Clinical Trial Protocol

	Document Number:	**c37763552-05**
EudraCT No.	2022-001134-11	
BI Trial No.	1305-0023 (FIBRONEER™ – ILD)	
BI Investigational Medicinal Product	BI 1015550	
Title	A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)	
Lay Title	A study to find out whether BI 1015550 improves lung function in people with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)	
Clinical Phase	Phase III	
Clinical Trial Leader	[redacted] Phone: [redacted]	
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]	
Current Version and Date	Version 4.0, 21 Sep 2023	
Original Protocol Date	Version 1.0, 29 Jun 2022	**Page 1 of 147**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date **Latest revision date**	29 Jun 2022 21 Sep 2023
BI trial No.	1305-0023
Title of trial	A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)
[redacted]**Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Trial sites	Multi-center trial conducted in approximately 400 sites and in 45 countries
Clinical phase	Phase III
Trial rationale	The purpose of this trial is to evaluate the efficacy, safety, and tolerability of BI 1015550 9 mg bid and 18 mg bid compared to placebo in patients with progressive fibrosing ILDs in addition to patient's standard of care over the course of at least 52 weeks. New treatments with better tolerability are needed for patients with ILDs to further reduce the decline in lung function and improve quality of life. Based on its anti-inflammatory and antifibrotic properties and the preliminary clinical evidence described, BI 1015550 may provide an additional treatment option to patients with progressive pulmonary fibrosis irrespective of concomitant treatment with standard of care.
Benefit-risk assessment and ethical considerations	Patients with progressive fibrosing ILDs who receive treatment with BI 1015550 have the potential benefit of slowing lung function decline, improving symptoms, and improving quality of life over a long-term period. The toxicology data support administration of BI 1015550 to women and men in the planned Phase III clinical trials in patients with IPF and other forms of progressive pulmonary fibrosis irrespective of background antifibrotic treatment, except for women who are pregnant or breastfeeding. Data from the Phase II trial 1305-0013 in patients with IPF indicated a beneficial treatment effect of 18 mg BI 1015550 bid, with the preservation of Forced Vital Capacity (FVC) over 12 weeks together with an acceptable safety and tolerability profile supporting further investigation in Phase III clinical trials as a treatment for progressive fibrosing ILDs.

Trial objectives	The primary objective is to demonstrate a reduction in lung function decline as measured by the change from baseline in FVC for BI 1015550 when compared to placebo in patients with progressive fibrosing ILDs. The main secondary objective of the trial is to demonstrate BI 1015550's ability in reducing the occurrence of clinically meaningful events such as acute ILD exacerbation, hospitalization for respiratory cause or death over the duration of the trial when compared to placebo in patients with progressive fibrosing ILD. An additional secondary objective of the trial is to show an effect of BI 1015550 on symptoms and lung function.
Trial endpoints	The primary endpoint is the absolute change from baseline in FVC [mL] at Week 52. The key secondary endpoint in this trial is time to the first occurrence of any of the components of the composite endpoint: time to first acute ILD exacerbation, first hospitalization for respiratory cause, or death (whichever occurs first) over the duration of the trial.
Trial design	A multi-center, multi-national, prospective, randomized, placebo-controlled, double blind clinical trial to investigate the efficacy and safety of BI 1015550 at a dose of 9 mg bid and 18 mg bid in patients with progressive fibrosing ILDs over at least 52 weeks.
Total number of patients randomized	Approximately 1041 patients
Number of patients per treatment group	Approximately 347 patients in both active treatment groups and in the placebo group.
Diagnosis, main inclusion and exclusion criteria	Inclusion criteria: • Patients ≥18 years old at the time of signed consent • Progressive fibrosing ILD other than IPF based on predefined criteria • FVC ≥45% of predicted normal • DLCO ≥25% of predicted normal corrected for hemoglobin (Hb) • On stable treatment with nintedanib for at least 12 weeks or not on treatment with nintedanib for at least 8 weeks Exclusion criteria: • Prebronchodilator FEV1/FVC <0.7 • Acute ILD exacerbation within 3 months and/or during the screening period • Treated with prednisone >15mg/day or equivalent within 4 weeks; cyclophosphamide, tocilizumab, mycophenolate, pirfenidone within 8 weeks; rituximab within 6 months • Active, unstable or uncontrolled vasculitis within 8 weeks • Any suicidal behavior in the past 2 years • Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months
Trial intervention and test product	BI 1015550

Dose and mode of administration	9 mg bid, oral 18 mg bid, oral
Comparator product	Placebo
Dose and mode of administration	Matching, oral
Duration of treatment	At least 52 weeks and up to approximately 130 weeks
Statistical methods	This trial's primary objective is to demonstrate the ability of BI 1015550 to reduce lung function decline based on FVC between baseline and at Week 52 when compared to placebo. Primary analysis for primary endpoint will be restricted maximum likelihood estimation based on a mixed-effect model for repeated measures (MMRM) analysis to compare change from baseline in FVC at Week 52 between treatment groups. This model will include discrete fixed effects for treatment at each visit, baseline intake of antifibrotic treatment at each visit, HRCT pattern at each visit, and continuous fixed effects for baseline FVC value at each visit. Once the last randomized patient completes the Week-52 assessment, the main analysis of the trial will be carried out by the sponsor, who will be unblinded to assess the benefit-risk of the two doses of BI 1015550 compared with placebo. Patients will remain on their randomized blinded treatment until the sponsor has reviewed the efficacy and safety data from the main analysis and communicated the end of the trial. Once this trial ends, a final analysis based on all data will be carried out.

FLOW CHART

Trial Periods	**Screening**	**Treatment Period A**									**Treatment Period B**		**Follow up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[1]**	**Every 12 weeks[1]**	**EOT[2]**	**EOS[17]**
Week	Up to -8 weeks to -1 week*	1	2	6	12	18	26	36	44	52			
Day		1	15	43	85	127	183	253	309	365			EOT +7d
Time window (days)			±3d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d		+3d
Informed consent	X												
Demographics	X												
Review of eligibility criteria	X	X											
Medical history	X												
Smoking Status	X												
L-PF (symptoms/impacts)[3]		X			X		X	X	X	X	X	X	
EQ-5D[3]		X		X	X	X	X	X	X	X	X	X	
HADS[3]	X	X			X		X	X	X	X	X		X
PGIS[3]		X			X		X	X	X	X	X	X	
C-SSRS[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
SpO2		X			X		X			X		X	
12-lead ECG	X				X					X		X	
Chest HRCT central Review[6]	X												
Spirometry[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Optional home spirometry[8]		X	X	X		X		X	X		X		
DLCO	X	X			X		X			X		X	
Laboratory test[9]	X	X		X	X		X	X	X	X	X	X	X
Vasculitis biomarkers storage[10]		X								X			
Pregnancy test[11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection testing[12]	X									X		X	
PK Sampling[13]			X	X	X		X						
ILD biomarkers sampling		X		X	X		X			X		X[14]	
DNA Banking (optional)[15]		X											
Serum/Plasma Banking (optional)[15]		X			X		X			X			
Health Care resource Utilization		X	X	X	X	X	X	X	X	X	X	X	
All AEs/SAEs/ AESIs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense trial drug		X		X	X	X	X	X	X	X	X		
IRT Call/Notification	X	X		X	X	X	X	X	X	X	X	X	

Trial Periods	Screening	Treatment Period A									Treatment Period B		Follow up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[1]**	**Every 12 weeks[1]**	**EOT[2]**	**EOS[17]**
Week	Up to -8 weeks to -1 week*	1	2	6	12	18	26	36	44	52			
Day		1	15	43	85	127	183	253	309	365			EOT +7d
Time window (days)			±3d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d		+3d
Administer trial drugs		X	X	X	X	X	X	X	X	X	X	X	
Return trial drug			X	X	X	X	X	X	X	X	X	X	
Compliance check			X	X	X	X	X	X	X	X	X	X	
Completion of patient participation												X[17]	X
Vital status data[18]										X		X	

* Screening may be extended up to 12 weeks to account for possible missing eligibility results, administrative, or organizational reason.

([1]) Following completion of V10 patients will continue to have study visits every 12 weeks until the start of EoT visits is announced. The global study will be completed after all patients have performed the EoT visit and the EoS visit (if not continuing in the separate extension trial).

([2]) In case of premature discontinuation of trial medication, the EOT visit should only be done if the discontinuation is permanent, and a Follow-up (FU) visit is to be performed 7 days (+3 days) after end of treatment. If a patient discontinued the trial medication more than a week prior to the EOT visit, this FU visit is not required. A scheduled visit may be missed if EOT or FU visit occurs within 4 weeks prior to scheduled visits. After the premature EOT, every effort should be made to collect data until the end of the trial.

([3]) Patient-reported outcomes collected either on paper questionnaires or as ePRO, at home within 3 days before the site visit or at the site visit. At the latest, the patients' questionnaires must be completed prior to the pulmonary function tests.

([4]) At Visit 1, the C-SSRS version to be used is the "screening/baseline" one. At all other visits, the version of C-SSRS to be used is the version "since last visit".

([5]) Vital signs will be taken as one measurement at predose.

([6]) Send chest HRCT not older than 12 months for central review. If the patient does not have a HRCT within 12 months of Visit 1 or the available HRCT scan fails to meet the required image acquisition specification, a new HRCT can be performed and submitted provided the patient meets all other inclusion and no exclusion criteria. To perform a HRCT within the trial, all local regulatory requirements to perform an HRCT have to be met. In Germany, no HRCT will be performed as trial procedure; only historical HRCT will be submitted.

([7]) Order of lung function measurements: 1. FVC followed by patient's rest; 2. DLCO: Two DLCO measurements will be performed approximately at the same time of the day, at least within the same half-day (morning vs. afternoon, reference time at Visit 2).

([8]) Assisted home spirometry will be offered at selected centers where every patient should have a training and measurement with the device ideally at Visits 2 or 3. If the requirement to use the iSpiro appears later in the trial, then this timepoint can be shifted. Remote measurement can be performed as per investigator's judgement but should not replace the on-site FVC measurement at Visits 2, 5, 7, 10, and EOT.

([9]) Safety laboratory tests will be performed predose. This includes blood and urine collection. Of note, in case of a suspected vasculitis event, additional blood sampling is required. For details please see Section 5.2.3.

([10]) Additional blood sample to be taken for storage and analysis in case of vasculitis adverse event during the trial.

([11]) Women of childbearing potential only. Serum pregnancy test to be performed at V1; urine dipstick pregnancy test to be performed at V2 and following visits (if positive, urine dipstick test to be followed by serum test for confirmation). More frequent pregnancy testing may be done if required.

([12]) Infection testing includes HBV, HCV, HIV, and tuberculosis (Section 5.2.3.2).

([13]) PK samples to analyze BI 1015550 will be collected predose (before drug administration).

([14]) Only drawn if EOT is performed at 52 weeks (study completion phase).

([15]) Collection of biobanking samples (plasma, serum, DNA) is optional and is not a prerequisite for participation in the trial. Only for patients who signed a separate informed consent. DNA sample will be taken at Visit 2 preferably or at any subsequent visit until EOT.

([16]) Includes assessment of exacerbations, hospitalizations for respiratory cause, vasculitis, and diarrhea

Footnotes continue on next page

([17]) Patients may be eligible to enter an extension trial if they complete this study on blinded treatment and meet the eligibility criteria for the extension trial.
For patients who complete all study visits and roll over to extension trial, end of study is EOT. A follow-up visit (EOS) is only required for those who do not roll-over in the separate extension trial (or could not roll-over within a week of EOT visit) and if the last drug intake was less than 7 days before the EOT visit.

([18]) Patients who discontinue trial treatment prematurely and have agreed to be contacted, should be called at least at the end of the 12-month observation period (52 weeks) and at the end of their scheduled trial participation to obtain their vital status information.

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Antifibrotic
ALAT	Latin American Thoracic Association
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
ANCA	Antineutrophil cytoplasmic antibodies
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the Curve
AZA	Azathioprine
BI	Boehringer Ingelheim
bid	bis in die (twice daily dosing)
BMI	Body Mass Index
CA	Competent Authority Cancer Antigen
cAMP	Cyclic Adenosine Monophosphate
CI	Confidence Interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
$C_{pre,ss}$	Predose Concentration of Analyte in Plasma at Steady State
(e)COA	(electronic) Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
(e)CRF	(electronic) Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report

CYP	Cytochrome P450
DBL	Database Lock
DILI	Drug Induced Liver Injury
DLCO	Diffusing Capacity (of Lung) for Carbon Monoxide
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eDC	Electronic Data Capture
EDMS	Electronic Document Management System
EDTA	Ethylenediaminetetraacetic Acid
eGFR	Estimated glomerular filtration rate
EOS	End of Study (corresponds with End of Trial)
EOT	End of Treatment
ePRO	Electronic Patient-Reported Outcome
EQ-5D	EuroQol 5 Dimensional Quality of Life Questionnaire
ERS	European Respiratory Society
ES	Entered Set
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EuroQol	European Quality of Life Group
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FU	Follow-up
FVC	Forced vital capacity
GBM	Glomerular Basement Membrane
GCP	Good Clinical Practice
GGT	Gammaglutamyl transferase
GLI	Global Lung Initiative
gMean	Geometric Mean
GMP	Good Manufacturing Practice
HA	Health Authority
HADS	Hospital Anxiety and Depression Scale
HBV/HCV	Hepatitis B or C Virus
HCRU	Health Care Resource Utilization
HIV	Human Immunodeficiency Virus
HPLC-MS/MS	High Performance Liquid Chromatography with Tandem Mass Spectrometry
HR	Hazard Ratio

HRCT	High-resolution Computed Tomography
i.v.	Intravenous
IB	Investigator's Brochure
IC_{50}	mean half-maximal inhibition
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMS	Isotope Dilution-mass Spectrometry
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
ILD	Interstitial Lung Disease
IMP	Investigational Medical Product
INN	International Non-Proprietary Name
INR	International Normalized Ratio
IPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISO	International Organization for Standardization
iSpiro	Handheld spirometer
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IXRS	Interactive Voice/Web Response Software
JRS	Japanese Respiratory Society
LABA	Long Acting Beta Agonist
LAMA	Long Acting Muscarinic Antagonist
LOAEL	Lowest Observed Adverse Effect Level
L-PF	Living with Fibrosis Symptoms and Impact Questionnaire
LPLT	Last patient last treatment
LPLV	Last patient last visit
LPS	Lipopolysaccharide
LTFU	Lost To Follow Up
MACE	Major Adverse Cardiovascular Event
MAR	Missing At Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration

MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Drug Regulatory Activities
mmHg	Millimeters Mercury
MMRM	Mixed-model repeated measures
MRD	Multiple Rising Dose
mRNA	Messenger Ribonucleic Acid
miRNA	Micro Ribonucleic Acid
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NOAEL	No observed adverse effect level
OC	Oral contraceptive
OPU	Operative Unit
p.o.	per os (oral)
PCR	Polymerase Chain Reaction
PDE	Phosphodiesterase enzyme
PDE4B	Phosphodiesterase 4B
PDE4i	Phosphodiesterase inhibitor
PF	Pulmonary Fibrosis
PF-ILD	Progressive Fibrosing Interstitial Lung Disease
PFT	Pulmonary Function Test
PGIS	Patient's Global Impression of Severity
PGx	Pharmacogenomics
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PPD	Purified Protein Derivative
PRO	Patient-Reported Outcome
PT	Preferred Term Prothrombin Time
PV	Pharmacovigilance
RA	Regulatory Authority
RBC	Red blood cells
RDW	Red Cell Distribution Width
REML	Restricted maximum likelihood
REP	Residual effect period
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RS	Randomized Set
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event

SAMA	Short-acting muscarinic antagonist
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SC	Steering Committee
SD	Standard Deviation
SMC	Safety Monitoring Committee
SMQ	Standardized MedDRA Queries
SoC	Standard of Care
SOP	Standard Operating Procedure
SpO2	Oxygen Saturation
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half-life time
TB	Tuberculosis
TBLC	Transbronchial lung cryobiopsy
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial Master File
TNF-α	Tumor Necrosis Factor alpha
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UGT	Uridine Diphosphoglucuronosyl Transferase
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
US	United States
V	Visit
vs.	Versus
vWF	von Willebrand Factor
WBC	White blood cells
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

BI 1015550, a preferential inhibitor of the phosphodiesterase 4B (PDE4B) isoenzyme which hydrolyzes and inactivates cyclic adenosine monophosphate (cAMP), is being developed by Boehringer Ingelheim (BI) for the treatment of idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis.

1.1 MEDICAL BACKGROUND

IPF and other progressive fibrosing ILDs (PF-ILDs) share common pathophysiologic characteristics; alveolar epithelial cell injury and subsequent dysregulated repair, characterized by excessive deposition of extracellular matrix and loss of normal parenchymal architecture and lung function [P11-07084]. In IPF, fibroblasts exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis [P12-03241]. Several growth factors are implicated in the proliferation, migration and transdifferentiation of the fibroblast and myofibroblast pool in pulmonary fibrosis.

As of date, nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and recommended in the recent guideline *Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline* [P22-03204]. Nintedanib is also approved in the US, the European Union and many other countries for the treatment of other fibrosing ILDs with progressive phenotype and recommended in the above guidelines for the treatment of Progressive Pulmonary Fibrosis. Despite the availability of these drugs, the medical need remains high in these devastating diseases.

1.2 DRUG PROFILE

BI 1015550 is an oral preferential inhibitor of the PDE4B with broad anti-inflammatory and antifibrotic activities. Based on its mode of action, BI 1015550 is hypothesized to have complementary activity to current therapies in IPF and other forms of progressive pulmonary fibrosis. BI 1015550 shows a mean half-maximal inhibition (IC_{50}) at 10 nM, with a nine-fold selectivity over phosphodiesterase 4D (PDE4 D; mean IC_{50} 91 nM) without relevant known interaction with other targets (78 receptors and 42 enzymes tested at the very high concentration of 10 000 nM). In-vitro anti-inflammatory activity has been confirmed for TNF-α (IC_{50}: 12 nM) and IL-2 release (IC_{50}: 5 nM) from purified human peripheral blood mononuclear cells.

Data from non-clinical toxicology studies

The toxicity profile for BI 1015550 has been assessed in safety pharmacology studies, genetic toxicity studies, and repeat dose toxicity studies in the rat, minipig, and monkeys of up to 26, 39, and 39 weeks, respectively. In addition, a fertility and early embryonic development (rat) and embryo-fetal development toxicity studies (rat and rabbit) were conducted. Decreased mating, fertility, and pregnancy indices were observed in male and female rats at a dose level that also caused evidence of severe toxicity in both sexes. In rats but not in rabbits fetal loss was increased. Teratogenicity and fetotoxicity was not observed. In long-term toxicity studies in rats (26 weeks), minipig (39 weeks) and monkeys (39 weeks) there was no microscopic evidence of changes in female reproductive organs or on male spermatogenesis. A sporadic menstrual cycle prolongation was observed in the 39-week study in female monkeys receiving ≥10 mg/kg/day, i.e., at approximately 4-fold human exposure at 18 mg bid. Vasculopathy and mortality secondary to vasculopathy are the primary findings defining the NOAEL and LOAEL in the rat and minipig, respectively. In contrast, vascular changes were not observed in 13-week and 39-week monkey studies at 30 mg/kg/day, supporting the decreased sensitivity of primates to PDE4i-induced vascular changes. Vasculopathy is a well characterized class-effect pathology associated with PDE4 inhibitors [R10-1559] and has not been demonstrated in humans administered marketed PDE4i apremilast and roflumilast.

Data from clinical studies

Treatment with BI 1015550 at 18 mg twice daily in a Phase II proof-of-concept trial preserved lung function in patients with IPF over a period of 12 weeks, either as a monotherapy or on top of approved antifibrotic standard of care (nintedanib or pirfenidone).

BI 1015550 showed acceptable safety and tolerability in the overall study population and in the subgroups of patients without or with background antifibrotic treatment.
In this trial 97 patients were exposed to BI 1015550 and 50 patients to placebo. The most frequently reported AEs were gastrointestinal disorders (32.0% in the BI 1015550 group, 24.0% in the placebo group). Diarrhea was the most common AE, with a higher frequency in the BI 1015550 group (23.7%) than in the placebo group (12.0%) and diarrhea was also the most common event leading to treatment discontinuation (3 patients, all in the BI 1015550 group and all on background treatment with nintedanib). However, the majority of diarrhea events were mild in intensity.
AEs leading to discontinuation of trial treatment were only observed in the BI 1015550 treatment group. Apart from the mentioned 3 patients with diarrhoea and 2 patients with COVID-19, all events occurred in single patients without any pattern or cluster.
Serious adverse events were reported in 10.0% of patients in the placebo group and 6.2% of patients in the BI 1015550 treatment group. There were two events with fatal outcome in the BI 1015550 treatment group, one patient with COVID-19 pneumonia and one patient with suspected IPF exacerbation and suspected vasculitis (the diagnosis of vasculitis could not be confirmed by the sponsor nor the independent external data monitoring committee). Risk factors were present in both fatal events.
There were no clinically relevant changes in vital signs (including body weight) and/or ECG parameters (including QTc) observed. No changes in the C-SSRS and no AEs of suicidal ideation or behavior were reported during trial treatment.

The primary endpoint for efficacy in this trial was met, with a relevant treatment effect in favor of BI 1015550 on the change from baseline in FVC at 12 weeks in patients with IPF. Treatment with BI 1015550 preserved FVC irrespective of background antifibrotic treatment, in contrast to the placebo groups in which a marked decline in FVC was observed. (non-AF stratum: -95.62 ± 30.75 mL under placebo vs. 6.10 ± 22.90 mL with BI 1015550; AF stratum: -77.70 ± 23.60 mL under placebo vs. 2.72 ± 18.13 mL).

