit except for the HRCT scan will be performed (see Section 9.1.1 for details). If a subject is withdrawn from the study prior to the end of the Treatment Period, an Early EoT visit will occur as soon as possible, but within 4 weeks. All assessments planned for the Day 183 visit will be performed except HRCT. If early EOT falls on or after Day 85 visit, HRCT should also be performed (see Section 9.1.2 for details).
[2] To be reconfirmed at randomization
[3] As required. Women of childbearing potential must have serum pregnancy test at screening and this test must be performed within 7 days prior to dosing. Subsequent testing may be urine (see Section 8.4 Safety for additional information).
[4] See Section 17 for additional cohort assessments, if needed
[5] Cardiac and Pulmonary exams must be performed. Symptom driven for all other organ systems
[6] ECG and DLCO will be performed using local site equipment
[7] Spirometry at screening visit will include Bronchodilator response.
[8] The 6MWT must be performed after all ECGs, PFTs and PROs have been completed. Each 6MWT consists of 2 separate walks.
[9] See Section 17 for specific assessments
[10] PK samples may be collected at unscheduled times
[11] See Section 17 for specific time point for study drug arm
[12] Genetic research ICF must be obtained before optional DNA sampling. This optional sample can be collected anytime on Day 1 visit or thereafter.
[13] See Section 17 for study drug administration
[14] Impacts and Symptoms Modules

8.1 Screening

It is permissible to re-screen a participant if the participant fails the initial screening for a cohort, if deemed feasible or necessary by the study site investigator. Participants who do not meet the IPF diagnosis inclusion criteria should not be re-screened or screened for subsequent cohorts. If a subsequent re-screen is required for a cohort after the first permissible re-screening, the case should be discussed with the Sponsor. Any assessments that fall out of the screening window must be repeated.

In the case where a safety laboratory assessment and/or PFTs at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to the first dose of study treatment. If the repeat value remains outside of the specified range, the participant must be excluded from the study. If PFTs are to be repeated, only the tests that are felt to be questionable should be repeated (i.e., spirometry or DLCO).

If a participant must be re-screened, for study entry, results from previous screening assessments may be used, as long as the screening windows for those assessments are met and all spirometry data used for subject qualification are derived from a single day.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg), Hepatitis B surface anti-body (HBsAb), and Hepatitis B core anti-body (HBcAb). Screening for Hepatitis C will be based in HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site e.g. western blot. Appropriate counseling will be made available by the investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the investigator.

This will be recorded as source data only by the use of an "S" for the corresponding criteria in Table 8-1 (Assessment Schedule) of the protocol.

8.1.1.2 Alcohol test, Drug screen, Urine cotinine

Not applicable

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the CRF.

Participant demographics: year of birth or age, sex, race/predominant ethnicity (if permitted), smoking history, and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, the diversity of the study population will be assessed as required by Health Authorities.

All prescription medications, over-the-counter drugs, and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

Pharmacodynamic samples will be collected at the timepoints defined in the Cohort Specific Assessment Schedule (Section 17). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

Pharmacodynamic (PD) samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

8.3.1 Appropriateness of efficacy assessments

- The 6MWT is a well standardized and simple test to assess physical performance
- DLCO is a pulmonary function test that assesses the diffusion of gas in the lungs
- HRCT is a method of radiographic examination which is more precise than chest x-ray for the diagnosis and monitoring of fibrotic diseases in the lung
- Spirometry is a component of pulmonary function testing that assesses volume of airflow movement

8.3.2 6-Minute Walk Test

A standardized Six-Minute Walk Test (6MWT) will be performed considering guidance for the test procedures described by ERS and ATS guidelines (Holland et al 2014). The six-minute walk will be carried out by a trained technician.

The 6MWT must be performed after all ECGs, PFTs and PROs have been completed.

Two walks will be conducted for each 6MWT and both scores will be recorded. The participant should rest for at least 30 minutes between walks and may use this time to perform other protocol activities.

Please refer to vendor training for additional details.

8.3.3 Diffusing Capacity (DLCO)

Diffusion capacity for carbon monoxide (DLCO) will be determined according to ATS guidelines (Graham et al 2017). DLCO should be adjusted for hemoglobin, using the hemoglobin value collected at the same visit.

Please refer to vendor manual for details.

8.3.4 High Resolution CT of Chest

High Resolution Computed Tomography (HRCT) will be performed at screening (which will be used as the baseline measure) and at Week 26. At the time points specified in the schedule, an HRCT scan of the lung, without contrast agent, will be acquired. The acquisition will include inspiratory and expiratory image sets at both assessment time points. In all participants within the study, the baseline and follow-up HRCT scan should be performed where possible on the same scanner. Protocol specific requirements of the HRCT and machine settings are provided to all sites as part of a separate Imaging Manual. Additionally, the imaging vendor will provide centralized review of the HRCT scans. The methods for assessment and recording are specified in the Imaging Review Charter.

In summary, evaluation of the HRCT scans may be used to assess extent of:

- Lung parenchymal classification analysis and valuation of change from baseline compared to week 26 of HRCT
  - Percent of lung or regional volume which constitutes normal lung tissue, areas of low attenuation (LAA), ground-glass opacity, reticulation, honey-combing, and composites of these indices.

HRCT involves exposure to radiation. The total amount of radiation for acquisition at baseline and Week 26 of HRCT scans will be optimized to be within the annual limits of exposure defined in both EU and NA guidelines. The total radiation received in this study is equivalent to approximately 3-5 years of normal radiation received in everyday life. This amount of radiation is considered to be a minor to intermediate risk and is necessary to obtain the research information desired.

Note: The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.3.5 Spirometry

Spirometry testing will be performed according to the American Thoracic Society guidelines (Graham et al 2019) at screening to assess participant's eligibility for the study and as detailed in the assessment schedule.

Please refer to vendor manual for details.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), that limits or prevents on-site study

visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Safety Assessments

Assessment	Specification
Physical Examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A limited physical exam that includes the examination of general appearance, vital signs (blood pressure [SBP and DBP] and pulse), and Cardiac and Pulmonary exams must be performed. Symptom driven for all other organ systems. A limited physical exam will be at all visits starting from day 29 except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent that meet the definition of an Adverse Event must be recorded as an adverse event.
Vital Signs	Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1. Body mass index (BMI) will be calculated using the following formula: • BMI = Body weight (kg) / [Height (m)]^2 The screening visit height measurement will be used for BMI calculations throughout the study.

8.4.1 Laboratory evaluations

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health Emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic, or natural disaster), that limits or prevents on-site study visits.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the investigator and shall be based, in part, upon the nature and degree of the observed abnormality.

In all cases, the investigator must document in the source documents the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant).

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments and allow proper assessments.

Special clinical laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-3 Laboratory Evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ert. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value and %s)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen
Coagulation	Prothrombin (PT), International normalized ratio INR), Activated partial thromboplastin time (APTT)
Hepatitis markers	Hepatitis B Virus DNA, Hepatitis B surface antigen (HBsAg), Hepatitis B surface anti-body (HBsAb), Hepatitis B core anti-body (HBcAb), Hepatitis C Virus RNA
Hepatic and renal follow-up	PT/INR urine PCR and albumin-creatinine ratios (refer to Section 16.1 and Section 16.2, hepatic and renal event follow-up to ensure recommended tests are listed) These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 16.1 and Section 16.2, hepatic and renal event follow-up
Additional tests	See Section 17 if applicable
Pregnancy Test	Serum / Urine pregnancy test (refer to Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the seated or supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (refer to flow diagram below).

Figure 8-1 Timing of study procedures

The Fridericia QT correction formula (QTcF) must be used for clinical decisions. The investigator must calculate QTcF if it is not auto calculated by the ECG machine.

Single local 12 lead ECGs are collected.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs on non-heat sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECGs will be reviewed locally for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified in Section 17.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities, i.e. pandemic epidemic, or natural

disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g. following country specific measures).

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

Pulmonary function and status are monitored by assessments, including spirometry, DLCO, CCI 6MWT, and PROs amongst others, which are detailed under the efficacy measures in the study. Cohort specific safety assessments are detailed in Section 17.

Further safety assessments (e.g. hematology, serum chemistry, coagulation, ECGs, vital signs, physical exams) are standard for investigations monitoring general safety in phase 2 clinical trials.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic, or natural disaster), that limits or prevents on-site study visits, COA data may be collected remotely.

Patient reported outcomes (PRO)

The participant must be given the PRO measure(s) to be completed at the scheduled visit before 6MWT. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant.

If self-administered:

The participant should be given sufficient space and time to complete the PRO measure(s).

The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses.

8.5.1.1 Leicester Cough Questionnaire

The Leicester Cough Questionnaire (LCQ) is a 19-item chronic cough/respiratory-specific measure designed to assess the impact of chronic cough on health-related quality of life (HRQoL), using a recall period of the last 24 hours. It can be completed in less than 5 minutes.

8.5.1.2 Living with IPF (Impacts and Symptoms Modules)

Living with IPF (L-IPF) is a tool that assesses symptoms and impacts of IPF. The Symptoms Module consists of 20 questions. This module is designed to assess symptoms experienced from IPF over the last 24 hours. The symptoms questions are in relation to physical activities, cough, and energy level. The last 5 questions are regarding supplemental oxygen use. The Impacts Module consists of 20 questions on how IPF affects quality of life over the last 7 days.

8.5.1.3 K-BILD

The King's Brief Interstitial Lung Disease (K-BILD) is a 15-item HRQOL questionnaire. The K-BILD questionnaire assesses 3 domains (breathlessness/activities, psychological and chest symptoms) with a 2-week recall.