Overall, in Phase Ic and II trials in patients with IPF, BI 1015550 at a dose of 18 mg bid for up to 12 weeks showed acceptable safety and tolerability, both in patients without or with background antifibrotic treatment (nintedanib or pirfenidone).

For a more detailed description of the BI 1015550 profile, please refer to the Investigator's Brochure (IB) current version [c02094779].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The purpose of this trial is to evaluate the efficacy, safety, and tolerability of BI 1015550 9 mg bid and 18 mg bid compared to placebo in patients with progressive fibrosing ILDs in addition to patient's standard of care. This trial's primary objective is to demonstrate the ability of BI 1015550 to reduce lung function decline based on Forced Vital Capacity (FVC) between baseline and Week 52 when compared to placebo.

Efficacy and safety of BI 105550 will be assessed in patients with progressive fibrosing ILDs both on approved antifibrotic therapy (i.e. nintedanib) (AF group) or not on an antifibrotic background therapy (non-AF group).

Despite the availability of nintedanib as antifibrotic therapy, there remains a high unmet medical need for more efficacious and better tolerated treatments for patients living with progressive fibrosing ILDs. Currently available treatments reduce the decline in FVC compared to placebo, but do not completely stop the deterioration of lung function over time; patients still experience worsening of symptoms and quality of life or experience exacerbations of their disease. Mortality remains high in this patient population. Suboptimal tolerability with current treatment options is an unmet need that can impact patient's ability to remain on standard of care.

Based on its anti-inflammatory and antifibrotic properties and the preliminary clinical evidence described, BI 1015550 may provide an additional treatment option to patients with pulmonary fibrosis irrespective of concomitant treatment with currently approved antifibrotics as standard of care.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

IPF and other progressive fibrosing ILDs are serious debilitating conditions characterized by worsening symptoms and quality of life, progressive loss of lung function, ultimately resulting in respiratory failure, and early death. At the same time, the currently approved antifibrotic treatments have limitations: they do not impact symptoms and cannot stop or reverse fibrosis, i.e. the disease trajectory.

Data from the Phase II trial 1305-0013 in patients with IPF indicated a beneficial treatment effect of 18 mg BI 1015550 bid, with the preservation of FVC over 12 weeks together with an acceptable safety and tolerability profile supporting further investigation in Phase III clinical trials as a treatment for IPF and other forms of progressive pulmonary fibrosis. Patients with IPF and other forms of progressive pulmonary fibrosis who receive treatment with BI 1015550 have the potential benefit of slowing lung function decline, improving symptoms, and improving quality of life over a long-term period.

1.4.2 Risks

There are no identified risks (side effects) for BI 1015550, based on the toxicology program or any clinical trials conducted for this product to date. Vasculitis and fetal loss are considered as important potential risks based only on nonclinical findings.

Apart from risks related to trial procedures, the risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs and from nonclinical and clinical data of compounds with a comparable mode of action. For clinical data including adverse events reported during clinical trials with BI 1015550 please refer to Section 1.2.

Table 1.4.2: 1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 1015550: compound/class specific (refer to Section 1.2)		
[redacted]		
Vasculitis	• Vasculopathy is an established nonclinical toxicity of PDE4 inhibitors. • Vasculitis has been shown in both the rats and minipigs following oral administration of BI 1015550 but not in 13- or 39-week studies in monkeys. • Vasculitis is listed as an important potential risk in the RMP for the marketed PDE4- inhibitor apremilast. • In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans	• Active vasculitis (unstable or uncontrolled) is an exclusion criterion. • Vasculitis assessment as part of AE questioning • Close clinical monitoring for AEs of vasculitis • Assessment of (suspected) vasculitis events by independent adjudication and data monitoring committee. Treatment interruption in case of any vasculitis adverse event. Restart only if not BI 1015550 related and considered acceptable by the investigator
Weight decrease in underweight patients (BMI <18.5 kg/m^2)	• For the marketed PDE4-inhibitors apremilast and roflumilast weight loss in underweight patients is an identified important risk. [redacted]	• Body weight evaluated regularly during the trial. • Patients who have a BMI <18.5 kg/m^2, and subsequently experience unexplained and clinically significant weight loss (>10%) will be discontinued from trial treatment.
Psychiatric disorders: • Depression and anxiety • Suicidality	• For the marketed PDE4 inhibitors depression is listed as a side effect. They are associated with increased risk of depression with some patients reporting suicidal ideation and/or attempts, with some reported cases of completed suicide. • High incidence of depression in the ILD population per se. • In IPF patients treated with 18 mg BI 1015550 bid for up to 12 weeks, no on-treatment events of suicidal ideation or behavior and no events of depression or anxiety were reported	• Acute or chronic severe depression defined as Hospital Anxiety and Depression Scale (HADS) subscore >14 at screening will be excluded • Any suicidal behavior in the past 2 years and any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the past 3 months or at Visit 1 are exclusion criteria. • Prospective monitoring for depression and anxiety will be performed using the HADS and the C-SSRS

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		• Patient's withdrawal criteria in case of new-onset severe depression defined as HADS subscore >14 and/or suicidal behavior or any suicidal ideation of type 4 or 5 in the C-SSRS.
Severe Infections including, serious, opportunistic and *Mycobacterium tuberculosis* infections	• Inhibition of the immune response due to the anti-inflammatory mode of action of BI 1015550 potentially increases the risk of infections, including COVID-19 • Serious infections were balanced between placebo and BI 1015550 in Phase II trial • Nasopharyngitis was more frequently reported under treatment with BI 1015550 in Phase Ic/II but not in Phase I trials and the numbers were very small	• Screening procedures for infections are defined for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or active tuberculosis are excluded from the trial. • Treatment of infections should be initiated promptly according to standards of care. • Treatment interruption in case of severe acute infection until the patient has recovered based on the investigator's medical judgement
MACE and tachyarhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast • In nonclinical studies with BI 1015550 no adverse cardiovascular findings detected • In clinical trials with BI 1015550 no relevant findings were observed	• These risks will be addressed by careful safety monitoring and safety measures such as o close clinical monitoring for AEs; o regular monitoring of vital signs and ECG assessments. • Adjudication committee for MACE events in Phase III
Malignancies	• Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus theoretically decrease immune defense against malignancies.	• Patients with a recent history of malignancy within 5 years will be excluded from participation in this trial except patients with appropriately treated basal cell carcinoma or in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix • In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue trial treatment • Diagnostics and treatment have to be initiated according to local standard of care.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, abdominal pain)	• Vomiting and diarrhea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. • Diarrhoea was the most frequently reported adverse event in Phase II with the majority of events being of mild intensity. • Gastrointestinal disorders are very common or common side effect of the approved antifibrotics.	• Increased awareness of symptoms. • Careful monitoring of hydration in patients with diarrhoea recommended. • Management strategies as described in approved labels of antifibrotics have to be followed. • Symptomatic treatment, e.g. loperamide, if required • Treatment interruption if needed
Reproductive toxicity: • Fetal loss • Decreased fertility	• No teratogenicity was seen in 2 species in preclinical studies and exposure with BI 1015550 via the semen is expected to be very low. • In rats, male and female fertility was potentially reduced. Long term toxicity studies with BI 1015550 in rat and monkey showed no microscopic evidence of changes in female reproductive organs or male spermatogenesis. For another PDE4 inhibitor with comparable nonclinical findings, clinical data showed no effect on male fertility and sperm in humans. • In monkeys, a sporadic prolongation in menstrual cycles was observed at approximately ≥4-fold human exposure at 18 mg BI 1015550 bid. • Fetal loss was increased in female rats treated with BI 1015550.	• Women of childbearing potential (WOCBP) need to use a highly effective method of contraception. WOCBP taking oral contraceptives (OCs) also have to ensure the use of one barrier method during sexual intercourse with their partner, e.g., condom to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhea • In case of vomiting or diarrhea, instructions in the label of the OC should be followed • In case of prolonged (>48h) or repeated vomiting/diarrhea, the use of an alternative highly effective contraceptive measure should be considered • Regular pregnancy testing for WOCBP • Treatment discontinuation in case of pregnancy
General safety topics		
Drug-induced liver injury (DILI)	• Rare but severe event, standard topic of interest for products in development thus under constant surveillance by sponsors and regulators.	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Trial procedures		
Blood Sampling	• As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal	• These risks will be addressed by careful safety monitoring and risk mitigation measures such as o close clinical monitoring for AEs; o selection of experienced sites and site staff

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	sensations (paraesthesia), impaired sensation of touch and persistent pain.	
Chest HRCT	• The more radiation is received over the course of a life, the greater risk of having cancerous tumors or of inducing changes in genes. The changes in genes possibly could cause abnormalities or disease in future offspring. The radiation in this trial is not expected to greatly increase these risks, but the exact increase in such risks is not known.	• New HRCT measurement only required in case no historical record (not older than 12 months at the time of screening) is available or in case of insufficient quality. • These risks will be addressed by careful safety monitoring and risk mitigation measures such as o close clinical monitoring for AEs o selection of experienced sites and site staff
Lung function measurements (Spirometry and DLCO)	• Risks and discomforts associated with lung function testing may include shortness of breath, dizziness, or headache during the breathing tests.	• These risks will be addressed by careful monitoring and risk mitigation measures such as o close clinical monitoring for AEs o selection of experienced sites and site staff • Training from vendor to conduct correct maneuver.
Other risks		
Administration of Placebo or BI 1015550	• If the patient is randomized to receive a placebo/BI 1015550, the patient´s condition could get worse during the course of the trial.	• In an event of disease worsening, treatment with standard of care is always an option per physician discretion for all randomized patients

1.4.3 Discussion

Treatment with BI 1015550 has the potential to provide significant benefit to patients with IPF and other progressive fibrosing ILDs by ultimately slowing lung function decline, improving symptoms and quality of life over a long-term period.
The obtained toxicology data support administration of BI 1015550 to women and men in the planned Phase III clinical trials in patients with IPF and other forms of progressive pulmonary fibrosis irrespective of background antifibrotic treatment, except for women who are pregnant or breastfeeding. Women of childbearing potential must use a highly effective method of contraception (for details please refer to Sections 3.3.2 and 4.2.2.3).

Data from the Phase II trial 1305-0013 in patients with IPF indicated a beneficial treatment effect of 18 mg BI 1015550 bid, with the preservation of FVC over 12 weeks together with an acceptable safety and tolerability profile supporting further investigation in Phase III clinical trials as a treatment for IPF and other forms of progressive pulmonary fibrosis. Based on the clinical and nonclinical data available to date, no risks (side effects) were identified. There are no listed events.

Considering the unmet medical need and anticipated benefit of BI 1015550, and the lack of compound or mechanism related safety signals, the benefit risk evaluation of BI 1015550 for the treatment of IPF and other progressive fibrosing ILDs is favorable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will evaluate efficacy and safety of BI 1015550 9 mg and 18 mg bid compared to placebo in patients with progressive fibrosing ILDs in addition to the patient's standard of care treatment.

The primary objective is to demonstrate a reduction in lung function decline as measured by the change from baseline in FVC for BI 1015550 when compared to placebo in patients with progressive fibrosing ILDs.

The main secondary objective of the trial is to demonstrate BI 1015550's ability in reducing the occurrence of clinically meaningful events such as acute ILD exacerbations, hospitalization for respiratory cause or death over the duration of the trial when compared to placebo in patients with progressive fibrosing ILDs. An additional secondary objective of the trial is to show an effect of BI 1015550 on symptoms and lung function.

2.1.2 Primary endpoint

The primary endpoint of the trial is the absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52.

2.1.3 Key Secondary endpoints

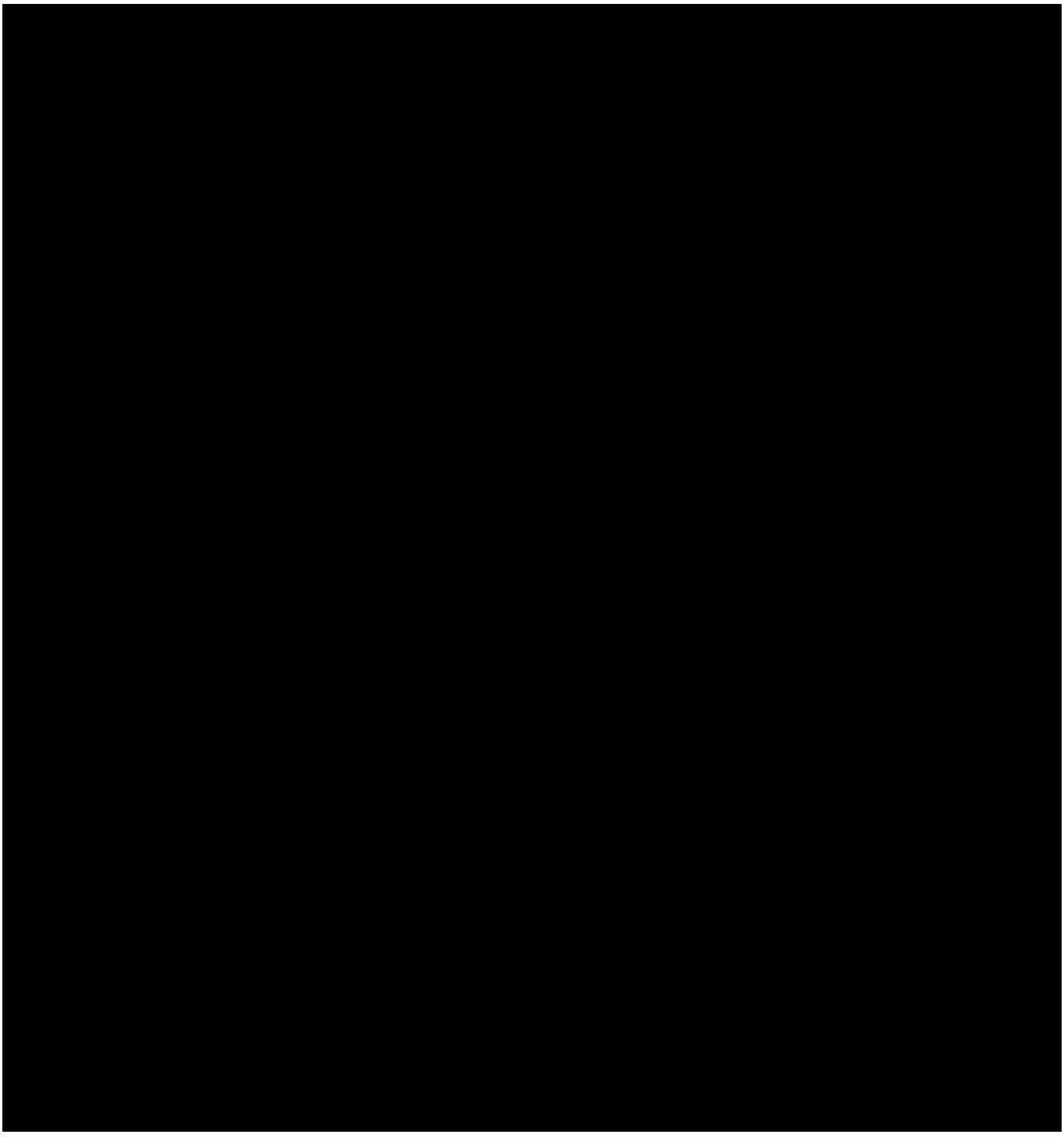
The key secondary endpoint in this trial is time to the first occurrence of any of the components of the composite endpoint: time to first acute ILD exacerbation, first hospitalization for respiratory cause, or death (whichever occurs first) over the duration of the trial.

2.1.4 Secondary endpoints

The secondary endpoints of the trial are:

- Time to first acute ILD exacerbation or death over the duration of the trial
- Time to hospitalization for respiratory cause or death over the duration of the trial
- Time to absolute decline in FVC % predicted of >10% from baseline or death over the duration of the trial
- Time to absolute decline in (DLCO) % predicted of >15% from baseline or death over the duration of the trial
- Time to death over the duration of the trial

- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Dyspnea domain score at Week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Cough domain score at Week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Fatigue domain score at Week 52
- Absolute change from baseline in FVC % predicted at Week 52
- Absolute change from baseline in DLCO % predicted at Week 52



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This Phase III trial (1305-0023) is a multi-center, multi-national, prospective, randomized, placebo-controlled, double blind clinical trial to investigate the efficacy and safety of BI 1015550 at a dose of 9 mg bid and 18 mg bid in patients with progressive fibrosing ILDs over at least 52 weeks.

A total of approximately 1041 patients will be randomized into the trial of which, 347 patients will be in each active treatment group and in the placebo group.

After signing the informed consent, the initial visit (Visit 1) will be conducted to determine eligibility. Eligible patients will enter the randomization visit (Visit 2) to allow collection of all clinical and safety information and review of all inclusion and exclusion criteria. Patients will be randomized in a 1:1:1 ratio into either BI 1015550 9 mg bid, BI 1015550 18 mg bid, or placebo and then enter the treatment phase for at least 52 weeks.

Patient randomization will be stratified by the presence of background treatment with antifibrotics (AF group vs. non-AF group).

- ***Non-AF group***: patients not treated with an approved antifibrotic medication (nintedanib) in the last 8 weeks prior to enrolment, (e.g. patients previously treated with antifibrotics, but discontinued that treatment or patients never treated with antifibrotics before).
- ***AF group***: patients on a stable treatment with an approved antifibrotic drug (e.g. nintedanib) for at least 12 weeks at study entry, and are planned to stay on this background treatment after randomization.

Patient randomization will also be stratified by HRCT pattern ("UIP or UIP-like fibrotic pattern" vs. "Other fibrotic patterns"), for details see Section 5.6.1.

The trial will be conducted in 2 parts: Treatment Period A of the trial will consist of Visits 2 through 10, until one year after randomization. Treatment Period B will begin following completion of the Week 52 visit (Visit 10); patients will continue treatment with blinded trial medication in Treatment Period B and have study visits every 12 weeks. Assuming a respective recruitment period (about 18 months), first randomized patients may be on trial treatment for up to 130 weeks.

The main analysis of this study will be performed once the last randomized patient reaches the Week-52 visit (Visit 10 at the end of Part A). At that time, a first database lock (DBL1; Figure 3.1: 1) will occur and all data will be unblinded to the sponsor. Efficacy and safety analyses will be performed on the data from Part A of the trial to assess the benefit-risk of BI 1015550 over 52 weeks. In addition, data collected in Part B of the trial (after 52 weeks) and available at the time of data cut-off for the main analysis will be reported together with data from Part A (i.e. over the whole trial).

Trial 1305-0023 Part B, will continue until all patients have completed the EOT visit and the EOS visit as applicable. A final database lock (DBL2; Figure 3.1: 1) will then occur and a final analysis based on the data over the whole trial will be carried out.

Depending on the results of the evaluation based on DBL1 and determination of the BI 1015550 dose with the more favorable benefit-risk profile, patients receiving trial medication until the end of Part B will be eligible for open-label treatment with BI 1015550 in a separate extension trial.

After review of the efficacy and safety data available at DBL1, the sponsor will communicate the end of the trial and all patients still on blinded study treatment will perform an End of Treatment (EOT) visit and an End of Study (EOS) visit if applicable. The trial ends when all patients complete these visits. Details on follow-up and rollover to the extension trial are given in Section 6.2.3.

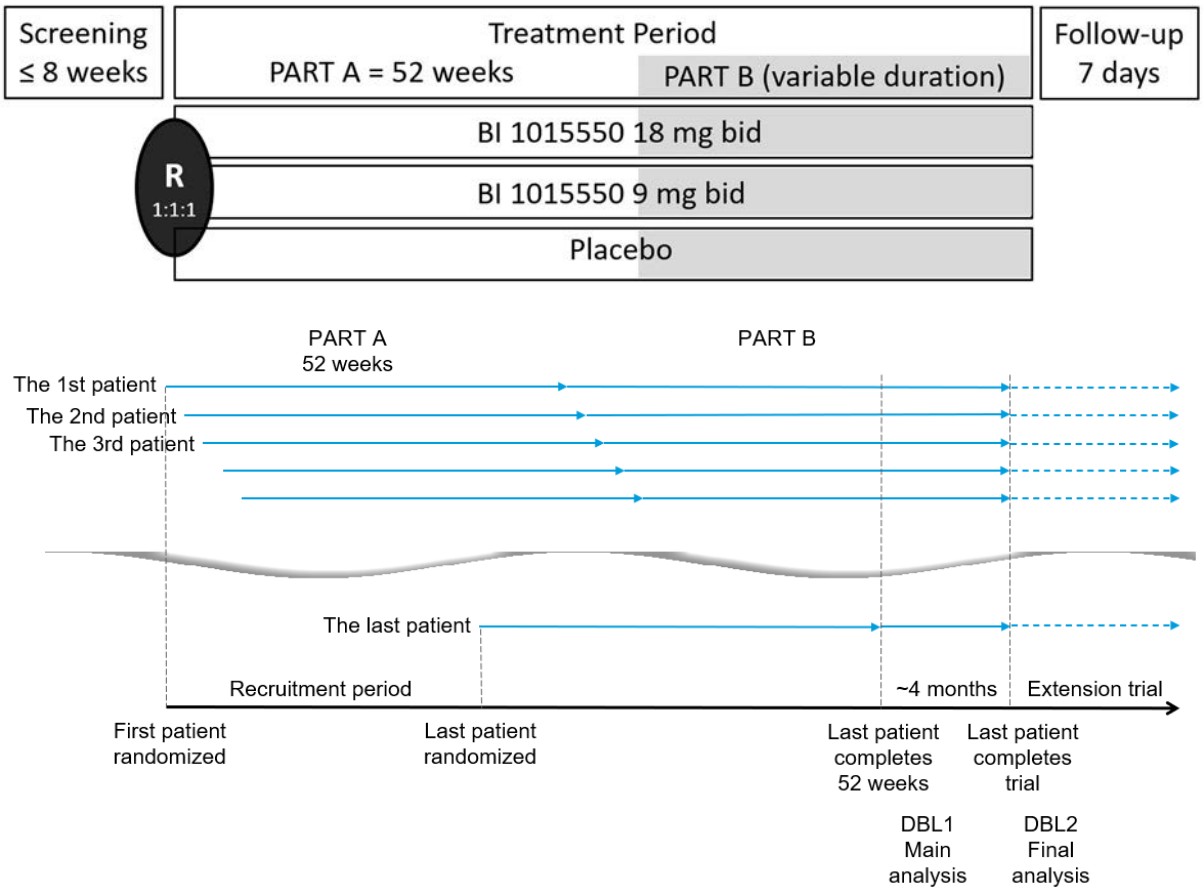


Figure 3.1: 1 Study design overview at patient level (upper panel) and trial level (lower panel)

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This trial is a placebo-controlled, randomized, double-blind trial to provide the highest scientific rigor and is thus considered the most appropriate design. FVC measurement over time is a widely accepted clinical endpoint in the indication of the trial for the evaluation of treatment effects on lung function. FVC assessments are supported by clinically meaningful outcomes and patient-reported outcomes as secondary endpoints. A placebo-controlled study design is considered justified in the trial, as it will be conducted in addition to the patient's standard of care at the time of enrollment:

- Patients who are on a stable treatment with antifibrotic treatment at the time of screening and randomization are planned to continue this background treatment during the trial.
- Patients without an AF background treatment at enrollment and randomization will be allowed to initiate a treatment with an approved antifibrotic agent in case of ILD progression and/or exacerbation after the first 12 weeks of treatment in the trial.
- Similarly, patients treated with certain immunosuppressive medication for the underlying condition (e.g. connective tissue diseases) can continue this treatment during the trial.