8.5.1.4 Raghu Scale for Pulmonary Fibrosis

The Raghu-Scale for Pulmonary Fibrosis (R-Scale for PF) is a questionnaire designed to assess the impact of lung disease on quality of life. R-Scale for PF consists of 5 questions with a 2-week recall.

8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in Section 17.

8.5.3 Biomarkers

The biomarkers selected in this study may explore the potential mechanism of action, pharmacodynamics, and safety responses to the drug treatment. The biomarker strategy may enhance our understanding of the mechanism of the compound on inflammation and fibrosis in humans with IPF disease. The pharmacogenetic assessment will be performed to examine the association of genetic variances related to drug response and metabolism. The timing and details of the samples collected are defined in the PK/PD and Biomarker Assessment Schedule in Section 17. Serum and plasma biomarkers will be collected, stored, and banked for future testing.

Exploratory Biomarkers

Serum and plasma samples will be collected for exploratory disease related biomarker analysis. Additional samples for biomarkers will be collected, banked, and stored.

Protein profiling of blood samples may be analyzed in multiplex, hypothesis-free platforms to study protein biomarkers.

Samples will be collected at the time points defined in the PK/PD and Biomarker Assessment Schedule (Section 17). The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of

the study. Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

Descriptions of the assays, platforms, and technologies to be used in the exploratory biomarker evaluations will be included in the associated bioanalytical data reports. Clinical samples for the assessment of exploratory biomarkers may be stored and their processing and analysis conditioned to the decisions to be made based on overall study outcome and/or future scientific needs. Exploratory biomarker samples remaining after analyses may be stored for up to 15 years to address additional relevant scientific questions.

To assess the impact of the drug on disease related biomarkers; markers may include but not limited to:

CCI

CCI

CCI

CCI

CCI

CCI

Samples will be the collected at the time point defined in the Assessment schedule (Section 17).

Detailed instructions for sample collection, numbering, processing, and shipment will be provided in the Central Lab Manual.

DNA sampling / Pharmacogenetics

Exploratory DNA Sampling (Optional)

The study includes an optional genetic research component which requires a separate informed consent signature if the participant agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the investigator presents these options to the participant.

The purpose of genetic research may be to better understand the safety and efficacy of treatment, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Sample(s) will be collected at the time point(s) defined in the PK/PD and Biomarker Assessment Schedule (Section 17).

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

DNA samples

The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the participant's medical records.

To maximize confidentiality, all samples will be double coded to prevent the exposure of the participant's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the participant's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

8.5.3.1 CCI

[redacted]

8.5.3.2 Use of residual biological samples

Residual blood, serum, and plasma samples may be used for another protocol specified endpoint. Any residual samples remaining after the protocol-defined analyses have been performed may be used for additional exploratory analyses. This may include but is not limited to using residual samples for protein binding, metabolite profiling or quantification, biomarkers of transporters or metabolic enzyme activity or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). The results from these exploratory analyses may not necessarily be included in the clinical study report.

8.5.4 Immunogenicity

Immunogenicity samples may be obtained in cohorts where the IP is thought to have the potential to elicit an immunogenic reaction, including the placebo groups in those cohorts.

In case of suspected allergic hypersensitivity, the participant should return to the site and a sample to assess immunogenicity will be collected.

In case of positive immunogenicity, backup of previous pre-dose PK samples could be used to better characterize the onset of immunogenicity response.

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

Please refer to Section 17.

Immunogenicity analytical method(s)

A validated ligand binding assay (i.e. ELISA, MSD, etc.) will be used for the detection of potential antibodies per Section 17. Confirmed immunogenicity positive samples will be further analyzed for presence of neutralizing antibodies using a validated method.

The detailed methods for immunogenicity assessment will be described in the Bioanalytical Data Report.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Participants who discontinue study treatment must return for an Early End of Treatment visit as soon as possible, but within 4 weeks after discontinuation of treatment. All assessments planned for the Day 183 visit will be performed. HRCT will only be done if discontinuation occurs after Day 85. If the End of Treatment visit occurs in the visit window for the next scheduled visit, then the scheduled visit may serve as the Early End of Treatment visit, and all assessments for the End of Treatment visit should occur at that time. Participants will go on to complete all remaining visits as scheduled, including the Day 183 visit and Safety Follow-up visit (see Table 8-1 for a list of assessments to occur at the End of Treatment and Safety Follow-Up visits). For participants who continue scheduled visits, the HRCT scan will be performed as scheduled at the Day 183 visit.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to instructions in Section 10.1.4
- If organ transplantation becomes necessary during the study treatment
- The participant is unwilling or unable to comply with the protocol
- Adverse event that puts the participant at risk if continuation on investigational product or in the study, at the discretion of the investigator.
- If a liver or renal event occurs, follow guidelines outlines in Section 16.1 (Appendix 1) and Section 16.2 (Appendix 2), respectively, regarding discontinuation of study treatment.

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

After discontinuation from study treatment, at a minimum the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If a participant is discontinued from the study, an Early End of Treatment visit will be scheduled or performed as soon as possible but within 4 weeks. All assessments planned for the Day 183 visit will be performed except HRCT. If early EOT falls on or after Day 85 visit, HRCT should also be performed (see Table 8-1 for a list of assessments to occur at the End of Treatment visit).

If a participant is unwilling or unable to attend, at the minimum, the End of Treatment visit, and decides to withdraw from the study, the reason for withdrawal will be documented and no further assessments will be obtained.

Please note, if a participant decides to discontinue from the study, a withdrawal of consent should NOT be completed unless the participant meets the particular criteria noted in Section 9.2.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until this "due diligence" has been completed.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant meets ALL three criteria:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, an End of Treatment visit will be scheduled or performed prior to the participant's withdrawal of consent/exercise data privacy rights. All assessments planned for the Day 183 visit will be performed except HRCT. If early EOT falls on or after Day 85 visit, HRCT should also be performed (see Table 8-1 for a list of assessments to occur at the End of Treatment visit).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study stopping rules

The Sponsor may terminate this study, or a cohort, at any time. The Sponsor will notify investigators if the study is to be placed on hold, completed, or terminated.

Cohort stopping rules

Enrollment in a cohort will be placed on hold if:

- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the cohort on hold

Additionally, the DMC will conduct regular reviews of all safety data in an unblinded format. Following each review, the DMC will provide a recommendation to the Sponsor regarding the appropriateness of continuing the cohort from a safety perspective, as well as any other recommendations relevant to study conduct and/or participant safety.

The DMC may recommend discontinuing the cohort if the event rate in the investigational treated arm is 20% higher compared with placebo. The events include, but may not be limited to:

- cumulative number of deaths and/or;
- number of lung transplantations and/or;
- cumulative number of participants with a confirmed absolute decline of % predicted FVC ≥15 from baseline.

The meeting intervals and procedures used to provide and assess the data will be described in detail in the DMC Charter.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their End of Study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator.

All randomized and/or treated participants will have a safety follow-up visit at least 30 days (see Section 17) after the last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3.

Continuing care should be provided by the investigator and/or referring physician based on participant availability for follow-up. This care may include:

- Enrollment into another Cohort, if eligible and applicable

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early study or cohort termination may include but are not limited to:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible for an EOT visit and enter into the safety follow-up period as per their respective cohort. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grades
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. The investigator is obligated to assess the relationship between any treatment used in the study (study treatment) and each occurrence of each AE. The investigator will use clinical judgement to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

   The causality assessment is one of the criteria used when determining regulatory reporting requirements.
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Details for Safety Follow-up are outlined for each cohort in Section 17.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at

each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant’s general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant.” Examples of such events are

intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

1. SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized and Treated Participants: SAEs collected between time participant signs ICF until EOS safety follow-up visit.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or EU Clinical Trial Regulation 536/2014 as per national regulatory requirements in participating countries.

Subjects will be followed for all SAEs until their last study visit. Thereafter, the event should be reported to Novartis Safety only if the investigator considers the SAE to be related to study treatment, unless otherwise specified by local laws/ regulations.

SAEs that are ongoing when the subject completes or discontinues the study will be followed by the investigator until the event has resolved, stabilized, or returned to baseline status. SAE outcome will be recorded on the CRF, as applicable. Only SAEs that are unresolved will continue to be followed by the investigator.

10.1.3.1 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled preventative health procedure (e.g. colonoscopy) will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 10.1.2 is met.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational product any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant, or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-3. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate

- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - These investigations can include based on investigator's discretion: serology tests, imaging, and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational use, and special diets
  - Imaging such as abdominal US, CT, or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase > 2-fold compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 48-72 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-4.

10.3 Committees

10.3.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of the clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a cohort and/or trial. If the sponsor does not follow the recommendations of the DMC to halt or early terminate the study, respective health authorities (HAs) and IRBs/IECs will be notified.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow for modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate.

After database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked, **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. The database for each cohort may be locked independently of the other cohorts. Any changes to the database after that time can only be made after written agreement by appropriate Novartis management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data available at the time of the analysis. Unless otherwise specified, placebo data from each cohort will be pooled. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The main rationale for pooling the placebo data is to reduce the number of participants exposed to placebo. The difference between the placebos from different cohorts is expected to have little impact on the key efficacy endpoints.

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants who received any study drug.

The PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all participants with available PD data and no protocol deviations with relevant impact on PD data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented when applicable.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

12.3 Treatments

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to investigational drug will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis supporting primary objectives

The primary aim of the study is to assess the efficacy of the investigational products, compared to placebo in IPF participants. This will be evaluated by assessing change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in percent predicted (FVC%p). Reduction of the decrease in change from baseline is considered a favorable outcome.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is change from baseline in FVC%p.