- Addition or changes to most immunomodulatory treatments will be allowed for the management of worsening of the underlying disease as medically indicated.

Stratification will be based on presence of AF background treatment and will facilitate the interpretation of the efficacy and safety data in patients that use BI 1015550 alone or in addition to an antifibrotic agent. The expected proportion of the respective subgroups of patients with or without background antifibrotic treatment corresponds to the current treatment/prescription practices across the participating countries (30% vs. 70%), so that patients can be accepted to the trial without modification of the ongoing SoC treatment.

The minimum treatment period of 52 weeks is selected according to the respective guidance from the American and European Clinicians organizations on the investigation of treatment effects on FVC in IPF and ILD (2015 ATS/ERS/JRS/ALAT Guideline [P15-07362]), where based on the natural decline during disease progression, a minimal follow up of the effects of new drugs for 52 weeks is recommended. However, clinical endpoint data are needed to provide evidence of a clinically meaningful effect beyond a decreased decline of FVC. Based on the incidence rates of these clinically meaningful events included in the key secondary endpoint (ILD exacerbation, respiratory hospitalization, and death), the blinded treatment should be extended to a long-term treatment beyond 52 weeks. This is reflected with the continuation of study participation for up to 130 weeks with the additional Treatment Period B for patients that are recruited early in the trial. The additional data collected while patients remain on blinded treatment beyond 52 weeks will provide supportive long-term efficacy and safety data on the effect of BI 1015550 in a controlled manner. Due to the varying length of follow-up in Part B of the trial, the efficacy analyses incorporating data from Part A and Part B will focus on time-to-event endpoints.

Cyclophosphamide, tocilizumab, mycophenolate, rituximab, and high dose steroids will not be allowed in this study (see Section 4.2.2.1). To avoid the potential confounding impact of these drugs on the assessment of the efficacy and safety of BI 1015550 in PF-ILD, their use will not be allowed. Patients whose rheumatoid arthritis or connective tissue disease is well managed by these medications should not be considered for participation in the current trial. In case a change in the rheumatoid arthritis or connective tissue disease treatment to another nonrestricted medication is indicated, this should have been done during the preceding management of the patient and would not be part of the evaluation in this clinical trial. Patients should not be taken off of a restricted medication solely for the purpose of participation in this trial.

This trial will include an option for participants and participant caregivers to complete anonymized questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analyzed as part of the clinical data for the trial (see Section 10.6).

3.3 SELECTION OF TRIAL POPULATION

Patients with progressive fibrosing ILDs will be screened at approximately 400 sites to ensure randomization of about 1041 patients, 347 in the active treatment arms and 347 in the placebo group.

During the recruitment period, the number of patients randomized with an approved background AF-treatment and without AF background treatment will be closely monitored. If necessary, recruitment of one group may be stopped in order to achieve sufficient representation of both groups.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at this time will be allowed to continue to randomization if eligible.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If retrospectively it is found that a patient has been randomized in error (did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

Patients diagnosed with progressive fibrosing ILDs who comply with trial requirements may qualify to participate in the trial. The diagnosis is based on:

- Presence of fibrotic lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent >10% on HRCT performed within 12 months of Visit 1 as confirmed by central review prior to Visit 2 (for details see Section 5.6.1) **and**
- Patients fulfill at least one of the following criteria for PF-ILD within 24 months of Visit 1, as assessed by the investigator:
    a. Clinically significant decline in FVC % pred based on a relative decline of ≥10%
    b. Marginal decline in FVC % pred based on a relative decline of ≥5-<10% combined with worsening of respiratory symptoms
    c. Marginal decline in FVC % pred based on a relative decline of ≥5-<10% combined with increasing extent of fibrotic changes on chest imaging
    d. Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging
    (Note: Changes attributable to comorbidities e.g. infection, heart failure must be excluded.)

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Patients ≥18 years old at the time of signed informed consent.

2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
3. Diagnosis of progressive fibrosing ILD other than IPF (physician confirmed; Section 3.3.1)
4. Patients may be either:
    - on a stable therapy* with nintedanib for at least 12 weeks prior to Visit 1 and during screening and are planning to stay on this background treatment after randomization. **stable therapy is defined as a tolerated regimen of nintedanib (with no dose changes) for at least 12 weeks.*
    - not on treatment with nintedanib for at least 8 weeks prior to Visit 1 and during the screening period (e.g. either AF-treatment naïve or previously discontinued) and do not plan to start or re-start antifibrotic treatment.
5. Forced Vital Capacity (FVC) ≥45% of predicted normal at Visit 1.
6. DLCO ≥25% of predicted normal corrected for hemoglobin (Hb) at Visit 1.
7. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control. WOCBP taking oral contraceptives (OCs) also have to use one barrier method; please refer to Section 4.2.2.3.
8. Patients treated with permitted immunosuppressive agents (other than corticosteroids) for an underlying systemic disease (e.g. MTX, AZA) need to be on a stable treatment for at least 12 weeks prior to Visit 1 and during the screening period.

3.3.3 Exclusion criteria

1. Prebronchodilator FEV1/FVC <0.7 at Visit 1
2. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
3. Acute ILD exacerbation within 3 months prior to Visit 1 and/or during the screening period (investigator-determined).
4. Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis.
5. Patients having developed ILD due to SARS-CoV-2 infection/COVID-19 **within 12 months of screening** (based on investigators judgement).
6. Major surgery (major according to the investigator's assessment) performed within 6 weeks prior to Visit 2 or planned during the trial period, e.g. hip replacement. Registration on lung transplantation list would not be considered as planned major surgery.
7. Any documented active or suspected malignancy or history of malignancy within 5 years prior to Visit 1, except appropriately treated basal cell carcinoma of the skin, *in situ* squamous cell carcinoma of the skin or *in situ* carcinoma of uterine cervix.
8. AST or ALT >2.5 x ULN or total Bilirubin >1.5 x ULN at Visit 1.
9. eGFR ≤30 mL/min/1.73 m2 at Visit 1. (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula or Japanese version of CKD-EPI for Japanese patients)
10. Patients with underlying liver cirrhosis (Child Pugh A, B, or C hepatic impairment).

[1] A woman is considered of childbearing potential (WOCBP), i.e.fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

11. Cardiovascular diseases, any of the following:
    a. Severe hypertension (uncontrolled under treatment ≥160/100 mmHg at multiple occasions) within 3 months of Visit 1
    b. Myocardial infarction, stroke or transient ischemic attack within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1
12. Use of any of the following medications: prednisone >15mg/day or equivalent within 4 weeks of Visit 1; cyclophosphamide, tocilizumab, mycophenolate, pirfenidone within 8 weeks of Visit 1; rituximab within 6 months of Visit 1.
13. Active vasculitis, unstable or uncontrolled within 8 weeks prior to Visit 1 or during the screening period.
14. Any suicidal behavior in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).
15. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months or at Visit 1 and/or Visit 2 (i.e. active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan).
16. Acute or chronic severe depression defined as HADS subscore >14 at Visit 1 and/or Visit 2.
17. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial. Please note: potent CYP3A4 inhibitors should not be taken 5 half-life times prior to Visit 1.
18. Patients treated with PDE1, PDE3, PDE4, PDE10 inhibitors and non-selective PDE inhibitors within 30 days before Visit 1
19. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
20. Inability to refrain from smoking on trial visit days.
21. History of allergy or hypersensitivity or contraindications to the class of drugs under study including known hypersensitivity to the drug or its excipients.
22. Patients with a significant disease or condition other than the ILD under study, which in the opinion of the investigator, may put the patient at risk because of participation, interfere with study procedures, or cause concern regarding the patient's ability to participate in the study.
23. Patients with active tuberculosis (TB).
24. Previous randomization in this trial or in trial 1305-0014.
25. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s) or receiving other investigational treatment(s).
26. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
27. History of stem cell therapy for the treatment of pulmonary fibrosis.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

However, if the patient agrees, they may remain in the trial, and even if continuing trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data, e.g. FVC measurement at Week 52.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the respective reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection and reporting (please see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

The End of Treatment (EOT) visit activities will be performed when a patient discontinues trial medication **permanently**.

A premature Follow-up (FU) visit is to be performed 7 days (+3 days) after end of treatment. If the patient discontinued the trial medication more than a week prior to the EOT visit, this FU visit is not required.

Ideally, patients who permanently discontinue trial medication should attend all remaining visits after treatment discontinuation. For those patients who are unable to complete the scheduled visits, at least phone contacts should occur at the scheduled visit time points. Should that not be acceptable, a phone contact at 52 weeks after randomization and at the end of the planned observation period should occur to collect the most relevant information: vital status (please see Section 5.2.6.2.1), adverse events, or last contact date in case of lost to follow-up (LTFU). Every effort should be done to obtain the vital status information in case of LTFU. The number of LTFU patients should be limited. The need to obtain vital status information will be part of the patient information/informed consent procedure.

An individual patient will discontinue trial treatment **permanently** if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he/she is not willing or able to adhere to the trial requirements in the future.
- The patient exhibits suicidality, in the clinical judgment of the investigator or according to the following criteria:
    - any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
    - any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)

- In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix
- The patient will undergo lung transplantation, with an assigned date of surgery.
- The patient becomes pregnant. For further details please refer to Section 5.2.6.2.3.
- Patients with a BMI <18.5 kg/m^2 that experience an additional, unexplained and clinically significant (>10%) weight loss during trial treatment

An individual patient should discontinue trial treatment **temporarily** if:

- The patient has a new onset of severe depression as defined by a HADS subscore >14.
    - Re-introduction of IMP could be considered after the patient has recovered, individual benefit-risk evaluation by the investigator and exclusion of BI 1015550-induced depression
- The patient fulfills the AESI definition of hepatic injury.
    - Re-introduction of IMP could be considered after the patient has recovered, individual benefit-risk evaluation by the investigator and exclusion of BI 1015550-induced liver injury
- The patient has an event suspicious of vasculitis
    - If thorough evaluation does not confirm a causal relationship between trial medication and the event, treatment may be restarted based on the investigator's medical judgement.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product or other trial treatment, e.g. CYP3A4 inhibitors as listed in Appendix 10.4.1,
    - Re-introduction of IMP could be considered at least 5 half-life times after the restricted medication has been stopped
- The patient has to stop trial treatment for medical reasons such as surgery, adverse events, other diseases.

For patients who temporarily pause the trial treatment due to specific adverse events (refer to Section 4.2.1) such as diarrhoea, severe infections, vasculitis, and concomitant medication related issues, every effort should be made to restart trial treatment if medically justified. The decision and associated reasoning for the restart of trial treatment should be documented in source data.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients or take any other appropriate action to guarantee the safety of the trial patients.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and

withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk assessment, please refer to Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator/the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Table 4.1.1: 1 BI 1015550 9 mg

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	9 mg
Posology:	bid
Mode of administration:	Oral

Table 4.1.1: 2 BI 1015550 18 mg

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	18 mg
Posology:	bid
Mode of administration:	Oral

Table 4.1.1: 3 Placebo matching BI 1015550 9 mg

Substance:	Placebo matching in size, weight, color, and shape to BI 1015550

Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	NA
Posology:	bid
Mode of administration:	Oral

Table 4.1.1: 4 Placebo matching BI 1015550 18 mg

Substance:	Placebo matching in size, weight, color, and shape to BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	NA
Posology:	bid
Mode of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

Preclinical in vitro data and indirect target engagement data from Phase I trials support antifibrotic and anti-inflammatory activity of BI 1015550 at plasma concentrations related to the dose of 9 mg bid and 18 mg bid.

The predicted BI 1015550 trough plasma concentration at the steady state of both 9 mg (72.46 nM) and 18 mg bid (158.7 nM) doses are above the IC_{50} values for the inhibition of target human PDE4B (10.3 nM). Furthermore, Phase I trials in healthy volunteers showed an indirect target engagement, using an ex vivo whole blood assay with an inhibition of LPS-stimulated TNF-α and IFN-γ release (anti-inflammatory activity), starting at multiple doses of 6 mg bid.

In the Phase I trials, single doses up to 48 mg and multiple doses up to 18 mg bid with up to 12 weeks of treatment have been evaluated in healthy volunteers and patients with IPF. The maximum tolerated dose was not reached as BI 1015550 was well tolerated. The selected 18 mg dose was tested in a Phase Ic trial (1305-0012) in IPF patients not on background antifibrotic treatment, administered for 4 to 12 weeks. In the Phase II trial (1305-0013), BI 1015550 at 18 mg bid dose was evaluated vs. placebo over a course of 12 weeks in 147 IPF patients, of whom 74 were on a background treatment with antifibrotic (AF group) and 73 without antifibrotic background treatment (non-AF group). This trial showed substantial evidence of treatment benefit of BI 1015550 on FVC change from baseline at 12 weeks in both the AF and non-AF groups [c37065416]. Treatment of BI 1015550 at a dose of 18 mg bid demonstrated an acceptable safety and tolerability in IPF patients over 12 weeks.

In addition, based on population PK/PD analysis of Phase II study 1305-0013 in IPF patients, the FVC response did not change as a function of exposure within the exposure range observed for the BI 1015550 18 mg bid dose given over 12 weeks. This suggested that the maximum effect of BI 1015550 on FVC has been reached with the 18 mg bid dose [c37934954] consistent with the observed clinical stabilization of FVC over the treatment period.

Based on the simulated exposure, 9 mg bid dose provides a sufficient differentiation in the distribution of exposure compared to 18 mg bid dose, supporting that 9 mg and 18 mg bid doses provide wide ranges of plasma exposure to explore dose-response and exposure-response relationship.

IPF and other forms of progressive pulmonary fibrosis are serious debilitating conditions characterized by worsening symptoms and quality of life, progressive loss of lung function, ultimately resulting in respiratory failure, and early death. At the same time, the currently approved antifibrotic treatments have limitations: they do not impact symptoms and cannot stop or reverse fibrosis. Under these circumstances, the highest BI 1015550 dose that is considered safe and well-tolerated (18 mg bid) was selected for the Phase III trials to maximize the potential for efficacy of the treatment, i.e. to preserve lung function and quality of life of patients. In order to provide further dose-response and exposure-response data, a dose of 9 mg bid has been chosen based on available preclinical data on target engagement and simulated exposure assessments, so that both efficacy and safety with this lower dose can be investigated with an expected therapeutic effect. Based on the data from the Phase II trial, demonstrating a stabilization in FVC and an acceptable safety and tolerability profile, these doses seem to provide a reasonable benefit to risk ratio for the patient treatment in this Phase III trial.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomized in 1:1:1 ratio to either BI 1015550 9 mg bid, BI 1015550 18 mg bid, or placebo at Visit 2. Randomization (stratified by patient's background AF-treatment at baseline and HRCT pattern) will be conducted via Interactive Response Technology (IRT). The appropriate medication number(s) will be assigned and documented in the CRF. Note that the medication number is different from the patient number (the latter is generated already during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

During Visit 2, after randomization the patient will begin treatment for at least 52 weeks. The treatment will be assigned by an IRT contact during Visits 2, 4, 5, 6, 7, 8, 9. Patients that are treated in Treatment Period B will be assigned treatment at Visit 10 and the respective visits of Treatment Period B (every 12 weeks). The patient will receive either active treatment at a dose of 9 mg, 18 mg, or placebo. The first dose of BI 1015550 or placebo will be administered to the patient at the end of Visit 2 (Day 1) under direct supervision of the investigator or designee. On the day of any further clinic visit, supervision of administration is not required but the treatment will preferably be administered to the patient during the visit.

Table 4.1.4: 1 Number of IMP kits dispensed at each visit

Trial visits	2	3	4	5	6	7	8	9	10	Treatment Period B
Number of IMP kits dispensed	2	0	2	2	3	3	3	3	4*	4 per visit

* IMP kits will only be dispensed in case Visit 10 is not replaced with the EOT visit.

The trial medication will consist of 2 tablets to be taken orally twice daily. The patient should swallow the trial medication in its entirety (without chewing) with a glass of water (~250 mL), observing a 12-hour dose interval. The patient should ensure to take the trial medication at the same time every day (±30 mins), ideally between 6:00 and 11:00 in the morning and between 18:00 and 23:00 in the evening. There are no specific requirements regarding the timing of doses in relation to meals.

If taken around the same time (approximately within an hour), patients on nintedanib background should take trial medication first, followed by the antifibrotic background medication. A missed dose should be skipped if the time window to the next dose is less than 8 hours. The next dose should be taken as scheduled. If an episode of vomiting happens after medication intake, redose with trial medication is not advised.

After a temporary interruption, trial treatment may be restarted (Section 3.3.4.1).The investigational product should only be dispensed to participating patients according to the protocol by authorized personnel as documented in the ISF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded regarding the randomized treatment assignments until the database is declared ready for analysis according to the sponsor's SOPs.

At the main analysis database lock (DBL1; see Section 3.1), the sponsor will be unblinded to assess the benefit-risk of both doses of BI 1015550 vs placebo and select the dose with the more favorable benefit-risk profile for the open-label extension trial. Patients, investigators, and other site personnel will remain blinded to the randomized treatment assignment until the end of the trial.

The trial medication is identified by a medication code number and packaging is identical. The color, size, and shape of the respective 9 mg and 18 mg BI 1015550 and the matching placebo tablets will be indistinguishable. The access to the randomization code will be kept restricted until its release for analysis at DBL1. Further details regarding the timepoint of unblinding the database for analysis is documented in the TSAP.

The randomization codes will be provided to bioanalytics before DBL1 to exclude placebo or comparator samples from the PK analysis. Bioanalytics will not disclose the randomization code or the results of their measurements until DBL1.

A dedicated database snapshot (not a partial DBL) will be generated prior to DBL1, after all patients have completed the last PK visit (i.e. Week-26 visit), to allow for development and refinement of the population PK model (for "fast-track" PK analysis). Details of the analysis will be defined in the PK/PD analysis plan. In addition, the data will be used for front-loading of descriptive analysis for PK. Only personnel involved in the population PK and descriptive analyses will be granted access to the unblinded PK data before DBL1, whereas the trial team

and all other functions not involved in the population PK and PK descriptive analyses will remain blinded (details will be provided in a separate logistics and access plan). The analysis plan for the population PK analysis will be finalized and signed prior to this dedicated database snapshot.

No formal interim report will be generated for the population PK analysis. The final PK and PK/PD analyses will be reported separately from the clinical trial report (CTR) after DBL1.

The external DMC will review unblinded data upon request, and only under conditions that ensure that patients, investigators, everyone involved in trial conduct or analysis, and anyone with any other participation in this double-blind trial will remain blinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

To avoid unblinding of the study team through drug safety reports which are to be unblinded as per regulatory requirements, a procedure will be maintained to keep codebreaking in these cases invisible to study team.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorized Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The trial medication will be tablets containing 9 mg of BI 1015550, 18 mg of BI 1015550 or the respective matching placebo in a double-dummy design. Each trial medication kit is packaged in a child-resistant tamper-evident wallet containing 112 tablets of 9 mg or 18 mg BI 1015550 or the respective matching placebo. Wallets will cover 4 weeks of treatment.

Each wallet will be labelled with a multi-language booklet or country specific label according to the requirements of the participating countries.

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiration dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA, as provided in the list of contacts) must be contacted immediately.

All unused trial medication must be returned to the Sponsor or appointed Contract Research Organization (CRO). Receipt, usage, and return must be documented on the respective forms/IRT system. Account must be given for any discrepancies.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB/ethics committee, HA/RA if applicable.
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the *curriculum vitae* of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution center or alternative disposal of unused products. If applicable, the sponsor or warehouse/drug distribution center will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiration ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the Investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Temporary treatment interruption is allowed to manage adverse events. All efforts should be made to re-start IMP after resolution of the adverse event according to the Investigator's assessment.

Please find management guidance for specific adverse events below:

Diarrhea
Depending on the intensity of the events, the following management strategies are recommended:

- Counselling of patients, including potential diet modifications
- Monitor and maintain adequate hydration
- Treatment with loperamide or other antidiarrheal medications
- For patients on antifibrotic medication, management strategies (e.g., dose reduction and/or temporary interruption) as described in the respective prescribing information should be followed

Temporary interruption of trial treatment can be considered, and trial treatment may be restarted when the patient has recovered according to investigator's assessment.