12.4.2 Statistical model, hypothesis, and method of analysis

The treatment effect of the primary endpoint will be analyzed using a Bayesian random slope model to assess the difference in reduction rate (slope) between the treatment group and placebo group. The statistical model will include the intercept, time (as continuous variable), the interaction of treatment and time, the interaction of baseline FVC%p and time,

and the background therapy as fixed effect, and the intercept and slope of time for each participant as random effects. A robust weakly informative prior for the placebo time slope (based on 9 phase II and III studies after 2012 with total of 492 participants) will be used in the Bayesian analysis. The robustified informative prior for the change from baseline in FVC%p is comprised of 3 components of normal distributed random variables with the following information in terms of weight (W), mean (M), and standard deviation (S):

Table 12-1 Composition of the robust weakly informative prior for the placebo tie slope

	Comp1	Comp2	Comp3
W	0.526	0.174	0.300
M	-2.93	-2.75	-3.00
S	0.865	1.837	4.754

By using this prior slope of placebo, a 3% decline at week 26 from the baseline for the placebo group is expected. The impact of using this placebo prior means that there would be in effect 11 more placebo participants contributing to the data analysis. A non-informative prior will be used for the rest of the parameters, assuming the change from baseline in FVC%p has a normal distribution with mean=0 and a very large SD (e.g. 1.E6). The Bayesian posterior mean estimation of the treatment effect over placebo for change from baseline FVC %p at the end of treatment (26 weeks) will be derived. Statistical evidence of treatment effect will be concluded if the probability that the effect is better than placebo by 90% and there is at least 50% probability that the effect over placebo is >1.3%. No adjustments for multiplicity will be applied for this exploratory study.

12.4.3 Handling of intercurrent events of primary estimand

Not applicable.

12.4.4 Handling of missing values not related to intercurrent event

Missing data will not be imputed.

12.4.5 Sensitivity analyses

The same Bayesian model stated in Section 12.4.2 will be repeated using non-informative prior for the placebo group. The Bayesian posterior probability of the treatment effect (treatment - placebo) for the statistical evidence stated in Section 12.4.2 will be derived.

If a participant who was not on background therapy at randomization initiates treatment with background therapy during the study, the subject's data collected after the initiation of background therapy will be excluded from the primary analysis. However, a sensitivity analysis that includes the excluded data may be performed.

If a participant discontinues the original background therapy during the treatment period, a protocol deviation will be filled and the data generated from the participant will be included in the formal analysis. A sensitive analysis may be conducted further by excluding these data.

12.4.6 Supplementary analysis

Frequentist approach of linear mixed model will be conducted to further validate the statistical results from main analysis. The model will include all fixed and random effect stated in Section 12.4.2.

A second mixed model will also be fitted with the interaction of the background therapy category and the treatment in order to assess the treatment effect within each background therapy category.

Subgroup analyses might be conducted to justify the impact on the robustness of the statistical estimate when the situation of participants entering the multiple cohorts occurs. Detailed information will be specified in the statistician analysis plan (SAP).

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Efficacy

Change from baseline to end of treatment epoch (26 weeks of treatment) in Forced Vital Capacity (FVC) expressed in mL will be analyzed using a similar model stated in Section 12.4.2 with both treatment and placebo group using non-informative prior.

Summary statistics of change from baseline in FVC by visit and treatment will be presented.

Progression-free survival (PFS)

Time to progression is defined by a composite endpoint. At the end of the treatment epoch, the Kaplan-Meier estimates of the proportion of participants with the composite endpoint, along with 80% two-sided confidence intervals using Greenwood's formula, will be provided. In addition, the Kaplan-Meier estimates will be plotted against time.

The composite endpoint including ANY of the following events:

- Absolute reduction from baseline of ≥ 10% predicted in FVC
- Non-elective hospitalization for respiratory events
- Lung transplant
- Death

Individual components of the composite endpoint will be summarized separately and if sufficient data is available, then further appropriate statistical analyses will be conducted.

Incidence of absolute decline in FVC ≥ 10% predicted

Binary output of absolute decline of ≥ 10% predicted in FVC (Yes/No) at the end of treatment epoch (26 weeks of treatment) will be assessed using logistic regression model with absolute decline of ≥ 10% (Yes/No) as dependent variable, and the treatment as explanatory variable. Baseline FVC%p and use of background therapy may be included as potential covariates. The estimated rate of the absolute decline of ≥ 10% predicted in FVC by treatment group and the difference between the treatment and the placebo group will be presented together with 90% confidence intervals.

The number and percentage of participants with absolute decline of ≥ 10% predicted in FVC will be presented by epoch/visit and treatment.

Pulmonary physiology

To assess the impact of the IPs on pulmonary physiology, change from baseline to the end of treatment epoch (26 weeks of treatment) in DLCO will be analyzed by fitting the same model as described for the primary endpoint in Section 12.4.2 with non-informative priors on both treatment arms in addition to summary statistics by treatment.

Exercise capacity

To assess the impact of the IPs on exercise capacity, change from baseline to the end of treatment epoch (26 weeks of treatment) in 6-minute walk distance will be analyzed by fitting the same model as described for the primary endpoint in Section 12.4.2 with non-informative priors on both treatment arms in addition to summary statistics by treatment.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will be summarized from initial treatment through the end of the Safety Follow-up.

The safety follow-up period will be a minimum of 30 days and may vary within each cohort. See Section 17 for details.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to dose suspension and/or discontinuation.

Any adverse events of special interest will be outlined in Section 17.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and epoch/visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by epoch, treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment group, subject and epoch/visit/time, and abnormalities will be flagged. Summary statistics will be provided by epoch, treatment, and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and epoch/visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by epoch, treatment, and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Immunogenicity

All immunogenicity results will be listed by treatment group, participant, and visit/time, if applicable within the cohort. See Section 17.

12.5.3 Patient reported outcomes

L-IPF (Impacts and Symptoms Modules), K-BILD, Leicester cough, and R-Scale for IPF questionnaires score will be reported by treatment group, patients, and epoch/visit/time. Summary statistics on the change from baseline of PRO score at the end of the treatment epoch will be provided by treatment and visit time.

12.6 Analysis of exploratory endpoints

12.6.1 Efficacy and/or Pharmacodynamic endpoint(s)

Disease exacerbation

Time to IPF exacerbations or suspected exacerbations will be assessed using the statistical method mentioned in Section 12.5.1 “Time to event analysis”. In addition, number and percentage of exacerbations will be summarized by epoch/visit/treatment.

Exploratory Progression-free survival (PFS)

Time to progression as defined by a composite endpoint including any of the following events:

· Absolute reduction from baseline of ≥ 5% predicted in FVC

· Non elective hospitalization for respiratory events

· Lung transplant or death

Same statistical analysis specified in Section 12.5.1 “Time to event analysis” will be applied to this endpoint.

Pulmonary imaging

Change from baseline to the end of treatment epoch (26 weeks of treatment) in quantitative high-resolution computed tomography (qHRCT) structural and functional metrics (interstitial fibrotic features) will be reported using summary statistics by treatment.

12.6.2 Pharmacokinetics

In order to assess the pharmacokinetics of the investigational products after multiple doses, investigational product concentrations will be measured.

Concentration data for each analyte in a cohort will be listed by treatment, subject, and epoch/visit/sampling time point. Descriptive summary statistics may be provided by visit, treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics may include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Cohort specific pharmacokinetic parameters will be calculated as described in Section 17.

Graphical presentation may be provided in addition.

12.6.3 PK/PD relationships

Relationships between PK and PD variables may be explored using population PK. Additional statistical analysis such as analysis of variance (ANOVA) or regression analysis may be performed, if necessary.

Modeling of the PK and PD data may be performed as appropriate. As the PK and PD data from the current study may be pooled with data from previous studies, the PK/PD analysis will be described and reported separately in a modeling plan and modelling report respectively.

12.6.4 Biomarkers

Change from baseline in soluble markers (which may include but are not limited to CCI [redacted] in the peripheral blood and protein profiling to explore the markers reflecting the treatment response will be reported using summary statistics by epoch and treatment.

For all biomarker data (as applicable) summary statistics will be provided by cohort, treatment group and visit/time. As applicable, values above the upper limit of quantification (ULOQ) will be imputed as ULOQ in graphical summaries (with a special symbol) and for the calculation of the summary statistics, and values below the lower limit of quantification (LLOQ) will be imputed as LLOQ/2 for these analyses. The number of values outside of the limits of quantification will be reported in each table. All biomarker data, change from the baseline, percent change from baseline will be listed by cohort, treatment group, participants, and visit/time. Graphical summaries (including spaghetti plots, boxplots, and mean plots with SD) may be provided by treatment and visit/time. Values below the LLOQ will be imputed as LLOQ/2 for these analyses. The number of values outside of the limits of quantification will be reported in each table.

CCI [redacted].

12.6.5 DNA

Exploratory DNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g. CSR addendum).

12.7 Interim analyses

In addition to those listed below, other interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

12.7.1 Cohort Completion Analyses

Data will be analyzed at the completion of each cohort in the trial.

Cohort completion analyses are planned when participants complete each cohort (End of Treatment). The unblinded analysis results including efficacy and safety assessment will be reviewed by the clinical team and further shared with Novartis teams and members of the DMC. The data will be used to determine if the noted efficacy was sufficient to allow early transition of the respective IP to a later stage study.

12.7.2 Within each cohort

Interim analyses are planned when sufficient participants complete their 26-week post-treatment assessments in each cohort (approximately 50%). Data from participants who have completed their 26-week post-treatment assessment and data from participants who have not completed the treatment epoch but have post-treatment assessments at the time of the IA will be included. The purpose of this unblinded IA is to assess early efficacy and to assess futility. The key endpoint to be evaluated at this IA will be the change from baseline in FVC %predicted.

There will be no pause in enrollment at the time of interim analysis, and participants may continue to be enrolled until the interim analysis is complete.