Severe infections (CTCAE >2), serious infections, opportunistic or *Mycobacterium tuberculosis* infections
Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has resolved and trial treatment may be restarted when the patient has recovered according to investigator's assessment.

Malignancies
In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should permanently discontinue trial treatment. Diagnostics and treatment must be initiated according to local standard of care.

Vasculitis
In case of events suspicious for vasculitis, trial treatment will be discontinued. A thorough work-up has to be initiated including at least but not limited to

- appropriate imaging, including angiography
- biopsy if possible
- appropriate laboratory screening, including measurements of vasculitis markers at the central lab, see Section 5.2.3.3. In addition, an analysis of the previously collected and

stored samples (baseline and/or Visit 10 samples) will need to be requested and considered.
- thorough documentation of all reported symptoms

Referral to a vasculitis expert is recommended. If required, vasculitis treatment should be initiated according to standard of care. If thorough evaluation does not confirm a causal relationship between trial medication and the event, trial treatment may be restarted based on the investigator's medical judgement.

New onset of severe depression or suicidality
In case of new onset of severe depression defined as HADS >14 or the patient exhibits any suicidal behavior or serious suicidality ideation defined as type 4 or 5 in the C-SSRS interview, trial treatment has to be discontinued. Referral to a psychiatrist for further diagnoses and initiation of treatment is recommended.
In case of severe depression: If thorough evaluation does not confirm a causal relationship between trial medication and the event, and the patient has recovered, trial treatment may be restarted based on the investigator's medical judgement. (in case of new-onset of suicidality treatment has to be permanently discontinued)

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Treatment with antifibrotic medication (nintedanib)

Treatment with antifibrotic treatment that is not registered for the disease under study, e.g. pirfenidone for PF-ILD, is not allowed.

AF group:

Patients who are on a stable dose of marketed antifibrotic treatment (nintedanib) should plan to remain on this treatment for the duration of the trial. Interruption and/or dose reductions of the background antifibrotic medication are left at the discretion of the investigator, e.g. to manage side effects in line with the respective prescribing information.

Non-AF group:

For patients not receiving nintedanib in the 8 weeks prior to study entry, nintedanib is a restricted medication during the full duration of the blinded treatment period. Nintedanib should not be initiated in the first 12 weeks of trial treatment. After that timeframe, initiation of nintedanib is only allowed as rescue medication in case of disease worsening defined as disease under study progression and/or ILD exacerbation (by investigator judgement).

Immunomodulatory treatment

Addition or changes in immunomodulatory treatment (except of dose adjustments of prednisone below 15 mg, which are allowed) should not occur during the first 6 months of blinded treatment. After 6 months from randomization, changes in immunomodulatory treatment are allowed for the management of worsening of the underlying disease as

medically indicated. Prednisone >15 mg/day or equivalent can be prescribed during the treatment period in case of (suspected) acute ILD exacerbation.

Other restricted concomitant medication

While enrolled in this trial, patients must not participate in another investigational drug or device trial or receive other investigational treatment(s).

Stem cell therapy for the treatment of pulmonary fibrosis is not allowed.

Treatment with non-selective PDE inhibitors as well as PDE4 inhibitors is not allowed.

Potent CYP3A4 inhibitors should not be administered during the screening and trial treatment periods. If short-term treatment with potent CYP3A4 inhibitor is needed (e.g., Paxlovid for the treatment of COVID-19; clarithromycin for antibiotic treatment), IMP should be temporarily discontinued (see Section 3.3.4.1 about conditions to re-introduce IMP). Non-exhaustive lists of potent CYP3A inhibitors and PDE inhibitors are provided in the Appendix 10.4.

Table 4.2.2.1: 1 Restrictions regarding concomitant treatment

Medication	**Prior to Study**[1]	**Screening Period**	**Treatment Period A and B**	**Follow up period**
Potent CYP3A inhibitors	Not permitted	Not permitted	Not permitted[2]	Permitted
Stem cell therapy for the treatment of pulmonary fibrosis	Not permitted	Not permitted	Not permitted	Not permitted
PDE4 and non-selective PDE inhibitors, pirfenidone	Not permitted	Not permitted	Not permitted	Not permitted
Prednisone >15mg/day or equivalent[3]	Not permitted	Not permitted	Not permitted[4,5]	Permitted
Cyclophosphamide, tocilizumab, rituximab, mycophenolate	Not permitted	Not permitted	Not permitted[5]	Permitted

1. Duration of restriction before screening see exclusion criteria Section 3.3.3
2. If any short-term treatment with potent CYP3A4 inhibitor is needed, IMP should be temporarily discontinued
3. Inhaled, intra-nasal, and topical corticosteroids are allowed
4. Prednisone >15mg/day or equivalent can be prescribed during the treatment period in case of (suspected) acute ILD exacerbation
5. After 6 months from randomization, changes are allowed for the management of worsening of the underlying disease as medically indicated.

4.2.2.2 Restrictions on diet and lifestyle

Patients should refrain from drinking grapefruit juice during the duration of the trial.

Patients should refrain from smoking or vigorous activity 1 hour before performing spirometry assessments.

4.2.2.3 Contraception requirements

Women of childbearing potential (WOCBP)[2] must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly throughout the trial, and for a period of at least 7 days after last trial drug intake. A list of contraception methods meeting these criteria is provided below and in the patient information.

Acceptable highly effective methods of contraception include:

- Non-oral hormonal methods of contraception associated with inhibition of ovulation:
  - Intravaginal or transdermal combinations of estrogen and progestogen
  - Injectable or implantable progestogen
- Oral hormonal contraceptives together with one barrier method (e.g. condom) to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhea. In case of vomiting or diarrhea, instructions in the label of the OC should be followed in addition. In case of prolonged (>48h) or repeated vomiting/diarrhea, the use of an alternative highly effective contraceptive measure should be considered
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized sexual partner with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate, provided that partner is the sole sexual partner of the study participant
- Complete abstinence from male-female sex when this is in line with the preferred and usual lifestyle of the study participant. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorized by the sponsor or delegate.

[2] A woman is considered of childbearing potential (WOCBP), i.e.fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 FVC

Spirometry measurements will be performed according to ATS/ERS 2019 guideline [R20-2419]. FVC will be assessed using standardized spirometry equipment which will be provided centrally with supplies of precalibrated disposable flow sensors. These sensors meet International Organization for Standardization (ISO) 26782 standards, but with a maximum permissible accuracy error of ±2.5%, in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Technical Statement [R20-2419].
As such there is no need to conduct daily calibration prior to use. Only these spirometers are to be used for this trial. Spirometry performance will be centrally reviewed.

Spirometry will be conducted with the patient in a seated position. It is preferable that the same trained individual performs the pulmonary function tests for a given patient. The best of three efforts will be defined as the highest FVC obtained on any of three blows meeting the 2019 ATS/ERS criteria (with a maximum of eight attempts). Predicted normal values will be calculated according to GLI (Global Lung Initiative).

Efforts should be made to schedule the spirometric measurements at approximately the same time of the day, at least within the same half-day (morning vs. afternoon), with reference to baseline measurement (Visit 2). On days of study visits, patients should be encouraged to refrain from vigorous activity and smoking within 1 hour of pulmonary function testing. If treated with bronchodilators, wash-out according to Appendix 10.1 should be advised before spirometry and documented in the source documents.

Spirometry results will be electronically transmitted. To ensure the quality of the primary endpoint measurement, a central spirometry review is put in place to provide feedback to the investigational site and the CRA on the quality of the data received from the site. In case unacceptable results for FVC/FEV1 at V1 or FVC at V10 are obtained after the review, the patient must be reassessed.

Further instructions regarding FVC measurements will be provided in the ISF.

Optional assisted home spirometry measurements

At selected sites with respective setup, assisted home spirometry can be conducted intermittently during the trial and as a fallback/contingency option.

For the assisted home spirometry, patients may be using a handheld spirometer (iSpiro) together with a mobile phone with the installed iSpiro App provided by site. Training of the patients on the use of the iSpiro device and App can be done at any visit, ideally at Visit 2 or Visit 3 together with a first recording. During the treatment phase, the iSpiro device and the respective phone with the App will be provided to the patient upon decision of the investigator in order to perform an assisted (via video call) home spirometry either at unscheduled visits or as a fallback solution if the patient is unable to get to the site for the scheduled visit.

These home spirometry measurements will not replace the onsite FVC measurement at Visit 2 (Day 1), Visit 5 (Week 12), Visit 7 (Week 26), Visit 10 (Week 52) and the visit for EOT; every effort should be made to obtain an onsite spirometry within the planned visit window.

5.1.2 Exacerbation of ILD

Based on the similarity between IPF and PF-ILDs, in the current study, the most recent definition of acute IPF exacerbation will be adapted for use as described below [P16-06899].

Acute exacerbation of ILD will be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following:

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

This event must be reported as adverse event in the category “acute exacerbation of disease under investigation”.

Events that are clinically considered to meet the definition of acute exacerbation of ILD but fail to meet all diagnostic criteria above due to missing CT data should be termed “suspected acute exacerbations of disease under investigation” (as long as this assessment persists). Both confirmed and suspected cases will be considered for the endpoint evaluation.

5.1.3 Time to death

Time to death will be based either on the date of death on the AE report for patients with AEs leading to death or will be based on the information from the vital status assessment.

5.1.4 Hospitalization due to respiratory cause

Hospitalization due to respiratory cause will be collected on a specific non-elective hospitalization CRF page. The CRF page will capture the date of hospitalization, whether the non-elective hospitalization was due to respiratory cause, and the primary admission diagnosis.

5.1.5 Patient-Reported Outcome Questionnaires

The patient will complete patient-reported outcome (PRO) questionnaires preferably according to the prespecified order defined hereafter:

Questionnaires completed by patient:

1. Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (L-PF)
2. EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D)
3. Hospital Anxiety and Depression Scale (HADS; Section 5.2.5.2)
4. Patient's Global Impression of Severity (PGIS) for Cough, Shortness of Breath, and Fatigue

Patients may complete these questionnaires at site or at home if they so choose to. The questionnaires may be completed either on paper versions, with site provided tablet, a mobile phone provided centrally or via an App downloaded to patient's personal device.

Patients are asked to be in a quiet area/room prior to any other trial related examination and should complete these questionnaires without any help from or interpretation by other people. If the patient is too sick to complete the questionnaires him/herself but is able to reply verbally, a member of the study team should read the instructions, questions, and response options aloud to the patient and collect the patient's verbal response in as neutral and unbiased a manner as possible. If this is not possible either, the questionnaires are not to be completed.

If done at home, patient should compile the questionnaire preferably the same half-day as the intended scheduled site visit (morning or afternoon) and within the last 3 days before the site visit.
For the compilation of paper questionnaires, the site personnel will check the patient questionnaires for completeness prior to the patient leaving the site, but the response to each item will not be tampered with, and a patient should not be influenced in any manner on how to respond to the question. Scores will be entered into the eCRF by the site-personnel.
For patient-reported outcomes compiled on electronic devices, completeness and consistency checks will be programmed into the App and no further check by site personnel is needed. Data from these patient outcome reports will be electronically submitted.

5.1.5.1 Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (L-PF)

The Living with Pulmonary Fibrosis (L-PF) questionnaire is a 44-item questionnaire with two modules: 1) Symptoms (23 scored items plus 5 oxygen questions) and 2) Impacts (21 items).

L-PF was developed with the input of patients with pulmonary fibrosis (PF) and thus is intended to capture perceptions specific to PF patients.

The Symptoms module yields three domain scores: 1) dyspnea, 2) cough , and 3) fatigue as well as a total Symptoms score . There are 5 additional questions pertaining to oxygen use at the end of the Symptoms module. The Impacts module yields a single Impacts score. Symptoms and Impacts scores are summed to yield a total L-PF score. Scoring is performed as a summary score, the mean of the dimension ratings multiplied by 100. For details, please refer to the TSAP.

The L-PF Symptoms and Impact Questionnaire (Appendix 10.2.1) will be self-administered by the patient at visits indicated in the flow chart.

5.1.5.2 EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D)

The EQ-5D was developed by the European Quality of Life Group (EuroQol Group) and is a standardized instrument for use as a measure of health outcomes [R96-2382]. The version used in this trial is the new five-level version (EQ-5D-5L).

The questionnaire essentially consists of 2 pages. The first page is the descriptive system with 5 questions to the patient´s health state today. Each question captures one dimension of health (e.g. mobility, self-care) and has five levels to answer. The second page records the patient´s self-rated health status of today on a vertical graduated (0 to 100) visual analogue scale.

The EQ-5D (Appendix 10.2.2) will be self- administered by the patient at visits indicated in the flow chart.

5.1.5.3 Patient's Global Impression of Severity (PGIS) of Cough, Shortness of Breath and Fatigue

The PGIS questionnaire will ask the patient to think about their cough and reflect how it was in the past 7 days: "recall whether you have had a cough and if so, how frequently it has occurred, how severe it has been, and whether cough has affected how you feel and how you function in your daily life. Considering all these, please rate the severity of your cough over the last 7 days by placing a tic in the one box corresponding to your response: not present, very mild, mild, moderate, severe, and very severe."

The patient will be asked to think about shortness of breath and reflect on the last 7 days: "call to mind how severe it has been and whether shortness of breath has affected how you feel and how you function in your daily life. Considering all these, please rate the severity of your shortness of breath over the last 7 days by placing a tic in the one box corresponding to your response: not present, very mild, mild, moderate, severe, and very severe."

If applicable, the patient will be asked to complete the PGIS fatigue to assess the patient's severity of fatigue. The measure consists of 1 item/question asking patients to rate their severity of fatigue on a 5-point Likert scale ranging from "no symptoms" to "very severe" including a recall "over the past 24 hours".

The PGIS (Appendix 10.2.4) will be self- administered by the patient at visits indicated in the flow chart.

5.1.6 DLCO

The site will use its own carbon monoxide diffusion capacity (DLCO) equipment and conduct all measurements with the same DLCO equipment in case that several devices are available at the site. Single-breath DLCO measurement will be carried out according to the ATS/ERS guideline on DLCO measurements [R06-2002]. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

Two acceptable DLCO measurements and the corresponding alveolar volume will be taken at time points indicated in the flow chart. Both acceptable DLCO measurements will be recorded. Maneuvers will be demonstrated before beginning of the test, and the patient will be carefully instructed.

Predicted DLCO value will be corrected for hemoglobin (Hb). The site has to enter the unadjusted predicted DLCO result without Hb correction in the eCRF. This value will be adjusted for the most recent Hb value.
At Visit 1, the most recent Hb value (ideally on the same day) will be entered into the eCRF to correct the DLCO value. During subsequent visits, Hb values will be transferred from the central lab and corrections will be done automatically (not visible into the eCRF).

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the calculation method used must be in compliance with the ATS/ERS guideline on DLCO measurements [R06-2002] and the prediction formula appropriate for that method.

Predicted DLCO corrected for Hb, with Hb expressed in g·dL-1 [R06-2002], will be calculated in the eCRF as:

- Males: DLCO predicted for Hb = DLCO predicted ×[1.7Hb / (10.22 + Hb)]
- Females: DLCO predicted for Hb = DLCO predicted ×[1.7Hb / (9.38 + Hb)]

Percent predicted DLCO corrected for Hb (unit: %) at Visit 1 will be calculated in the eCRF with the following formula:

Percent predicted DLCO corrected for Hb = (Mean value of two DLCO measurements, expressed in mmol/min/kPa) / Predicted DLCO corrected for Hb) * 100

For each patient, spirometry testing and DLCO should always start at approximately the same time of day. DLCO must be performed after spirometry on the same day.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A physical examination will be performed at the time points specified in the flow chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurements of height and body weight will be performed at the time

points specified in the flow chart. The results must be included in the source documents available at the site.

All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flow chart, prior to blood sampling. Additionally, SpO2 will be measured via pulse oximetry.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3.1: 1. For the sampling time points please see the flow chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the eDC system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

5.2.3.1 Routine safety lab tests

Table 5.2.3.1: 1 Safety laboratory tests

Functional lab group	Test name
Hematology	Hematocrit
	Hemoglobin
	Red blood cells (RBC)
	White blood cells (WBC)
	Platelet count
	MCV
	MCH
	MCHC
	RDW
Automatic WBC differential (relative and absolute)	Neutrophiles total
	Lymphocytes total
	Eosinophiles
	Basophiles
	Monocytes
	Lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT)
	Prothrombin Time (PT)
	INR
Enzymes	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Alkaline phosphatase (AP)
	Gammaglutamyl transferase (GGT)
	Creatine kinase (CK)
	Lipase
	Amylase
Substrates	Glucose
	Creatinine
	Urea Nitrogen
	Uric Acid
	Total bilirubin
	Direct bilirubin
	Total protein
	Albumin
	Globulin
	Albumin / Globulin ratio
	C-Reactive Protein (CRP)
	Total cholesterol
Electrolytes	Calcium
	Sodium
	Potassium
	Chloride
	Phosphate
Serum Pregnancy test (only for female patients of childbearing potential) at screening (V1) and at any visit where urine pregnancy test is positive	Human Serum Chorionic Gonadotropin

Functional lab group	Test name
Urinalysis (qualitative determination)	Urine nitrite Urine protein Urine glucose Urine ketone Urine bilirubin Urine hemoglobin (detects erythrocytes) Urine leukocyte esterase (detects leucocytes) Urine pH Specific gravity
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)
Urine Pregnancy test (only for female patients of childbearing potential) at V2 and following visits	Human Chorionic Gonadotropin in the urine

eGFR will be analyzed and calculated by the central laboratory at the same timepoints as other safety laboratory parameters (refer to flow chart). eGFR will be calculated by using the CKD-EPI formula and using the Jaffe assay for serum creatinine measurement, IDMS standardized.

5.2.3.2 Infection serology

The following lab tests for infection serology will be performed as indicated in the flow chart:

- Hepatitis B surface antigen (qualitative) and Hepatitis B core antibody (qualitative)
- HBV-DNA PCR (quantitative), which should be conducted if Hepatitis B core antibody is positive and Hepatitis B surface antigen is negative
- Hepatitis C antibodies (qualitative), where a positive Hep C antibodies test result should be confirmed by PCR
- HIV-1 and HIV-2 antibody (qualitative)
- IGRA-T (e.g. QuantiFERON®-TB Gold IT Test, provided by central lab):
  If the first QuantiFERON®-TB-Gold Plus (or if applicable, T-Spot®) test result is undetermined, a retest should be performed.
  If the retest QuantiFERON®-TB-Gold Plus test result is undetermined, a PPD skin test should be performed.
  For specific countries (e.g. Japan): T-Spot® TB test may be performed at local labs instead of QuantiFERON®-TB test

  In case of positive TB test, further diagnostic work up to confirm/exclude the diagnosis of latent or active is needed (documentation on respective eCRF page).

5.2.3.3 Immunological vasculitis markers

At Visit 2, Visit 10 and in case of a suspected vasculitis an additional blood sample will be taken. It will be stored and analyzed for the following immunological vasculitis markers:

- MPO-ANCA
- PR3-ANCA

- IL-6
- antiglomerular basement membrane (GBM) antibodies
- anti-C1q antibodies (immune complex-associated small-vessel vasculitis)
- rheumatoid factor
- antinuclear antibodies
- complement C3, C4, CH 50, anti-C1q antibodies.

Due to stability matter during storage, ANCA markers (MPO-ANCA and PR3-ANCA) from Visit 2 and Visit 10 are analyzed upon receipt, but investigators will not receive these results as it could influence their judgement regarding a suspected vasculitis. The rest of the analysis of immunological vasculitis markers is performed if an unscheduled "Vasculitis event" is collected. In this situation, the site will receive the result for all vasculitis markers previously performed (from V2 and V10 if already done) and from the unscheduled "Vasculitis event" kit. These results are shared by the trial team to the site via the CRA.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the flow chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

5.2.5 Other Safety parameters

5.2.5.1 Suicidal risk (C-SSRS)

Prospective monitoring will be conducted throughout this trial using the Columbia Suicide Severity Rating scale (C-SSRS).

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening/baseline' version) with the aim to exclude patient's suicidal ideation type 4 to 5 within the preceding 3 months or at Visit 1 or any suicidal behavior in the past 2 years. The lifetime history of suicidal ideation and behavior will also be recorded.

After Visit 1, the assessment 'since last visit' will be performed at each clinic visit ('since last visit' version).

Appendix 10.3 details how the C-SSRS will be assessed.

C-SSRS results will be reported in terms of AEs as described in Section 5.2.6.2.

5.2.5.2 Depression and anxiety

Prospective monitoring using the Hospital Anxiety and Depression Scale (HADS).

This questionnaire is patient friendly and easy to use and takes less than 5 minutes for completion. The questionnaire comprises seven questions for anxiety and seven questions for depression that are scored separately. Cut-off scores are available for quantification: The HADS questionnaire has been validated in many languages, countries and settings including general practice and community settings and is one of the tools recommended by National Institute for Health and Care Excellence (NICE) for diagnosis of depression and anxiety and is included in the American Thoracic Society's list of patient-reported outcome measures for use in ILD [R22-1857, R22-1856]. The HADS (Appendix 10.2.3) will be self-administered.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.
The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

Adverse event report for diarrhea events

In case of events of diarrhoea the following definitions should be followed:
Diarrhoea is defined ≥3 loose/liquid stools per day (WHO definition)
Diarrhoea episode = 2 diarrhoea episodes are separated by at least 7 days without any diarrhoea

Adverse event report for depression and anxiety

AE reporting based on the Hospital Anxiety and Depression Scale (HADS): new onset of moderate depression, defined as HADS subscore of >10, has to be reported as AE; new onset of moderate anxiety, defined as HADS subscore of >10, has to be reported as AE. HADS subscore of ≤10 should only be reported as an AE if clinically relevant. See Section 5.2.6.1.4 for reporting of AESI based on HADS.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardize the patient and may require medial or surgical intervention to prevent one of the other outcomes listed in the above definitions. 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.