The Bayesian posterior probability of the treatment effect (treatment – placebo) will be calculated for the endpoint. If there is more than 60% probability that the treatment effect at the end of treatment epoch (26 weeks of treatment) is <0 (treatment worse than placebo), then this will act as evidence to suggest that the investigational product has not had a beneficial effect on the endpoint in this population. This data, together with other key endpoints, will be used to assess whether the cohort could be stopped for futility.

Similarly, if there is enough information at this interim analysis to conclude that there is 90% posterior probability that the treatment effect is >0 (treatment better than placebo) in the endpoint, and there is 50% posterior probability of the treatment effect > 1.3%, then this information, together with other key endpoints, will be used to consider early evidence of efficacy and decision of launching later stage of the clinical trials for the respective investigational product.

If the study is not stopped for futility or for early evidence of efficacy at the time of the IA, the cohort will continue until all participants have completed the cohort.

Within cohort IAs, unblinded interim analysis results will be reviewed by the clinical team. The clinical team may communicate interim results (e.g. evaluation of efficacy criteria or information needed for planning/modifying another study) to relevant Novartis teams and members of the DMC.

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study's participants or assessing clinical data (e.g. ECGs, images, symptoms) obtained in the study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Without considering the drop-off rate,40 participants per active treatment group and at least 40 participants on placebo of each cohort will give at least 80% power to detect a treatment improvement in change from baseline in FVC%p (treatment – placebo) for at least 2% in patients with IPF assuming the standard deviation is around 5%.

The sample size calculation is based on the primary efficacy endpoint of change from baseline in FVC%p at week 26. The criteria for this calculation aimed for a 90% level of proof that difference in change in FVC%p from baseline to week 26 between treatment and placebo and the mean treatment effect is at least 1.3% better than placebo effect with 50% probability. The former targets proof that the treatment produces a statistically significant improvement in change from baseline in FVC, while the latter targets proof of clinical relevance.

The sample size calculation also takes into account the interim analysis step with futility and early efficacy criteria defined in Section 12.7. The overall type I error at the end of study will be approximately 13%.

Additional participants may be enrolled if more than 15% of the planned randomized participants have not completed the 26 weeks of treatment, as per protocol requirements. Prior to enrolling additional participants, a DMC review of safety data will occur to ensure there are no tolerability/safety issues that would advise against enrolling additional participants.

Refer to Section 17 for cohort specific sample size after considering drop off rate and randomization ratio between the treatment group and placebo group.

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after cohort completion (defined as cohort last participant last visit) and finalization of the cohort study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT or CTIS public website etc.).

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you.

Any data analysis carried out independently by the Investigator must be submitted to Novartis before publication or presentation.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring, or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols, and internal SOPs, and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You card
- Treatment information
- Plain language trial summary

14 Protocol adherence

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST, and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 16-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	• Discontinue study drug
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-3 Isolated total bilirubin elevation

Criteria	Recommendation
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to local institutional guidelines.
Grade 2 (>1.5 – 3.0 ULN)	Maintain treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
Grade 3(>3.0 - 10 ULN)	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
Grade 4(>10 x ULN)	Discontinue study treatment

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase > 2-fold compared to baseline	Consider causes and possible interventions Follow up within 2-5 days
Urine Event	
New onset dipstick proteinuria >=+3 OR	Consider causes and possible interventions Assess serum albumin & serum total protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset dipstick hematuria >=+3	Repeat assessment to confirm Distinguish hemoglobinuria from hematuria Urine sediment microscopy Assess serum Creatinine Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed	
Monitor subject regularly (frequency at investigator's discretion) until either:	
Event resolution: sCr within 20% of baseline or	
Event stabilization: sCr level with +-20% variability over last 2 months	

17 Cohort Specific Information

This section contains details that pertain to specific cohorts and should be considered as supplementary to information presented in the preceding core protocol sections and respective Investigator Brochures or country-specific product labels for marketed investigational products. If there are no cohort- or treatment-specific details presented for a given topic (e.g. cohort- or treatment-specific eligibility criteria, study restrictions, food effects, etc.), the information in the corresponding section in the core protocol for that topic should be implemented without further adjustment.

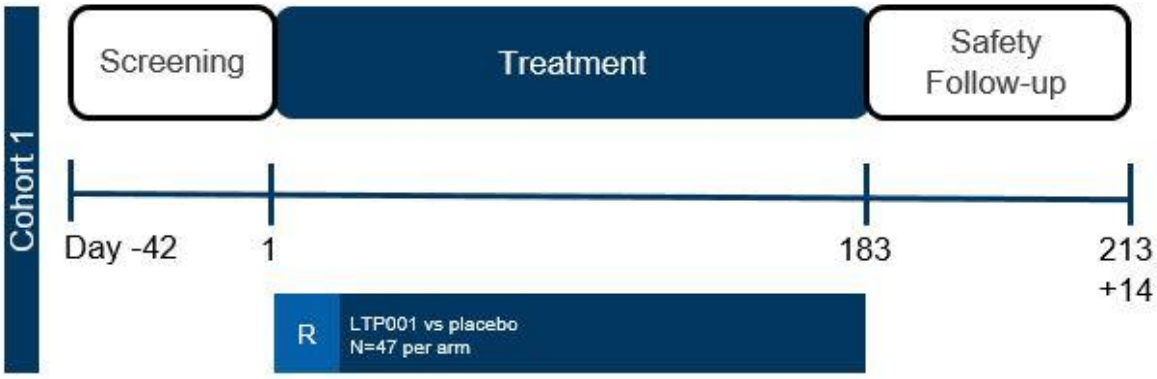
17.1 Cohort 1 LTP001

Cohort 1 will assess the safety and efficacy of LTP001 in participants with mild to moderate IPF.