For Japan only:
An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.
The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.
Every occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections “AE Collection” and “**AE reporting to sponsor and timelines**”.

SAE reporting in case of Suicidal Risk assessed by the C-SSRS
All C-SSRS reports of suicidal ideation type 4 and 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.

For 'self-injurious behavior, no suicidal intent' (type 11) standard AE/SAE reporting rules are to be applied.

For each negative report (Suicidal ideation type 1, 2, or 3) after the start of the trial, the investigator is to decide based on clinical judgement whether it represents an adverse event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

- Potential severe DILI
- Vasculitis
- Severe infections (CTCAE >2), serious, opportunistic or mycobacterium tuberculosis infections. Refer to Appendix 10.5.
- New onset of severe depression, defined as HADS subscore >14
- New onset of severe anxiety, defined as HADS subscore >14

Management of specific AEs is described in Section 4.2.1, specific additional procedures to be performed in case of a suspected AESI are described in this section:

Potential Severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- ALT and/or AST elevations ≥10-fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analyzed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

For patients with abnormal aminotransaminase levels between >1 and <3 x ULN at baseline:

- An elevation of AST and / or ALT ≥3-fold the baseline value combined with an elevation of bilirubin ≥2-fold ULN or ≥2-fold the baseline value (if bilirubin is

elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other; or;
- Aminotransferase elevations ≥5-fold the baseline value.

Vasculitis events
In this trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels. The investigator should monitor for any signs and symptoms of vasculitis at all times and specifically as part of the AE questioning.

In case of (suspected) events of vasculitis, further work-up and management as outlined in Section 4.2.1 has to be followed, including biopsy, appropriate imaging/angiography, laboratory measures (e.g. additional lab sample for immunological and further inflammation markers). Details will be collected on a dedicated eCRF page and events will referred for adjudication to an independent adjudication committee.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on CTCAE grading (see ISF for grading of specific events).

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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:
- The event is consistent with the known pharmacology of the trial drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).

- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pretreatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the trial drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (= the End of Trial (EOS) visit):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

Vital Status Data Collection
Patients who discontinue trial treatment prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must any occurrence of cancer, report all deaths/fatal AEs regardless of relationship, and trial drug related SAEs and trial drug related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

With receipt of any further information to these events, a follow-up reports have to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

Should the eDC system not be available for more than 24 hours, reporting must occur via the BI paper SAE forms.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.3 Independent safety monitoring and adverse events with additional information collection

An independent data monitoring committee (DMC) will conduct regular reviews of the trial safety data as detailed in the DMC charter.

An independent adjudication committee will review all fatal cases (to review the primary cause of death). The independent adjudication committee will also review all adverse events categorized as major adverse cardiovascular events (MACE).

A separate independent adjudication committee will review all events categorized as vasculitis (SMQ vasculitis broad).

Before providing any copy of patients' source documents to the sponsor, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.
Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse event 'Diarrhea/gastrointestinal events', the adverse events in the Standard MedDRA Query (SMQ) 'vasculitis" and in case of positive TB tests (see Section 5.2.3.2).

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Cpre,ss (predose concentration of analyte in plasma at steady state) will be the main PK parameter determined in this study. Further PK parameters might be calculated as appropriate.

Date and clock time of PK sampling, the two preceding and the current drug administration will be recorded in the CRFs. The actual sampling times will be used for determination of the PK parameters.

PK sampling will be performed at the time points indicated in the flow chart.

5.3.2 Methods of sample collection

For quantification of drug plasma concentrations of BI 1015550, venous blood will be collected using a prelabeled EDTA (Ethylenediaminetetraacetic acid) containing blood drawing tube at the times indicated in the flow chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. A detailed description of sample collection and handling is provided in the Lab Manual in the ISF.

Plasma samples will be discarded at latest 6 months after the final clinical trial report has been signed.

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKERS

Biomarkers associated with ILD pathology will be explored in serum, plasma, and whole blood and will be correlated with clinical endpoints.

5.4.1 Pharmacodynamics biomarkers

[redacted]

Total mRNA expression levels in whole blood and miRNA levels in plasma will be evaluated to investigate the drug's mode of action or the pathology and course of the disease.

All biomarkers assessed in this trial are considered exploratory and qualified assays will be used according to the sponsor's procedures. Characteristics of the analytical methods for the analysis of plasma and serum biomarkers will be given in detail in the analytical report.

Genome-wide expression profiling will be performed by RNA sequencing including bioinformatics analysis. Further characteristics of the analytical method for the analysis will be given in detail in the analytical report.

Changes in serum and plasma biomarkers, and in gene expression (RNA) levels will be analyzed over time, pre- and post-treatment with BI 1015550.

All assessed biomarkers will either be analyzed at the sponsor or at a CRO. The results of biomarker analyses will be reported separately in biomarker reports.

5.4.1.1 Methods and timing of sample collection

Whole blood will be collected for the preparation of serum, plasma, and RNA expression analysis.

Overall about 75 mL blood will be taken for explorative biomarker assessment during the course of the trial.

Remaining samples may be used for method development and evaluation and will be stored for a maximum of 3 years after approval of the clinical trial report.

Details about sample collection and sample handling will be provided in the ISF. A detailed overview of biomarker sample collection visits is outlined in the flow chart.

A detailed description of biomarker sample collection and sample handling is provided in the ISF.

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Any country not approving the biobanking will not participate in this process.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment, and storage are provided in the laboratory manual. For sampling timepoints see flow chart.

Serum/plasma from the original whole blood sample will be stored at an external biobanking facility contracted by the sponsor.

The following samples will be banked:

Unspecified pharmacogenomics (PGx) samples (DNA banking)

An additional blood sample (approximately 8.5 mL) for DNA banking will be collected in PAXgene Blood DNA tube at Visit 2. The DNA banking sample, derived from the original blood sample, will be stored at Boehringer Ingelheim. The stored DNA may be retrospectively analyzed.

Unspecified serum/plasma samples (serum/plasma banking)

Whole blood will be collected for the preparation of serum and plasma for banking purposes. In total, a maximum of 74 mL of blood will be drawn for the purpose of serum/plasma banking.

5.6 OTHER ASSESSMENTS

5.6.1 Chest HRCT assessment

Screening chest HRCT will be used in all patients to determine study eligibility and randomization stratification.

An historical HRCT can be used to determine eligibility, providing the scan was performed within the 12 months prior to screening. If a historical scan is not available, or an available scan fails to meet the required image acquisition specification, an HRCT may be performed after consent to determine eligibility.

All HRCT scans will be sent to a vendor for central review and confirmation of and the presence of relevant fibrotic ILD (>10% extent), prior to randomization. Confirmation of eligibility must be available prior to randomization Visit 2.

Eligible patients will have fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%.

Patients will be stratified according to their fibrotic pattern.
"UIP or UIP-like fibrotic pattern" is defined by criteria A, B and C, criteria A and C, or criteria B and C as described below.

A=Definite honeycomb lung destruction with basal and peripheral predominance
B=Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C=Atypical features are ABSENT, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Patients with PF-ILD who do not meet these criteria will be stratified into the group of patients with "Other fibrotic patterns". The following co-existing features will be accepted as other fibrotic patterns (but not limited to):

- ground glass opacity
- upper lung or peribronchovascular predominance
- mosaic attenuation
- air trapping
- centrilobular nodules

The following co-existing features will not be considered as other fibrotic patterns and therefore, patients would not qualify for the trial:

- widespread consolidation
- progressive massive fibrosis

If required, the HRCT scan should be performed as close to screening date as possible, preferably once eligibility is confirmed based on other parameters, to avoid unnecessary scans for patients who are found ineligible based on other criteria.

To perform a HRCT within the trial, all local regulatory requirements to perform an HRCT have to be met. In Germany, no HRCT will be performed as trial procedure; only historical HRCT will be submitted.
In addition to central reading of the HRCT scans, there is the intention to apply a computer scoring technology. If feasible, this technology will only be applied for scientific reasons and learnings and results will not be part of the clinical trial report. Determination of eligibility will, however, always be based on the central visual reading.

5.6.2 Health care resource utilization (HCRU)

For the purpose of a separate health economic analysis (such as cost-utility analysis), health care resource utilization (HCRU) data will be collected throughout the trial. Resource use data collected for calculating direct costs will include unscheduled hospitalizations,

healthcare provider visits, and emergency room/intensive care unit use. Non-medical resource use data will include changes in work productivity.

The economic evaluation of the HCRU data will not be part of the clinical trial report.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted for primary and secondary endpoints are using standard methods. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used as measurements to assess drug response. Measures conducted for exploratory endpoints might be new methodologies used in clinical trials but not yet validated for PF-ILD.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of 2 parts: Treatment Period A and B. Treatment Period A will consist of Visits 2 through 10, which will occur within one year of randomization. Following completion of the Week 52 visit (Visit 10), patients will continue to have trial visits every 12 weeks (Treatment Period B) until the end of the trial.

The trial will last until the last patient completes the EOT Visit and the Follow-up Visit as applicable (see Figure 3.1: 1).

After giving his/her informed consent, the patient will be screened for inclusion (see Section 3.3.2) and exclusion criteria (see Section 3.3.3) for the trial at Visit 1 and Visit 2 (refer to flow chart Treatment Period A). Visit 2 can be performed once the results from central laboratory of Visit 1 and central chest HRCT review are obtained. If for any reason the screening phase for an individual patient lasts for more than 8 weeks, then the laboratory examination for Visit 1 has to be repeated before randomization. The screening phase must be no longer than 12 weeks.

The patient will be randomized at Visit 2 if all inclusion criteria (including positive HRCT review and acceptable spirometry measurements) and none of the exclusion criteria (lab exclusion criteria referring to Visit 1 results) are fulfilled.

The acceptable time windows for visits are provided in the flow chart. Study measurements and assessments scheduled to occur ‘before’ trial medication administration on Day 1 are to be performed prior to the trial drug administration (including predose values for PK and biomarkers).

If a patient misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the execution of the investigational plan as per this clinical trial protocol may not be feasible.

With the consent of the patient, the sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual trial participant visits and assessments, home healthcare nurse visits, direct-to-patient/direct-from-patient shipments of trial treatment or bio-sample pick up from the patient's home. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations.

Based on a thorough assessment of the benefits and risks, some specific visits may be performed remotely, e.g. via telephone and/or internet-based means of communication, performance of assisted home spirometry and ePRO collection where applicable, or at the patient's home where a respective study nurse or home healthcare nurse service is feasible.

The visits may also be performed as a combination of home and remote visits, see descriptions of procedures in Section 6.2.2.2.
All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

In regards to the timing of the investigations/assessments, the following aspects should be adhered to:

- the patients' questionnaires (L-PF [symptoms/impact], EQ-5D-5L, HADS, PGIS) are to be completed preferably in the order of the flow chart before any other visit assessments or treatments, and if possible, before any interaction with the investigator or other members of the study team. Alternatively, the patient can complete them at home within 3 days before the site visit. At the latest, the patients' questionnaires must be completed prior to the pulmonary function tests.
- the C-SSRS interview should be done second, before any other procedure or assessment at the site
- for the pulmonary function tests: FVC (spirometry) must be performed before DLCO
- if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the patient and possible influence on physiological parameters.
- IRT call and IMP dosing/dispensing should always be done as the last procedure after all visit assessments, except at Visit 1 where the IRT call may be done earlier during the patient's visit.

6.2.1 Screening period

Screening Period
After informed consent is obtained, inclusion and exclusion criteria should be checked according to flow chart.

- During the screening visit, demographics information will be collected. This includes: age on the day of informed consent (in years)
- Sex (male, female; to describe the patient's sex at birth),
- Gender identity (male, female, other; in order to describe how the subject self-identifies regardless of their genotypic or phenotypic sex)

- For women: childbearing potential (yes/no) in order to characterize the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed unless not acceptable according to local regulations.

Patients will be asked to give informed consent to the DNA, plasma and serum banking samples (please note: the banking samples must not be taken prior to Visit 2). Participation is voluntary and is not a prerequisite for participation in the trial.

For information regarding laboratory tests, ECG, vital signs, height, body weight and physical examination, SpO2, refer to Sections 5.2.1 to 5.2.4.

For information on spirometry (FEV1 and FVC) and DLCO refer to Sections 5.1.1 and 5.1.6.

For information on the patient-reported outcomes/questionnaires and specific safety related questionnaires refer to Sections 5.1.5 and 5.2.5.

For information on chest HRCT, refer to Section 5.6.1.

Re-screening:
If patients fail on specific exclusion criteria during the first screening visit, they may be re-screened under the following conditions:

- If the patient was treated and cured from the acute infection.
- If the patient was treated for depression and HADS values are <14, not earlier than 3 months after the first screening.
- Other reversible conditions after respective treatment or resolution

If a patient results in a screen failure the patient must be registered as a screen failure in IRT system. However, re-screening of a previously screen failed patient will be permitted once. Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).

Re-screened patients will need to sign a new informed consent before any re-screening procedures and will be given a new unique patient number.
If a patient is re-screened and there are valid screening determinations from patient's previous participation in the trial, like for example safety labs, performed within 8 weeks prior to randomization (Visit 2), these do not need to be repeated.

If the Investigator believes that an ineligible laboratory test result is the result of an error or extenuating circumstance, then the test can be repeated once without the patient having to be re-screened.

6.2.2 Treatment periods

6.2.2.1 Conduct of a regular site visit

At the beginning of each visit during treatment phase, Investigator and site personnel should check the well-being of the patient as well as prepare all requirements for conduct of the visits that are necessary.

For information regarding laboratory tests, ECG, vital signs, height, body weight and physical examination, SpO2, refer to Sections 5.2.1 to 5.2.4.

For information on spirometry (FEV1 and FVC) and DLCO refer to Sections 5.1.1 and 5.1.6.

For information on the patient-reported outcomes/questionnaires and specific safety related questionnaires refer to Sections 5.1.5 and 5.2.5.

Each patient will receive the first dose of BI 1015550 or placebo at the end of Visit 2 (Day 1) under direct supervision of the investigator or designee. Patients will take trial medication twice daily (bid) orally from that timepoint onwards. On the day of any further clinic visit, supervision of administration is not required but trial medication will preferably be administered to the patient during the visit (as the last procedure, see Section 6.2).

The patient will have to bring back all IMP kits, used and unused at each on-site visit, including Visit 3. At Visit 3, the patient will have to bring back the IMP kits dispensed at Visit 2 to cover the trial medication intake until Visit 4.

FVC should be measured at approximately the same time of day, at least within the same half-day (morning or afternoon, with reference to the time at Visit 2).

6.2.2.2 Conduct of a fallback visit (remote/home visit)

If a patient is not able to travel to the site for a trial visit (Force majeure or physical disablement), remote visits (by phone or video call) should be performed instead. Especially for Visits 2, 5, 7, 10, and EOT, patients should be encouraged to perform a site visit as close as possible to the intended timepoint per flow chart including visit windows to perform an onsite spirometry.

Trial medication may be shipped from the site directly to the patient (if acceptable according to local laws and regulations).

The following assessments can be done remotely:

- Collect and assess adverse events, concomitant therapies, assess trial medication compliance.
- Specific data for investigator reported data: C-SSRS interview, evaluation of vasculitis symptoms and HCRU questions.
- Patient-reported outcomes: the patient questionnaires can be compiled electronically by the patient on the provided device or via the App on his own device. If paper questionnaires had been handed out at the last visit, the questionnaires should be

answered on the day (or within 3 days) of the remote visit and sent back to the site thereafter.
- Assisted home spirometry: for sites with the respective setup, see Section 5.1.1 and the respective home spirometry manual.
- Urine dipstick pregnancy test performed by the patient at home.

If home visits are possible (e.g. by a Home Healthcare Nurse or qualified site staff visiting the patient), the following assessments can be done at the patient's home:
- collection of blood and urine samples to be sent to the central lab or local lab
- vital signs
- trial medication compliance assessment
- dispensing of the next treatment kits, if possible

If blood and urine sampling for central lab at the patient's home is not possible, safety lab analyses including the routine safety lab tasks as per Table 5.2.3.1: 1 should be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and documents a clinically relevant safety issue as an adverse event.

6.2.2.3 End of treatment visit

As described in Section 3.1, after the confirmation of the benefit-risk evaluation for a potential start of the extension trial based on the main analysis, all patients still on blinded study treatment will perform an EOT visit.

For premature treatment discontinuations, follow instructions in Section 3.3.4.1.

6.2.3 Follow-up period and trial completion

A follow-up period of a minimum of 7 days (+3 days) after the end of treatment will be required. All patients will complete a visit at the end of the follow-up period for AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination.

Patients may be eligible to enter an extension trial if they complete this study on blinded treatment and meet the eligibility criteria for the extension trial. For these patients, the last visit in this trial and the end of this trial is the EOT visit. For patients who do not roll over to the separate extension trial (or could not roll over within a week of the EOT visit), the follow-up visit is required as the regular EOS visit.

Patients prematurely discontinuing trial treatment permanently will perform the EOT visit at the time of permanent discontinuation and the follow-up visit 7 days (+3 days) later. As this is taking place before the end of study, the patients should perform all regular trial visits as indicated in Section 3.3.4.1. For these off-treatment visits, PK samples can be skipped.

The follow-up visit can be skipped if the treatment had been discontinued at least 7 days before the actual EOT visit or if the following regular visit after the end of treatment is planned at 7-21 days after the last dose was administered.

For patients who withdraw consent – at time of trial medication discontinuation, end of study is an EOT visit followed by a follow-up visit.

All abnormal values (including laboratory parameters) at the last study visit (EOS) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. All (S)AEs persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

If needed in the opinion of the investigator, after the EOS visit additional FU visits may be scheduled for continued safety monitoring.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

As a default, a patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period
- Lost to follow-up
- Refusal to be followed up
- Death

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is a multi-center, multi-national, prospective, randomized, placebo-controlled, double blind clinical trial to investigate the efficacy and safety of BI 1015550 at a dose of 9 mg bid and 18 mg bid, in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD). The eligible patients will be randomized to BI 1015550 9 mg bid, BI 1015550 18 mg bid and placebo in 1:1:1 ratio, stratified by intake of AF treatment at baseline and HRCT pattern ("UIP or UIP-like fibrotic pattern" vs. "Other fibrotic patterns").

The primary endpoint is the absolute change from baseline in FVC [mL] at Week 52. The primary endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM) as detailed in Section 7.2.3.

The key secondary endpoint is time to the first occurrence of any of the components of the composite endpoint: time to first acute ILD exacerbation, first hospitalization for respiratory cause, or death. The key secondary endpoint will be analyzed using a Cox proportional hazards model as detailed in Section 7.2.4 with data from the whole trial, i.e. including data beyond 52 weeks.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Multiplicity adjusted analyses will be performed on the primary and key secondary endpoints. The graphical testing procedure [R16-4473] as depicted in Figure 7.1: 1 will be used to test the primary and key secondary endpoints for both dose levels. As the graphical

testing procedure abides the closed test principle, it holds strong control of family-wise type I error rate at two-sided alpha level of 0.05.

Statistical hypotheses to be tested for the primary endpoint are:

- H_{01}: there is no difference in the mean change from baseline in FVC in mL at Week 52 between BI 1015550 18 mg bid and placebo vs.
  H_{a1}: there is a difference in the mean change from baseline in FVC in mL at Week 52 between BI 1015550 18 mg bid and placebo.
- H_{02}: there is no difference in the mean change from baseline in FVC in mL at Week 52 between BI 1015550 9 mg bid and placebo vs.
  H_{a2}: there is a difference in the mean change from baseline in FVC in mL at Week 52 between BI 1015550 9 mg bid and placebo.

Statistical hypotheses to be tested for the key secondary endpoint are:

- H_{03}: there is no difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between BI 1015550 18 mg bid and placebo vs.
  H_{a3}: there is a difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between BI 1015550 18 mg bid and placebo.
- H_{04}: there is no difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between BI 1015550 9 mg bid and placebo vs.
  H_{a4}: there is a difference in the time to first acute ILD exacerbation, first hospitalization for respiratory cause or death between BI 1015550 9 mg bid and placebo.

The hypothesis testing of the key secondary endpoint is based on data collected up to the main analysis (all data up to DBL1; see Figure 3.1: 1). A supplementary analysis of the key

secondary endpoint using all data collected over the whole trial will be performed after DBL2.

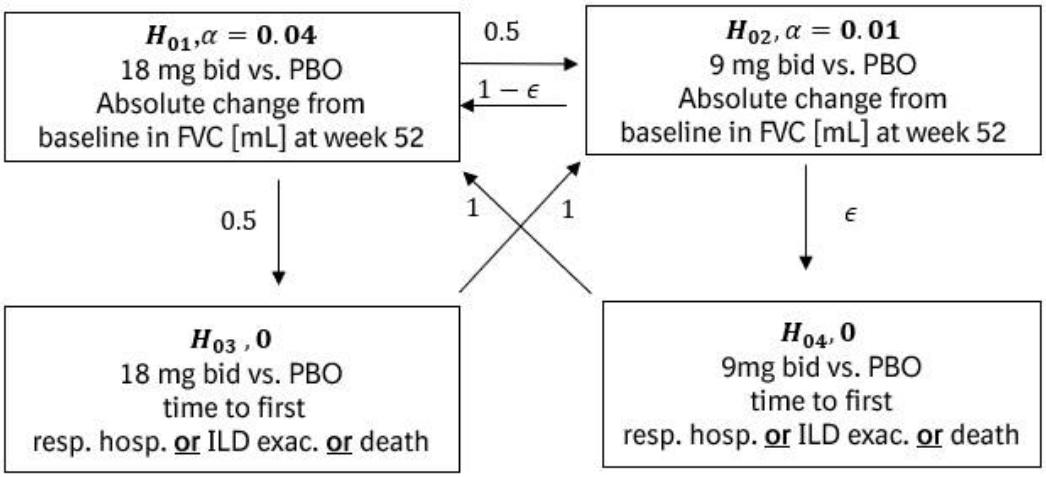


Figure 7.1: 1 Graphical testing procedure for hypothesis testing strategy

The testing procedure will start from testing of H_{01} and H_{02} for the primary endpoint. 4% level of the alpha level will be initially allocated to the comparison between 18 mg bid and placebo. 1% level of the alpha level will be initially allocated to the comparison between the 9 mg bid arm and placebo. At this step, no alpha is reserved for tests of the key secondary endpoint.

- If neither H_{01} nor H_{02} is rejected, all α is deemed as "spent" and no further testing will be performed.
- If at least one of H_{01} or H_{02} is rejected, the retained α from the successful hypothesis will be propagated according to the weights on the arrows leaving that hypothesis as depicted by the Figure 7.1: 1.

Note that ϵ is set to a negligible amount of 0.0001 at the start, to reflect the priority on hypotheses for 18 mg bid vs. placebo, namely H_{01} and H_{03}, over the 9 mg bid vs. placebo. The testing process continues if there is at least one hypothesis in the procedure that can be rejected at its allocated α level at that point. Each time a hypothesis is rejected, the graph is updated to reflect the reallocation of α. This iterative process of updating the graph and reallocating α is repeated until all hypotheses have been tested or when no remaining hypotheses can be rejected at their corresponding α levels at that point.

The primary objective of the trial will be achieved if either H_{01} or H_{02} is rejected and this trial is considered positive.

No adjustment for multiplicity is planned beyond primary and key secondary objective analyses.

7.2 PLANNED ANALYSES

7.2.1 General considerations

All planned efficacy and safety analyses, including for the primary and key secondary endpoints will be carried out at DBL1 (Figure 3.1: 1) and the statistical hypotheses described in Section 7.1 will be tested. After DBL2, analyses of the efficacy endpoints defined as "over the duration of the trial" and all safety analyses will be repeated to include all data collected until the end of the trial.

The following analysis sets will be defined for statistical analyses:

Entered Set (ES): This patient set includes all patients who signed informed consent. The ES will be used for the analysis of protocol deviations.

Randomized Set (RS): This patient set includes all entered and randomized patients. The RS will be used for the analyses of patient disposition.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug. The FAS will be used for baseline demographics and characteristics, protocol deviations, and all efficacy analyses, in which patients will be analyzed as their randomized treatment group.

Treated Set (TS): This patient set includes all randomized patients who received at least one dose of study drug. The TS will be used for all safety analyses, in which patients will be analyzed according to the actual treatment they received.

Data from of patients who are screened but not randomized will be listed but not included in any summary statistics or inferential statistics. Definitions and handling of important protocol deviations (IPDs) will be included in the DV domain specifications and will be stored within the trial master file (TMF) in the electronic document management system (EDMS). All potential important protocol deviations will be discussed during trial oversight meetings and report planning meetings. All final decisions concerning IPDs will be made before un-blinding.

Further Analysis Sets will be defined in the TSAP, if needed.

7.2.2 Handling of intercurrent events

The expected intercurrent events of interest in this trial are:

- Change of background antifibrotic therapy from baseline
- Start of a restricted medication
- Treatment discontinuation
- Death
- Lung transplant

The strategies for handling intercurrent events in this trial are as follows:

Primary strategy for primary and key secondary objectives:

All intercurrent events except for death and lung transplant will be handled according to the treatment policy approach as defined in ICH E9(R1). Use of the "treatment policy" approach disregards the intercurrent event and uses the value of the variable regardless of the occurrence of the intercurrent event (e.g., start of a restricted medication).

The intercurrent event of death will be primarily handled using a mixture of composite and hypothetical strategy as defined in ICH E9 (R1). Use of the "hypothetical approach" considers the effect of what would have happened if the intercurrent event did not occur. Use of the "composite approach" considers that a poor outcome will be expected (see also Section 7.3.1). The intercurrent event of lung transplant will be primarily handled using hypothetical strategy as defined in ICH E9 (R1).

Table 7.2.2: 1 Handling of intercurrent events as per ICH E9 (R1) within the different strategies

Intercurrent event	**Primary strategy for primary objective**	**Primary strategy for key secondary objective**
Change of background antifibrotic therapy	Treatment policy	Treatment policy
Start of a restricted medication	Treatment policy	Treatment policy
Treatment discontinuation or interruption (any cause)	Treatment policy	Treatment policy
Death	Hypothetical/ Composite	Composite (event)
Lung transplant	Hypothetical	Hypothetical (censored)

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

The secondary strategy will handle change of background antifibrotic therapy and treatment discontinuation by a hypothetical approach. Remaining intercurrent events will be handled in the same way as the primary strategy.

Any intercurrent events that are not listed will be decided by blinded review based on the general principle outlined and secondary strategies will be documented in the TSAP.

7.2.3 Primary objective analyses

Planned analyses for primary endpoint

The primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline in FVC at Week 52 between treatment groups. The analysis will include the fixed, categorical effects of treatment at each visit, baseline intake of AF treatment at each visit, HRCT pattern at each visit, and the fixed continuous effects of baseline FVC value at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The statistical model will be as follows:

$$y_{ijkmn} = \beta_j S_i + \tau_{jk} + f_{jm} + \omega_{jn} + e_{ij}$$

$$e_{ij} \sim N_Z(0, \Sigma)$$

- y_{ijkmn} = change from baseline in FVC value (mL) for patient i in intake of AF treatment at baseline stratum m and HRCT pattern stratum n at visit j receiving treatment k,
- S_i = FVC baseline measurement [mL] of patient i, i=1,2,…
- β_j = coefficient of baseline effect at visit j
- τ_{jk} = the effect of treatment k at visit j, j=1,…,Z and k = 1, ..,Y ,
- f_{jm} = the effect of intake of AF treatment at baseline stratum m at visit j, m=1,2. Intake of AF treatment at baseline is used as reported in the CRF (“No” as the class of reference, regardless of any mis-assignment to treatment based on identification of the wrong stratum in IXRS)
- ω_{jn} = the effect of HRCT pattern stratum n at visit j, n=1,2. HRCT pattern is used as reported in the CRF (“Other fibrotic patterns” as the class of reference, regardless of any mis-assignment to treatment based on identification of the wrong stratum in IXRS)
- e_{ij} = the random error associated with the jth visit of the ith patient. Errors are independent between patients.
  Σ = an unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α according to the multiple testing strategy specified in Section 7.1. The primary treatment comparison will be the contrast between treatments at Week 52.

Baseline is defined as data collected at Visit 2 prior to administration of first dose of study medication, or screening data if Visit 2 data are missing.

The primary analysis will be performed on the FAS. Patients will be analyzed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomization and is therefore consistent with regulatory guidance.

A treatment policy estimand will be used for primary analysis (i.e., all available data from the FAS in each active treatment arm and the placebo within the first 52 weeks will be used, including baseline and data retrieved post treatment discontinuation for patients who prematurely discontinued randomized treatment and after use of antifibrotic (rescue) therapy for patients not on AF therapy).

7.2.3.1 Sensitivity Analyses

Sensitivity analysis will be performed to assess whether background therapy status and HRCT pattern influence the primary efficacy analysis. This will use the same primary analysis model with additional covariates of antifibrotic treatment at baseline, HRCT pattern and two corresponding interactions with treatment and visit.

MMRM analyses assume that data are missing at random (MAR). For the primary outcome, tipping point analyses will assess how robust the primary analysis is against deviations from the MAR assumption by imposing a penalty for missing data. The tipping point analysis for the longitudinal FVC data will be based on the Multiple Delta Adjustment Method. A delta adjustment, dependent on a shift parameter and the weeks between visits, will be added to each imputed value. Shift parameters will be selected by arm covering plausible and implausible cumulative changes of FVC values at Week 52.

Additional sensitivity analyses based on different missing data imputation scheme as detailed in Section 7.3.1 will be conducted.

On-treatment, while-compliant-to-protocol analyses and models with modified sets of covariates will be conducted as further sensitivity analyses.

Further details will be specified in the TSAP.

7.2.3.2 Subgroup Analyses

Subgroup analyses will include at least gender, age, antifibrotic treatment at baseline and HRCT pattern. A complete list of subgroup analyses will be specified in the TSAP.

7.2.3.3 Supplementary Analyses

Further details will be specified in the TSAP.

7.2.4 Secondary objective analyses

7.2.4.1 Analysis of key secondary endpoint

The key secondary endpoint of time to first acute ILD exacerbation, first hospitalization for respiratory cause or death will be analyzed with a Cox proportional hazards model using data over the whole trial, i.e., including data beyond 52 weeks. The equality of the hazard rates will be tested by the Wald test for the treatment effect at a two-sided significance level deemed for test in each step as specified in Section 7.1. The model will include the treatment effect, HRCT pattern , intake of AF treatment, age (continuous), FVC % predicted and DLCO % predicted (corrected for hemoglobin) at baseline as covariates. Breslow's method for handling ties will be used. Kaplan-Meier plots by treatment group will be presented. In

addition, percentage of patients with event at Week 52 will be presented both descriptively and by Kaplan-Meier estimates.

In general, for all time-to-event endpoint, the time to the event of interest will be computed as (event date − first drug intake date) +1. All events observed after first drug intake date until trial termination will be included in the analysis except for events occurring after a lung transplantation as outlined in Section 7.2.2. Patients who do not have an event during the trial period will be censored at the individual day of trial completion or the last day that the patient was known to be free of the event, whichever is earlier. The time to censoring will be computed as (individual day of trial completion or the last day known to be free of the event – first drug intake date) + 1. For patients who have more than one event during the trial, the time to the first event will be considered for the analysis.

Same as for the primary endpoint, the primary analysis will be performed on the FAS using a treatment policy estimand listed in Section 7.2.2.

On-treatment, while-compliant-to-protocol analyses and models with modified sets of covariates will be conducted as further sensitivity analyses. In addition, handling change of background antifibrotic therapy or treatment discontinuation will also be evaluated by hypothetical approach (censored) and composite approach (addition of antifibrotic therapy considered as event).

Further details will be specified in the TSAP.

7.2.4.2 Analysis of other secondary endpoints

Absolute change from baseline in the various Living with Pulmonary Fibrosis (L-PF) (domain) scores at Week 52 will be analyzed by a restricted maximum likelihood (REML) estimation based approach using a mixed-effect model with repeated measurements (MMRM) analysis comparing the change from baseline in respective L-PF (domain) Score at Week 52 between treatment groups. The analysis will include the fixed, categorical effects of treatment at each visit, baseline intake of AF treatment at each visit, HRCT pattern at each visit, and the fixed continuous effects of baseline at each visit. Analogous models will be used to analyze absolute change from baseline in FVC % predicted at Week 52 and absolute change from baseline in DLCO % predicted at Week 52.

In general, for all time-to-event endpoints, the time to the event of interest will be computed as (event date − first drug intake date) +1. All events observed after first drug intake date until trial termination will be included in the analysis except for events occurring after a lung transplantation as outlined in Section 7.2.2. Patients who do not have an event during the trial period will be censored at the individual day of trial completion or the last day that the patient was known to be free of the event, whichever is earlier. The time to censoring will be computed as (individual day of trial completion or the last day known to be free of the event – first drug intake date) + 1. For patients who have more than one event during the trial, the time to the first event will be considered for the analysis.

Time to event secondary efficacy endpoints will be analyzed using a Cox proportional hazards model using data from the whole trial i.e. including data beyond 52 Weeks. The equality of the hazard rates will be tested by the Wald test for the treatment effect at the

two-sided 5% significance level. The model will include the treatment effect, HRCT pattern , intake of AF treatment, age (continuous), FVC % predicted and DLCO % predicted (corrected for hemoglobin) at baseline as covariates as covariates. Breslow's method for handling ties will be used. Kaplan-Meier plots by treatment group will also be presented. In addition, percentage of patients with event at Week 52 will be presented both descriptively and by Kaplan-Meier estimates.

Any p-values presented for the other secondary endpoints will be considered nominal in nature and no adjustment for multiplicity will be made.

7.2.5 Further objective analyses

All further endpoints will be considered exploratory in nature. The analysis of further endpoints over 26 or 52 weeks will be performed with the same models and procedures as described for the primary and secondary endpoints.

Restricted maximum likelihood estimation based on a random slope and intercept model will be used to compare the adjusted annual rate of decline in FVC [mL/year] as measured over 52 weeks between treatment groups. This model will include fixed effects for time, treatment, baseline, intake of AF treatment at baseline, HRCT pattern, as well as treatment-by-time and baseline-by-time interactions. Random effects for time and intercept will be included for each patient.

Further time to event endpoints will be assessed using similar analysis models as respective secondary time to event endpoints (e.g. Cox regression models, Kaplan-Meier plots).

The annualized rate of hospitalization due to respiratory cause over the whole trial will be analyzed using negative binomial regression with logarithm of the exposure as an offset. The analyses will include the treatment effect, intake of AF treatment at baseline, HRCT pattern, and other key covariates of interest with more detail to be provided in the TSAP. The mean number of events per patient year by treatment arm, the rate ratio, and corresponding 95% confidence interval will be presented.

7.2.6 Safety analyses

All safety assessments described below will focus on data collected within the first 52 weeks and additional safety analyses will be repeated to include data over the whole trial.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

Kaplan-Meier plots will be produced for the time to premature treatment discontinuation, for the time to first dose reduction and for the time to first treatment interruption.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the

REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analyzed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Summary tables will be produced for the adjudication results of MACE and deaths.

Further details will be specified in the TSAP.

7.2.7 Other Analyses

7.2.7.1 Pharmacokinetic Methods

In the Clinical Trial Report, plasma concentrations of BI 1015550 will be tabulated with descriptive statistics. A population PK analysis may be performed on BI 1015550 plasma concentrations. If so, a separate population PK analysis plan will be written, and results will be reported separately.

7.2.8 Interim analyses

Not applicable

7.3 HANDLING OF MISSING DATA

7.3.1 Efficacy endpoints

In the primary analysis of primary endpoint, missing data will not be imputed except for death, where a poor outcome will be assigned, see Table 7.3.1: 1. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption".

A tipping point analysis is planned as sensitivity analysis, see Section 7.2.3.1. The effect of missing data on the primary endpoint will be further investigated using multiple imputation techniques.

These four subsets of patients will be used in sensitivity analyses to estimate the treatment effect under differing assumptions around the persistence of efficacy after withdrawal of trial medication.

1. Patients with an FVC result at Week 52 who received trial medication until Week 52.
2. Patients with an FVC result at Week 52 who prematurely discontinued trial medication prior to Week 52.
3. Patients without an FVC result at Week 52 who were alive at Week 52.
4. Patients without an FVC result at Week 52 who died prior to Week 52.

Table 7.3.1: 1 describes the planned sensitivity analyses for handling missing primary endpoint data. Sensitivity analyses 1 and 2 will only be performed if there are at least 10 patients included in patient subset 2 in each treatment group.

Table 7.3.1: 1 Sensitivity analyses for handling missing primary endpoint data

Analysis	**Patient subset 3: No FVC result but alive at Week 52**		**Patient subset 4: No FVC result but died Week 52**	
	Handling of missing FVC	Underlying assumption	Handling of missing FVC	Underlying assumption
Primary analysis	Missing data handled by model	Assumes missing at random. Discontinued patients would have behaved similarly to patients who did not discontinue.	Impute based on 10th percentile[1] of all observed values (change from baseline) in each treatment arm at each visit	Patients who died before Week 52 would have expected a poor outcome
Sensitivity analysis 1	**Retrieve dropout:** based on the point estimates for drug and placebo in patient subset 2.	Patients without a result would have behaved similarly to discontinued patients with a result who are in the same treatment group	Impute based on 10th percentile[1] of all observed values (change from baseline) in each treatment arm at each visit	Patients who died before Week 52 would have expected a poor outcome.
Sensitivity analysis 2	**Follow reference:** based on the point estimates for all placebo patients in	Patients without a result would have behaved similarly to all patients in the placebo arm		

	patient subset 1 & 2.			

[1] 10th is selected based on pooled INPULSIS I/II data considering both to reflect a negative outcome and balance for estimation efficiency for avoiding extreme values.

In the analysis of all other continuous endpoints, missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption".

In the primary analysis of time-to-event endpoints, missing or incomplete data will be handled using standard survival analysis techniques (i.e. censoring), except for death which will be handled as event.

Additional details on the handling of missing data and sensitivity analysis will be specified in the TSAP prior to unblinding.

7.3.2 Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards. Other missing safety data will not be imputed.

7.4 RANDOMIZATION

Patients will be parallel randomized in blocks to double-blind treatment. The randomization will be stratified by intake of AF treatment at baseline (Yes/No), and HRCT pattern ("UIP or UIP-like fibrotic pattern" vs. "Other fibrotic patterns"), within the IRT system. Approximately equal numbers of patients will be randomized to BI 101550 18 mg bid, BI 1015550 9 mg bid and placebo in a 1:1:1 ratio.

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

Results from the Phase II study (1305-0013) show substantial improvement of BI 1015550 over placebo in FVC change from baseline to Week 12. Given the uncertainty of whether a similar progressive patient population will be recruited in the current trial and a potential of lower FVC decline under Placebo based on comparison between the INBUILD trial (1199-0247) and pooled INPULSIS trials (1199-0032 and 1199-0034), the following assumptions will be made. For trial 1305-0023 in PF-ILD patients, we assume lower treatment effects compared to 1305-0014, 85-90 mL in patients not on background antifibrotic treatment and 55-60 mL in patients on background antifibrotic treatment. 30% of patients are expected to be on background antifibrotic treatment.

Additionally, 25% of Placebo patients not on antifibrotic treatment, are expected to initiate antifibrotic therapy on average at Week 26 and 12.5% of BI 1015550 patients not on AF treatment expected to switch AF treatment after 26 weeks. Under the linearity assumption of FVC decline assumed treatment effect at Week 52 in patients not on background treatment will be reduced by 12.5%. Based on all above-mentioned assumptions, a treatment effect of 71 mL for BI 1015550 vs. placebo in FVC change from baseline at Week 52 is expected for trial 1305-0023. A common adjusted standard deviation (SD) of FVC change of 280 mL is assumed based on estimates from INBUILD and INPULSIS trials.

An effective sample size of 336 patients per group will detect a treatment effect of 71 mL with 91% power under two-sided alpha of 5%. With 336 patients per arm and a two-sided type I error rate of 0.05, a treatment effect size of 80, 65, 55, and 45 can be detected for each of the primary endpoint with 96%, 85%, 72%, and 55% power respectively.

Calculations were performed using R Version 4.0.2.

For the key secondary endpoint time to first acute ILD exacerbation, first hospitalization for respiratory cause or death, assumptions for the power calculations are derived from the pivotal INBUILD trial (1199-0247) as well as the pooled pivotal INPULSIS trials (1199-0032 and 1199-0034) in IPF. The proportion of Placebo patients with at least one event of the composite outcome observed until Week 52 was estimated between 14.6% and 18.3% based on extrapolation for INBUILD and INPULSIS patients. Scenarios including 15%, 17.5% and 20% are presented in the power calculations. As the treatment effect on the key secondary endpoint is unknown, the power was evaluated for hazard ratios in the range of 0.60 to 0.75 for the treatment effect of BI 1015550 vs. placebo over the duration of the trial. Accrual time for 1305-0023 is expected to be 16 to 20 months. Table 7.5: 1 provides power calculations for time to first acute ILD exacerbation, first hospitalization for respiratory cause or death on different combined scenarios. Power calculations assuming a 1:1:1 randomization, are based on the effective sample size of 336 patients per arm with linear accrual rate have been performed based on a two-sided Log-rank test comparing BI 1015550 18 mg bid vs. placebo, with a significance level of 5%. No correction for dropouts has been incorporated into the power calculation for the key secondary endpoint.

Table 7.5: 1: Power evaluation for secondary endpoint based on a two-sided, two-sample Log-rank test with a significance level of 5% considering different effect sizes, event rates and accrual time

52 Week event rate for key secondary endpoint (placebo)	Hazard Ratio	Accrual time in months	Expected number of events/Local Power[1]
15%	0.75	16	145/41%
15%	0.70	16	141/56%
15%	0.65	16	137/71%
15%	0.60	16	133/84%

52 Week event rate for key secondary endpoint (placebo)	Hazard Ratio	Accrual time in months	Expected number of events/Local Power[1]
17.5%	0.75	16	168/46%
17.5%	0.75	20	182/49%
17.5%	0.70	16	163/63%
17.5%	0.70	20	177/66%
17.5%	0.65	16	159/78%
17.5%	0.65	20	173/81%
17.5%	0.60	16	136/89%
17.5%	0.60	20	154/91%
20%	0.75	16	190/51%
20%	0.70	16	185/68%
20%	0.65	16	180/82%
20%	0.60	16	175/92%

[1] numbers reflecting comparison between one active dose arm and placebo arm

Based on the range of plausible assumptions and hazard ratios considered, local power of the key secondary ranges from 40%-50% for a hazard ratio of 0.75 to around 84%-92% for a hazard ratio of 0.6 as often targeted in pivotal trials.

Calculations were performed using “rpact” package version 3.0.4 in R Version 4.0.2.