Approximately 94 patients will be randomized in a 1:1 ratio to one of the following treatment arms:

- Arm 1: LTP001 [redacted] mg CCI [redacted]
- Arm 2: Matching placebo

Figure 17-1 Cohort 1 Study Design



R = Randomization

17.1.1 Introduction

This cohort will evaluate LTP001. CCI [redacted]

CCI [redacted]

17.1.2 Background

CCI [redacted]

Preclinical Data

CCI [redacted]

Clinical Data

CCI [redacted]

CCI

[redacted]

Dosing Rationale

CCI

[redacted]

CCI [redacted]

Additional details about dosing and potential risks of LTP001 can be found in the Investigator's Brochure.

Procedural risks

CCI [redacted]

Potential Benefits

CCI [redacted]

17.1.3 Study Treatment

CCI [redacted]

Table 17-1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

17.1.4 Specific Exclusion Criteria

101. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception for 3 months prior to screening, during dosing, and until End of Study visit (30 days post last treatment). Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Bilateral tubal ligation, surgical bilateral oophorectomy with or without hysterectomy, total hysterectomy, or bilateral salphingectomy at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is not considered to be of child-bearing potential.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

102. Sexually active males must use a condom during intercourse while taking drug and for 24 hours after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of

the drug via seminal fluid. In addition, male participants should not donate sperm while taking drug and for 24 hours after stopping study medication.

CCI [redacted]

17.1.5 Specific Restrictions for Study Participants

No specific restrictions for the LTP001 cohort.

17.1.5.1 Prohibited Medications

Use of the treatments displayed in the below table are not allowed.

Table 17-2 CCI [redacted]

CCI [redacted]

17.1.6 Permitted concomitant therapy requiring caution and/or action

Not applicable for LTP001.

17.1.7 CCI [redacted]

CCI [redacted]

[redacted]

Table 17-3 CCI

17.1.8 Pharmacokinetics

PK samples will be collected at the visits defined in Table 17-3. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data.

PK samples will only be evaluated in participants on active treatment.

LTP001 will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 0.05 ng/mL.

Concentrations will be expressed in mass per volume units and will refer to the free base.

Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

17.1.8.1 Pharmacokinetic analytical method(s)

Descriptive summary of LTP001 plasma concentration data will be provided by treatment, and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum.

Appropriate PK parameters e.g. Cmax, Tmax, and partial AUCs may be assessed using non-compartmental analysis (Certara Phoenix). The sparse sampling may limit potential parameter estimation. A population PK model may also be used for PK analysis.

17.1.9 Exploratory Biomarkers

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 17-3). The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study. Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

Target engagement markers of LTP001 may include but are not limited to CCI [redacted]).

RNA sequencing

The expression of targeted genes will be examined using RNA (or other nucleic acid) analytical technologies, such as expression microarrays, polymerase chain reaction, Nanostring, Next Generation Sequencing techniques, or others.

17.1.10 Specific Study Design Considerations

The post-treatment safety follow-up in Cohort 1 will be 30 (+14) days following the last drug administration.

CCI [redacted]

[redacted]

Table 17-4 LTP001 Specific Safety Assessments

Test Category	Test Name
Thyroid	Triiodothyronine, Free/Total Thyroxine, Thyroid stimulating hormone
Endocrine Function Tests	Aldosterone, Cortisol, Insulin-like growth factor 1, Adrenocorticotropic hormone, Testosterone

17.1.11 Statistical considerations

17.1.11.1 Sample size calculation

As the first cohort in this platform study, the randomization ratio between the treatment group and placebo group is determined as 1:1. Assuming the drop-off rate of 15% Raghu et al 2018b, 47 patients will be randomized into each treatment group with a total of 94 patients for this cohort. The sensitivity of power to changes in assumptions with different drop off rate is listed in Table 17-5.

Table 17-5 Sensitivity of power to changes in assumptions for N=47 per group

True treatment difference for LTP001 vs Placebo (%)	Power for primary endpoint (type I error around 10%)		
	With 10% drop-out rate (38 per group)	With 15% drop-out rate (40 per group)	With 20% drop-out rate (43 per group)
1.6	64%	65%	65%
1.8	72%	72%	73%
2	79%	79%	80%
2.2	84%	85%	85%
2.4	89%	89%	90%