As a graphical testing procedure is used for the hypothesis tests in this Phase III trial and the controlled one-sided type I error rate for each hypothesis test depends on the result of other endpoints, it is very complicated, if not impossible, to derive the mathematical formula for the power of each efficacy endpoints considered in the graphical testing procedure. As a result, we conducted simulations to approximate the power for each efficacy endpoint (i.e. the probability of rejecting each null hypothesis) using the graphical testing procedure under five different scenarios of the effect size for each efficacy endpoint and dose level with the proposed graph. 336 effective patients per arm, two-sided family-wide type I error rate of 0.05, and 0.4 correlation among efficacy endpoints. The probability of rejecting at least one dose in primary endpoint, namely H_{01} or H_{02}, as well as the probability of rejecting both primary and secondary endpoint for high dose are calculated.

Simulation results as presented in Table 7.5: 2 suggest that with 336 effective sample size per arm, there is at least 94% power to detect an effect size of 71 mL in FVC change from baseline at Week 52 for at least one dose is significant (Scenario #1). Regardless of effect size of the 9 mg bid arm, probability of detecting a significant FVC effect of 71 mL in the 18 mg bid arm is between 89% to 90%. Furthermore, if 18 mg bid arm has an effect of 71 mL

in primary endpoint and HR of 0.6 in key secondary endpoint, the probability of rejecting both H_{01} and H_{03} is between 70% to 78% depending on relative effect size of the 9 mg bid arm. The simulation results also show a well-controlled type-I error under the null hypothesis (Scenario #5) with the proposed testing strategy.

Additional simulation results, which are not displayed here, also show that the transition weight from H_{01} to H_{02} ranging from 0.5 to 0.7 does not impact the marginal power for the primary and key secondary efficacy endpoints much. Hence we choose 0.5 as the transition weight given the desirable success probabilities of 89% to 94% for primary endpoint and 70% to 78% for key secondary endpoint 18 mg bid arm under various conditions.

In summary with 336 effective patients per arm, simulation results show satisfactory operational characteristics of the proposed graphical testing procedure under Scenarios #1-5 which are considered plausible for this Phase III trial.

Table 7.5: 2 Multiplicity adjusted probabilities of success for each hypothesis and positive study under different scenarios of effect sizes from simulations.

	18 mg bid FVC [mL] change from baseline at Week 52[1]	**9 mg bid FVC [mL] change from baseline at Week 52[1]**	**18 mg bid time-to resp hosp. or exac. or death[2]**	**9 mg bid time-to resp hosp. or exac. or death[2]**
Scenario #1 (both doses achieve target effect)	**71**	**71**	**0.6**	**0.6**
Probability of rejecting each hypothesis	90%	87%	78%	67%
Probability of rejecting at least one dose primary endpoint	94%			
Scenario #2 (low dose approx. 70% of high dose)	**71**	**50**	**0.60**	**0.72**
Probability of rejecting each hypothesis	89%	60%	75%	33%
Probability of rejecting at least one dose primary endpoint	90%			
Scenario #3 (low dose approx. 50% of high dose)	**71**	**36**	**0.60**	**0.80**

	18 mg bid FVC [mL] change from baseline at Week 52[1]	**9 mg bid FVC [mL] change from baseline at Week 52[1]**	**18 mg bid time-to resp hosp. or exac. or death[2]**	**9 mg bid time-to resp hosp. or exac. or death[2]**
Probability of rejecting each hypothesis	89%	36%	72%	12 %
Probability of rejecting at least one dose primary endpoint	89%			
Scenario #4 (low dose no effect)	**71**	**0**	**0.60**	**1**
Probability of rejecting each hypothesis	89%	3.7%	70%	0.2%
Probability of rejecting at least one dose primary endpoint	89%			
Scenario #5 (null effect)	**0**	**0**	**1**	**1**
Probability of rejecting each hypothesis	3.9%	1.3%	0.1%	<0.1%
Probability of rejecting at least one dose primary endpoint	4.6%			

Probability calculated based on 50 000 simulation iterations. Total alpha-level = 0.05 (two-sided), 1:1:1 randomization ratio with 336 patients per arm.
[1] For FVC change from baseline at Week 52, SD assumed to be 280 mL.
[2] For composite endpoint: placebo event rate at 52 weeks = 17.5%, accrual period = 16 months, no dropout, correlation between endpoints for each dose = 0.4.

Based on the proportions of early treatment discontinuation, patients with missing data and missing data patterns as observed in our Phase II trial 1305-0013 and INBUILD trial, we project 20% patients will prematurely terminate treatment in our Phase III trial. Since BI will take every measure to collect all data at planned visits from early dropout, we anticipate 75% of these dropouts will have efficacy outcome collected after treatment termination and can be used for analysis. Based on these estimations, we assume a 5% rate for missing data. Furthermore, an information content of 0.34 estimated from pivotal INPULSIS trials, which provides average amount of information by a non-completing patient is assumed. Based on these estimations, we apply a 3.3% correction for missing data in sample size calculation for

this Phase III trial. This gives the total number of 1041 randomized patients, with 347 randomized patients in each treatment arm.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC/EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the Sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.
The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The

investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB/IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

For adverse events, an end date may not always be available (e.g. due to hospital discharge and later recovery, or change in treating physician), but should be recorded in the source if known.

For eCRF all data need to be derived from source documents, which need to be available on-site (this could be for example physician's notes in patient files, printouts, patient diaries).

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to

retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.
Copies of source documents necessary for evaluation of adverse events will be provided to the adjudication committee members or the pharmacovigilance department. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, i.e. HRCT or biopsy reports, DLCO report with proper documented medical evaluation (in validated electronic format, if available)
- Patient-reported outcome forms and C-SSRS questionnaire if done on paper
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.

For the spirometry, electronic patient-reported outcomes and C-SSRS questionnaire data will be transferred to the data base from the respective vendor and the electronic records are regarded as source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of trial participant data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymized data will be transferred to the sponsor by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the patient files and clinical data is strictly limited: personalized treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and patients will be informed as appropriate.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place

- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay / equipment validation depending on the intended use of the biomarker data
- Samples and / or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Steering Committee (SC) consisting of independent experts and sponsor representatives will be established to support the Coordinating Investigator who will be the chair of the SC. The composition of the SC will be documented in the TMF. The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor and summarised in a SC charter.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate safety data on a regular basis. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend

continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs) / Health Authorities (HAs), IRBs / ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

An independent adjudication committee will review all fatal cases and adjudicate all deaths due to cardiac or respiratory causes. The adjudication committee will a will also review all adverse events categorized as major adverse cardiovascular events (MACE). A separate independent adjudication committee will review all events suspicious for vasculitis.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organize, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central images service, a central ePRO service, a central spirometry service, a central patient and site engagement service and an IRT vendor will be used in this trial. Details will be provided in the respective vendor specific instruction manuals as applicable, in the ISF.

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10. APPENDICES

10.1 SPIROMETRY: BRONCHODILATOR WASHOUT RECOMMENDATIONS

Based on ATS/ERS 2019 guidelines for the conduct of spirometry, the following washout of bronchodilators is recommended before spirometry (see Table 10.1: 1). According to the ongoing treatment, the investigator should advise the patient on the washout on/before the days of the onsite spirometry and document it in the source documents.

Table 10.1: 1 Minimal washout timeframes for bronchodilators before spirometry

Bronchodilator Medication	**Withholding Time**
SABA (e.g., albuterol or salbutamol)	4-6 hours
SAMA (e.g., ipratropium bromide)	12 hours
LABA (e.g., formoterol or salmeterol)	24 hours
Ultra-LABA (e.g., indacaterol, vilanterol, or olodaterol)	36 hours
LAMA (e.g., tiotropium, umeclidinium, aclidinium, or glycopyrronium)	36-48 hours

10.2 PATIENT-REPORTED OUTCOMES

10.2.1 Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (LPF)

Instructions for Completing the
Living with Pulmonary Fibrosis (L-PF) Symptoms Questionnaire

Complete this questionnaire to assess the symptoms you may have experienced from Pulmonary Fibrosis (PF) over the last 24 hours.

Keep in mind:
- you are not being asked to compare yourself to anyone else
- you are not being asked to compare how you are now with any time in the past

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Items 1-12: The first 12 items ask about your symptoms in relation to physical activities, some of which you may not have done in the **last 24 hours**. If you did not perform an activity, we would like to know whether it was because you did not have the opportunity to do it (for example, maybe your home doesn't have stairs, so you did not walk up a flight of stairs), or whether you avoided the activity because it was too difficult.

If you did the stated activity, then reflect on the last 24 hours, and consider whether, on average, doing the activity at your usual pace or intensity level made you short of breath—and if so, how much.

If you normally use oxygen when you perform a given activity, then consider your response as if you were using supplemental oxygen.

Please select the box that best describes your experience.

1. Did you get dressed in the last 24 hours?

Yes — How short of breath did getting dressed make you?

Not at all [0] [1] [2] [3] [4] Extremely

No — I did not get dressed in the last 24 hours because:

A — I avoided this activity because it was too difficult to perform

B — Not applicable, because I did not want or have the opportunity to do it

2. Did you walk up one flight of stairs in the last 24 hours?

☐ Yes How short of breath did walking up one flight of stairs make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No I did not walk up one flight of stairs in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

3. Over the last 24 hours, how short of breath have you been while sitting down, relaxing, reading, or watching TV?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

4. Did you walk up a short, gradual incline (like a wheelchair ramp into a building) in the last 24 hours?

☐ Yes How short of breath did walking up a short, gradual incline make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No I did not walk up a short, gradual incline in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

5. Did you perform a grooming activity (e.g., brush teeth, shave, fix hair) in the last 24 hours?

☐ Yes How short of breath did grooming make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No I did not perform a grooming activity in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

6. Did you walk outside on a level surface (approximately 150 feet/45 meters, or the distance of half a typical city block) in the last 24 hours?

☐ Yes — How short of breath did walking outside on a level surface make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No — I did not walk outside on a level surface in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

7. Did you walk from room to room inside your home in the last 24 hours?

☐ Yes — How short of breath did walking from room to room inside your home make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No — I did not walk from room to room inside my home in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

8. Did you leave your home in the last 24 hours?

☐ Yes — How short of breath did getting ready to leave your home (e.g., find keys, put on coat, lock doors) make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 **Extremely**

☐ No — I did not leave my home in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

9. Did you bathe or shower in the last 24 hours?

☐ Yes — How short of breath did bathing or showering make you?

Not at all ☐0 ☐1 ☐2 ☐3 ☐4 Extremely

☐ No — I did not bathe or shower in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

10. Did you do light cleaning around the house in the last 24 hours?

☐ Yes — How short of breath did doing light cleaning around the house make you?

Not at all ☐0 ☐1 ☐2 ☐3 ☐4 Extremely

☐ No — I did not do light cleaning around the house in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

11. Over the last 24 hours, how short of breath were you after eating a meal or snacks?

Not at all ☐0 ☐1 ☐2 ☐3 ☐4 Extremely

12. Did you lift and carry a light load (e.g., less than 10 lbs) a short distance (e.g., from one room to another) in the last 24 hours?

☐ Yes — How short of breath did lifting and carrying a light load a short distance make you?

Not at all ☐0 ☐1 ☐2 ☐3 ☐4 Extremely

☐ No — I did not lift or carry a light load a short distance in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

Items 13-18: Each item focuses on cough. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

13. Over the last 24 hours, how often did you cough?

Not at all 0 1 2 3 4 **Constantly**

If you chose "0", please skip to Item 19.

14. Over the last 24 hours, how often did you cough when you took a deep breath?

Not at all 0 1 2 3 4 **Constantly**

15. Over the last 24 hours, how often did you cough when you were breathing hard or fast?

Not at all 0 1 2 3 4 **Constantly**

16. Over the last 24 hours, how often did you cough when you over-exerted yourself?

Not at all 0 1 2 3 4 **Constantly**

17. Over the last 24 hours, how often did coughing make you short of breath?

Not at all 0 1 2 3 4 **Constantly**

18. Over the last 24 hours, how often did you feel an annoying tickle in your throat?

Not at all 0 1 2 3 4 **Constantly**

19-23: These items primarily focus on your energy level. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

19. Over the last 24 hours, how was your energy level?

Extremely low 0 1 2 3 4 **Excellent**

20. Over the last 24 hours, of all that you wanted to get done, how much did you actually get done?

Nothing 0 1 2 3 4 **Everything**

21. Over the last 24 hours, how much energy did you have to do all the things you like to do?

No energy 0 1 2 3 4 **A lot**

22. Over the last 24 hours, how much did coughing have a negative effect on your energy?

No effect at all 0 1 2 3 4 **A lot**

23. Did you become short of breath in the last 24 hours?

Yes How long did it take you to recover when you became short of breath?

No time at all 0 1 2 3 4 **An extremely long time**

No Please continue to the next page.

Finally, we would like to ask you 5 questions about your supplemental oxygen use.

Oxygen Question 1. Do you ever use supplemental oxygen?
(Place an "X" in one box)

- [ ] Yes →→ proceed to Oxygen Question #2.
- [ ] No →→ skip Oxygen Questions 2-5

Oxygen Question 2. I use supplemental oxygen...
(Place an "X" in one box)

- [ ] 1 →→ only when I sleep (answer Oxygen Question #3)
- [ ] 2 →→ only when I perform a physical activity (such as getting dressed or walking) (answer Oxygen Question #4)
- [ ] 3 →→ when I sleep or perform a physical activity (such as getting dressed or walking) but not at rest (answer Oxygen Questions #3 and #4)
- [ ] 4 →→ all the time (answer Oxygen Questions #3-5)

Oxygen Question 3. When I sleep, I most often use an oxygen flow rate of_____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Oxygen Question 4. When I perform a physical activity (such as getting dressed or walking), I most often use an oxygen flow rate of_____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Oxygen Question 5. At rest, I most often use an oxygen flow rate of_____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Thank you for taking the time to complete the L-PF Symptoms Questionnaire.

Instructions for Completing the Living with Pulmonary Fibrosis (L-PF) Impacts Questionnaire

The goal of this questionnaire is to determine how Pulmonary Fibrosis affects your quality of life.

Quality of life refers to your perceptions of your overall position in life in relation to:

- your goals and expectations
- your standards and values
- your concerns and judgments

Among other things, quality of life encompasses:

- your physical health (conditions/diseases, symptoms, therapies)
- your psychological state (outlook, emotional well-being)
- your level of independence
- the relationships you have with pertinent features of your environment

Reflect on your life: has Pulmonary Fibrosis affected your quality of life? **As you respond to the items, reflect on your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.**

Items 1-16: For these items, reflect on the **last 7 days** as you consider where you are on the scale between the two statements.

On average, over the last 7 days...

1. **How much did shortness of breath prevent you from doing things you wanted to do?**

Not at all [0] [1] [2] [3] [4] **Extremely**

2. **How much did fear of becoming too short of breath limit your physical exertion?**

Not at all [0] [1] [2] [3] [4] **Extremely**

3. **How was your stamina when you exerted physically?**

Extremely poor [0] [1] [2] [3] [4] **Excellent**

4. **How frustrated were you by the time it took you to complete a physical activity?**

Not at all [0] [1] [2] [3] [4] **Extremely**

5. **How frustrated were you by the speed it took you to complete a physical activity?**

Not at all [0] [1] [2] [3] [4] **Extremely**

6. **How frustrated were you by your need to rest during or after completing a physical activity?**

Not at all [0] [1] [2] [3] [4] **Extremely**

7. **How much did coughing embarrass you?**

Not at all [0] [1] [2] [3] [4] **Extremely**

8. **How much did coughing frustrate you?**

Not at all [0] [1] [2] [3] [4] **Extremely**

On average, over the last 7 days...

9. How much did coughing interrupt your conversations (in person or on the phone)?

Never 0 1 2 3 4 All of the time

10. How frightening was your coughing to you?

Not at all 0 1 2 3 4 Extremely

11. How much was your cough a problem for you?

Not at all 0 1 2 3 4 Extremely

12. How much hassle or inconvenience has pulmonary fibrosis caused you in your day-to-day life?

None 0 1 2 3 4 A lot

13. How much did you have to rest in the middle of doing a simple chore inside the house?

Not at all 0 1 2 3 4 A lot

14. How much did you have to pace yourself to make it through the day?

Not at all 0 1 2 3 4 A lot

15. How much did it take to get yourself ready to leave the house?

Very little time 0 1 2 3 4 Extremely long time

16. How much were you forced to depend on other people to do things for you?

Not at all 0 1 2 3 4 A lot

Only five more...

For Items 17-19: Think broadly about your shortness of breath, cough and energy level over the last 7 days. Have these symptoms affected how you have felt physically? Psychologically? Have they disrupted your life? Or limited you in terms of what you would like to do or how you would like to do it? Now, please respond to Items 17-19.

On average, over the last 7 days...

17. How has shortness of breath affected your quality of life?

Made my quality of life extremely poor	0	1	2	3	4	No negative effect

18. How much has your cough affected your quality of life?

Made my quality of life extremely poor	0	1	2	3	4	No negative effect

19. How much has your energy level affected your quality of life?

Made my quality of life extremely poor	0	1	2	3	4	No negative effect

For these last two Items: Think broadly again about whether Pulmonary Fibrosis has affected you and your quality of life over the last 7 days. **Reflect on your symptoms and other aspects of your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.**

On average, over the last 7 days...

20. How have you felt in terms of physical health?

Extremely poor	0	1	2	3	4	Excellent

21. How has your quality of life been?

Extremely poor	0	1	2	3	4	Excellent

The end.
Thank you for taking the time to complete the L-PF Impacts Questionnaire.

10.2.2 EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D)

This trial uses the English version for the United Kingdom [R12-1920].

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

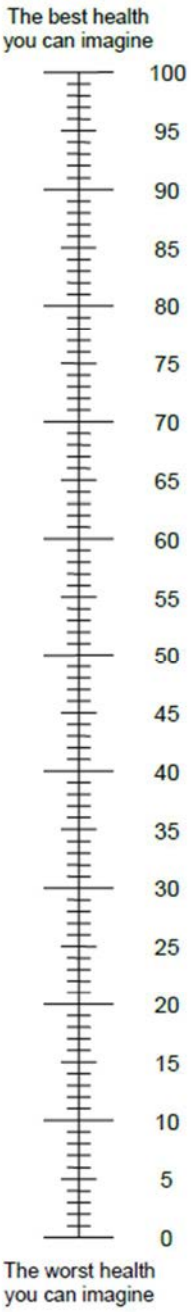
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



10.2.3 Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D			A	D
		I feel tense or "wound up"	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Never	Never		0
		I enjoy the things I used to enjoy	**I get a sort of anxious feeling like "butterflies" in the stomach**		
	0	Definitely	Never	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and fairly badly	Definitely		3
2		Yes, but not too badly	Often I don't take as much care as I should		2
1		Sometimes, but it doesn't worry me	Sometimes I don't take as much care as I should		1
0		Never	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Definitely	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Never	Never	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever have		0
2		A lot of the time	Somewhat less than I used to		1
1		Not too often	Much less than I used to		2
0		Almost never	Rarely		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often	3	
	2	Not often	Often	2	
	1	Sometimes	Not very often	1	
	0	Most of the time	Never	0	
		I can sit at ease and feel relaxed	**I can enjoy a good book, radio or television program**		
0		Always	Often		0
1		Usually	Sometimes		1
2		Not often	Not often		2
3		Never	Very seldom		3

Please make sure you have answered all the questions.

	A	D
TOTAL		

10.2.4 Patient's Global Impression of Severity (PGIS) for Cough, Shortness of Breath, and Fatigue

Cough

Please think about cough and reflect on the last 7 days: call to mind whether you have had a cough and if so, how frequently it has occurred, how severe it has been, and whether cough has affected how you feel and how you function in your daily life.

Considering all these, please rate the severity of your cough over the last 7 days by placing a tic in the one box corresponding to your response:

☐(0)	☐(1)	☐(2)	☐(3)	☐(4)	☐(5)
Not present	Very mild	Mild	Moderate	Severe	Very severe

Shortness of breath

Please think about shortness of breath and reflect on the last 7 days: call to mind how severe it has been and whether shortness of breath has affected how you feel and how you function in your daily life.

Considering all these, please rate the severity of your shortness of breath over the last 7 days by placing a tic in the one box corresponding to your response:

☐(0)	☐(1)	☐(2)	☐(3)	☐(4)	☐(5)
Not present	Very mild	Mild	Moderate	Severe	Very severe

Fatigue

Please choose the response below that best describes the overall severity of your fatigue over the past 24 hours.

(Select one response)

☐	☐	☐	☐	☐
No symptoms	Mild	Moderate	Severe	Very severe

10.3 COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a brief measure which is designed to assess severity and change of suicidality by integrating both, behavior and ideation. The C-SSRS was designed to address the need for a summary measure to track change in the severity of suicidality across both clinical settings and treatment trials.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsel, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes and causes only a low burden on patients. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.
The investigator is to review all positive and negative reports for plausibility and clinical relevance. Doubtful reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the patient during the clinic visit and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the patient's safety have to be initiated.

At screening, C-SSRS (screening/baseline version) will be used with the aim to exclude patients with suicidal ideation type 4 to5 within the preceding 3 months or at Visit 1 or any suicidal behavior in the past 2 years.
Subsequently, the C-SSRS "since last visit" will be performed at the time points given in the flow chart.

All positive reports during trial treatment are treatment-emergent adverse events (AEs).
The results of further medical, including psychiatric examinations, should be documented as adverse events where appropriate.

The original Columbia Suicidal Severity Rating scales used in this trial are attached in the following appendix sections.

10.3.1 Visit 1 – Screening/baseline version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation* Past X Months - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

10.3.2 C-SSRS – since last visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted]. *In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.4 RESTRICTED MEDICATIONS TABLES

Lists of medication can be found in the sections below. The lists are not exhaustive and will not be updated during the course of the trial.
Investigators are advised to verify product labelling information.

10.4.1 Strong CYP3A4 inhibitors

Strong CYP3A4 inhibitors:

- boceprevir
- ceritinib
- clarithromycin
- cobicistat
- conivaptan
- diltiazem
- idelalisib
- indinavir
- itraconazole
- ketoconazole oral administration
- LCL161
- mifepristone
- mibefradil
- nefazodone
- nelfinafir
- posaconazole
- ribociclib
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- troleandomycin
- VIEKIRA PAK2
- voriconazole

Combinations of CYP3A4 inhibitors:

- danoprevir/ritonavir
- elvitegravir/ritonavir
- indinavir/ritonavir
- lopinavir/ritonavir
- paritaprevir/ritonavir/ombitasvir/dasbuvir
- saquinavir/ritonavir
- tipranavir/ritonavir

10.4.2 Equivalent doses of corticosteroids

Table 10.4.2: 1 Equivalent Doses of Corticosteroids

Drug	Equivalent dose (mg)	Conversion factor
Prednisone	5	x 1
Prednisolone	5	x 1
Triamcinolone	4	x 1.25
6-Methylprednisolone	4	x 1.25
Dexamethasone	1	x 5
Betamethasone	0.75	x 6.7
16-Methylprednisolone	6	x 0.8
Fluocortalon	5	x 1
Cloprednol	3,75-5	x 1.0-1.5
Deflazacort	6	x 0.8
Cortisol (hydrocortisone)	20	x 0.25
Cortisone	25	x 0.20

10.4.3 Restricted PDE inhibitors

Compound	Indication
Non-selective	
Theophylline (Theolair, Slo-Bid, Theo 24)	Asthma and bronchoconstriction
Aminophylline (Phyllocontin)	Asthma and bronchoconstriction
Oxtriphylline (Choledyl)	Asthma and bronchoconstriction
Dyphylline (inhibits PDE3, 4, 7, adenosine 2 receptors) (Dilor, Lufyllin)	Asthma and bronchoconstriction
Pentoxifylline (inhibits PDE4, 5, adenosine 2 receptors) (Trental, Pentoxil)	Intermittent claudication
Ibudilast (highest affinity for PDE10A, 4, 11, 3) (Ketas, Pinatos, Eyevinal)	Asthma and dizziness related to cerebral infarction
	Allergic conjunctivitis
Tofisopam (highest affinity for PDE4, 10, 3, 2) (Emandaxin, Grandaxin)	Anxiety

Compound	Indication
Dipyridamole (highest affinity for PDE8, 1, 3, 2, adenosine deaminase and ENT1) (Persantine)	Post-operative thromboembolism
PDE3 with potential PDE4-cross reactivity	
Milrinone (Primacor, Corotrope)	Congestive heart failure
Amrinone (Inamrinone, Inocor)	Congestive heart failure
Enoximone (Perfan)	Congestive heart failure
Pimobendan (Acardi)	Heart failure
PDE4	
Roflumilast (Daliresp, Daxas)	Chronic obstructive pulmonary disease
Apremilast (Otezla)	Psoriasis and psoriatic disorders
Crisaborole (Eucrisa)	Moderate atopic dermatitis (patients >2 years old)
Drotaverine (also inhibits L-type voltage-operated calcium channel) (No-Spa, Doverin)	Functional bowel disorders; pain caused by smooth muscle spasm

10.5 OPPORTUNISTIC INFECTIONS

These include *Pneumocystis jirovecii*, BK virus disease including polyomavirus-associated nephropathy (PVAN), *Cytomegalovirus* (CMV), post-transplant lymphoproliferative disorder (Epstein–Barr virus [EBV]), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), *Scedosporium/Pseudallescheria boydii*, fusarium), legionellosis, *Listeria monocytogenes* (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, *Penicillium marneffei*, *Sporothrix schenckii*, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), *Trypanosoma cruzi* infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617].

10.6 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaires:
This trial will include an option for participants to complete anonymized questionnaires, 'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators.

Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.

Optional Caregiver Feedback Questionnaires:
If applicable, this trial will include an option for caregivers to complete anonymized questionnaires, 'Caregiver Feedback Questionnaire', to provide feedback on the clinical trial experience. Individual caregiver level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the caregiver. Providing feedback is optional and not required for participation in the trial.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		26 Jul 2022
EudraCT No.		2022-001134-11
BI Trial No.		1305-0023
BI Investigational Medicinal Product		BI 1015550
Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)
Global Amendment due to urgent safety reasons		
Global Amendment (non-substantial changes)		X
Section to be changed		Synopsis (statistical methods)
Description of change		Updated wording for MMRM model: This model will include discrete fixed effects for treatment at each visit, baseline intake of antifibrotic treatment at each visit, HRCT pattern at each visit, and continuous fixed effects for baseline **FVC value** at each visit.
Rationale for change		Clarification for consistency with Section 7.2.3
Section to be changed		Flow chart (number of days for visit assignment)

Description of change		The number of days for Visit 4 was changed from 35 to 43. The number of days for Visit 7 was changed from 169 to 183.
Rationale for change		Changed to correct the calculated number of days for visit assignments based on the conversion of trial weeks into days.
Section to be changed		Flow chart (footnote ** on ESR collection)
Description of change		Updated wording in footnote: Central laboratory ~~will~~ **may** not provide the material for ESR collection **to some countries**. **Instead,** material from local site has to be used to perform the test locally. ESR should also be measured in case of potential vasculitis.
Rationale for change		Clarification that material for ESR collection may be provided to countries by central laboratory.
Section to be changed		Flow chart (footnote 11)
Description of change		Addition of sentence: **More frequent pregnancy testing may be done if required.**
Rationale for change		Clarification on pregnancy tests.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 5.1.1 FVC
Description of change		Deletion of phone call: During the treatment phase, the iSpiro device and respective phone with the App will be provided to the patient upon decision of the investigator in order to perform an assisted (via ~~phone or~~ video call) home spirometry either at unscheduled visits or as a fallback solution if the patient is unable to get to the site for the scheduled visit.
Rationale for change		Clarification as the provided device does not offer the facility to have a phone call without video connection.
Section to be changed		Section 6.2.2.2 Conduct of a fallback visit (remote/home visit)
Description of change		Added sentence: **Trial medication may be shipped from the site directly to the patient (if acceptable according to local laws and regulations).**
Rationale for change		Clarification on the fallback visit

Section to be changed		Section 6.2.2.2 Conduct of a fallback visit (remote/home visit)
Description of change		Added bullet point to assessments that can be done remotely: • **Urine dipstick pregnancy test performed by the patient at home.**
Rationale for change		The possibility of urine pregnancy testing done during remote visits was missing.
Section to be changed		Section 6.2.2.2 Conduct of a fallback visit (remote/home visit)
Description of change		Updated wording: If blood **and urine** sampling for central lab at the patient's home is not possible, safety lab analyses including the routine safety lab tasks as per Table 5.2.3.1: 1 should be performed at a local lab.
Rationale for change		Clarification on safety lab analyses during home visits.
Section to be changed		Section 7.5 Determination of sample size
Description of change		Deletion of asterisks for 2 footnotes in Table 7.5: 2: ~~*~~ Probability calculated based on 50,000 simulation iterations. Total alpha-level = 0.05 (two-sided), 1:1:1 randomization ratio with 336 patients per arm ~~**~~ multiplicity adjusted for interim analysis using group sequential design with Wang-Tsiatis alpha spending function (delta = 0.25)
Rationale for change		Clarification as these notes refer to the whole table.
Section to be changed		Throughout the CTP
Description of change		Typographical errors and minor formatting issues amended
Rationale for change		To increase readability

11.2 GLOBAL AMENDMENT 2

Date of amendment		10 May 2023
EudraCT No.		2022-001134-11
BI Trial No.		1305-0023
BI Investigational Medicinal Product		BI 1015550
Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)

Global Amendment due to urgent safety reasons	
Global Amendment (substantial changes)	X

Section to be changed		Flow Chart (screening period)
Description of change		The minimum period for screening was reduced to 1 week
Rationale for change		Provide more flexibility for randomizations
Section to be changed		Flow Chart (lab tests)
Description of change		The erythrocyte sedimentation rate (ESR) test was removed.
Rationale for change		Local workup is crucial for the reliability of the results, but sites are not familiar with the sample handling and procedures. Therefore test results are often inconclusive.
Section to be changed		Flow Chart (temporary discontinuation of trial treatment)
Description of change		Footnote #2 was modified as follows: **In case of premature discontinuation of trial medication, the** ~~End of Treatment (~~**EOT**~~)~~ visit should **only** be done ~~in cases of premature trial medication~~ **if the** discontinuation **is permanent, and** ~~with~~ a Follow-up **(FU)** visit **is** to be performed 7 days (+3 days) after end of treatment. **If the patient discontinued the trial medication more than a week prior to the EOT visit, this FU visit is not required**. A scheduled visit may be missed if EOT or F**U**~~ollow up~~ visit occurs within 4 weeks prior to scheduled visits. After the premature EOT, every effort should be made to collect data until the end of the trial.
Rationale for change		Clarification of procedures in case of temporary vs. permanent discontinuation of trial treatment.
Section to be changed		Flow Chart (patient-reported outcomes)
Description of change		Addition to Footnote #3: **At the latest, the patients' questionnaires must be completed prior to the pulmonary function tests.**
Rationale for change		Clarification of the timing of the patients' questionnaires (consistent with the change in Section 6.2)
Section to be changed		Flow Chart (pregnancy tests)
Description of change		Footnote #11 was modified as follows: Women of childbearing potential only. **Serum pregnancy test to be performed at V1; urine dipstick pregnancy test to be performed at V2 and following visits (if positive, urine dipstick test to be followed by serum test for confirmation).** More frequent pregnancy testing may be done if required.
Rationale for change		The type and timing of the pregnancy tests were clarified.

Section to be changed		Flow Chart (design of extension trial)
Description of change		Footnote #17 was updated to remove the design of the extension trial ("open-label") and clarify when a follow-up visit is needed.
Rationale for change		The extension trial design is not finalized and might also contain a double-blind start until the decision about the final intended marketed dose. The follow-up visit can be skipped if the following regular visit after the end of treatment is planned at 7-21 days after the last dose was administered.
Section to be changed		Section 1.2 Drug profile
Description of change		Sentence added to the drug-drug interaction subsection: **In a clinical drug-drug interaction study with midazolam (sensitive CYP3A4 substrate), BI 1015550 was not shown to have a clinically relevant CYP3A induction.** Subsection on the data from non-clinical toxicology studies updated to reflect the fact that the toxicology summary remained applicable when considering the data from the 39-week study in monkeys and sentence added: **A sporadic menstrual cycle prolongation was observed in the 39-week study in female monkeys receiving ≥10 mg/kg/day, i.e., at approximately 4-fold human exposure at 18 mg bid.**
Rationale for change		Addition of data from a recent drug-drug interaction study with midazolam Addition of data from a recent 39-week oral (gavage) toxicity and toxicokinetic study in Cynomolgus monkeys with a 8-week recovery period
Section to be changed		Section 1.4.2 Risks (Table 1.4.2: 1, PK interaction with strong CYP34A inhibitors)
Description of change		Mitigation strategy updated as follows: ~~This is also applicable for Paxlovid in the treatment of Covid-19: i~~**If short-term** treatment with ~~Paxlovid~~ **potent CYP3A4 inhibitor** is needed, trial medication needs to be paused
Rationale for change		Application of the mitigation strategy to all potent CYP3A4 inhibitors, not just Paxlovid.
Section to be changed		Section 1.4.2 Risks (Table 1.4.2: 1, Vasculitis)

Description of change		Summary of data updated to reflect the fact that vasculitis was not observed following oral administration of BI 1015550 in 13- or 39-week studies in monkeys
Rationale for change		Addition of data from a recent 39-week oral (gavage) toxicity and toxicokinetic study in Cynomolgus monkeys with a 8-week recovery period
Section to be changed		Section 1.4.2 Risks (Table 1.4.2: 1, Severe infections)
Description of change		Patients with **active** tuberculosis are excluded from the trial.
Rationale for change		Mitigation strategy updated to reflect the change in EC23 (Section 3.3.3)
Section to be changed		Section 1.4.2 Risks (Table 1.4.2: 1, Reproductive toxicity)
Description of change		Summary of data updated as follows: • **In monkeys, a sporadic prolongation in menstrual cycles was observed at approximately ≥4-fold human exposure at 18 mg BI 1015550 bid.** • ~~Efficacy of oral hormonal contraceptives can be impacted by potential BI 1015550 related CYP3A induction~~ Mitigation strategy on reproductive toxicity updated as follows: • Women of childbearing potential **(WOCBP)** need to use a highly effective method of contraception. ~~Of note, oral hormonal contraceptives are not considered a highly effective method due to potential drug interactions.~~ **WOCBP taking oral contraceptives (OCs) also have to ensure the use of one barrier method during sexual intercourse with their partner, e.g., condom to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhea** • **In case of vomiting or diarrhea, instructions in the label of the OC should be followed** **In case of prolonged (>48h) or repeated vomiting/diarrhea, the use of an alternative highly effective contraceptive measure should be considered**
Rationale for change		The potentially reduced efficacy of OCs from potential CYP3A induction by BI 1015550 was ruled out by a drug-drug interaction trial on the PK of midazolam, a recommended substrate of CYP3A4. Based on these results, OCs are now allowed as highly effective measure of contraception in WOCBP, associated with one barrier method to prevent the risk of potentially reduced efficacy of the OCs in case of severe vomiting and diarrhea.

Section to be changed		Section 3.2 Discussion of trial design (participants and caregivers questionnaires)
Description of change		The following paragraph was added: **This trial will include an option for participants and participant caregivers to complete anonymized questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analyzed as part of the clinical data for the trial (see Section 10.6).**
Rationale for change		To identify where improvements can be made in the clinical trial process, the sponsor wants to collect the participants' and caregivers' feedback on their clinical trial experience.
Section to be changed		Section 3.2 Discussion of trial design
Description of change		Addition of a cross-reference to Section 4.2.2.1 (Restrictions regarding concomitant treatments) in the paragraph discussing the prohibited treatments in this study.
Rationale for change		The cross-reference helps the readers to find further information on prohibited treatment.
Section to be changed		Section 3.3.2 Inclusion criteria (IC6, also in synopsis)
Description of change		Inclusion criterion 6 was updated as follows: DLCO ~~corrected for Hemoglobin (Hb) [Visit 1]~~ ≥25% ~~and <90%~~ **of** predicted ~~of~~ normal **corrected for hemoglobin (Hb)** at Visit 1.
Rationale for change		The upper limit for DLCO was deleted since it is not relevant as an exclusion criterion. Exclusion criteria regarding lung function are sufficiently covered by the criteria based on FVC (EC5). The wording regarding the correction for Hb of predicted value of DLCO was clarified.
Section to be changed		Section 3.3.2 Inclusion criteria (IC7)
Description of change		Inclusion criterion 7 was updated as follows: Women of childbearing potential (WOCBP) must be ready and able to use highly effective methods of birth control. ~~Of note, oral hormonal contraceptives are not considered a highly effective method due to potential drug-drug interactions~~ **WOCBP taking oral contraceptives (OCs) also have to use one barrier method**; please refer to Section 4.2.2.3.
Rationale for change		Based on the results of a drug-drug interaction trial on the PK of midazolam, OCs are now allowed as highly effective measure of contraception in WOCBP, associated with one barrier method to prevent the risk of potentially reduced

		efficacy of the OCs in case of severe vomiting and diarrhea (also see change to Section 1.4.2).
Section to be changed		Section 3.3.2 Inclusion criteria (IC8)
Description of change		Inclusion criterion 8 was updated as follows: Patients treated with permitted immunosuppressive agents **(other than corticosteroids)** for an underlying systemic disease (e.g. MTX, AZA) need to be on a stable treatment for at least 12 weeks prior to Visit 1 and during the screening period
Rationale for change		It was clarified that this criterion does not concern corticosteroids.
Section to be changed		Section 3.3.3 Exclusion criteria (EC1, also in synopsis)
Description of change		Exclusion criterion 1 was updated as follows: ~~Relevant airways obstruction (p~~Prebronchodilator FEV1/FVC <0.7~~)~~ at Visit 1
Rationale for change		Any FEV/FVC ratio <0.7 should be avoided as the risk of emphysema and obstruction is high and would influence efficacy endpoint measurements. This criterion was therefore simplified.
Section to be changed		Section 3.3.3 Exclusion criteria (EC10)
Description of change		Exclusion criterion 10 was updated as follows: Patients with underlying ~~chronic~~ liver ~~disease~~ **cirrhosis** (Child Pugh A, B, or C hepatic impairment).
Rationale for change		Clarification following a question from a site (as Child Pugh only refers to liver cirrhosis, not chronic liver disease).
Section to be changed		Section 3.3.3 Exclusion criteria (EC23)
Description of change		Exclusion criterion 23 was updated as follows: Patients with ~~positive~~ **active tuberculosis (**TB**)** ~~test at Visit 1 unless they have completed treatment for active or latent tuberculosis in line with local guidelines~~.
Rationale for change		No negative effect of BI 1015550 on latent tuberculosis is expected based on new preclinical data (immunophenotype in a 39-week monkey study). The TB diagnosis was simplified, relying on the site's expertise.
Section to be changed		Section 3.3.3 Exclusion criteria (EC27 - new)
Description of change		Exclusion criterion 27 was added: **History of stem cell therapy for the treatment of pulmonary fibrosis.**
Rationale for change		The effect on the lung of such treatment in the longer term is currently unknown.
Section to be changed		Section 3.3.4.1 Discontinuation of trial treatment

Description of change		The following paragraph was updated as follows: ~~All patients who prematurely discontinue trial medication will need to complete an End of Treatment (EOT) visit at the time of discontinuation, and~~ **The End of Treatment (EOT) visit activities will be performed when a patient discontinues trial medication permanently.** ~~a~~**A premature** Follow-up (FU) visit **is to be performed 7 days (+3 days)** ~~1 week later~~ **after end of treatment. If the patient discontinued the trial medication more than a week prior to the EOT visit, this FU visit is not required**. ~~Patients who prematurely discontinue trial medication will be asked to remain in the trial and to return to all regularly scheduled visits until the end of the trial.~~ Ideally, ~~the~~ patient**s** who **permanently discontinue trial medication** should attend all remaining visits after treatment discontinuation.
Rationale for change		The procedures in case of temporary vs. permanent discontinuation of trial treatment were clarified.
Section to be changed		Section 4.1.4 Drug assignment and administration (supervision and timing)
Description of change		The need for supervision during administration was clarified: The patient will receive either active treatment at a dose of 9 mg, 18 mg, or placebo. **The first dose of BI 1015550 or placebo will be administered to the patient at the end of Visit 2 (Day 1) under direct supervision of the investigator or designee.** On the day of **any further** clinic visit~~s~~, **supervision of administration is not required but** the treatment will **preferably** be administered to the patient during the visit. The timing of administration was clarified to say that the trial medication should be taken at the same time every day (±30 mins), **ideally** between 6:00 and 11:00 in the morning and between 18:00 and 23:00 in the evening, and that **if taken around the same time (approximately within an hour), p**~~P~~atients on nintedanib background should take trial medication first, followed by the antifibrotic background medication ~~after some minutes~~.
Rationale for change		Supervision remains mandatory during the first administration but is not mandatory for any of the following administrations including further clinic visits. Simplified for facilitation of scheduling the visits.

		The timing of administration was clarified due to questions on the timeframe, e.g. when a baseline patient visit ends at 12:00. The order of administration would only have an influence in case intake of antifibrotic and BI 1015550 is close to each other timewise (potential effect of side effects like vomiting).
Section to be changed		Section 4.1.5.1 Blinding and procedures for unblinding
Description of change		The following sentence was added: **If the 9 mg dose is considered futile based on the respective interim analysis (see Section 7.2.8), the patients will be re-assigned to the 18 mg dose in a blinded manner and the 18 mg dose will be given at the next scheduled visit.**
Rationale for change		The management and handling of patients and data in case the dose of 9 mg bid is considered as futile were clarified.
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment (immunomodulatory treatment)
Description of change		The paragraph was edited as follows: Addition or changes in immunomodulatory treatment **(except of dose adjustments of prednisone below 15 mg, which are allowed)** should not occur during the first 6 months of blinded treatment. After 6 months from randomization, changes in immunomodulatory treatment are allowed for the management of worsening of the underlying disease as medically indicated. **Prednisone >15 mg/day or equivalent can be prescribed during the treatment period in case of (suspected) acute IPF exacerbation.**
Rationale for change		Restrictions regarding immunomodulatory treatment were clarified.
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment (CYP3A4 inhibitors)
Description of change		Restrictions regarding potent CYP3A4 inhibitors were updated to clarify that, if any short-term treatment with potent CYP3A4 inhibitor is needed, IMP should be temporarily discontinued and a cross-reference to Section 3.3.4.1 was added about the conditions to re-introduce the IMP. A footnote was also added to Table 4.2.2.1.
Rationale for change		The sentence was added to be consistent with Table 1.4.2: 1 (about trial-related risks) and with Section 3.3.4.1 (about temporary discontinuation of trial treatment).

Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment (Table 4.2.2.1: 1, about pirfenidone)
Description of change		The restrictions regarding pirfenidone during the follow-up period were updated from permitted to not permitted.
Rationale for change		Treatment with pirfenidone is not allowed during the whole trial (follow-up included) because pirfenidone is not marketed for PF-ILD (only for IPF).
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment (including Table 4.2.2.1: 1, about stem cell therapy)
Description of change		The following restriction was added: **Stem cell therapy for the treatment of pulmonary fibrosis is not allowed.**
Rationale for change		The effect on the lung of such treatment in the longer term is currently unknown (also see addition of EC 27).
Section to be changed		Section 4.2.2.2 Restrictions on diet and lifestyle
Description of change		The restriction regarding the consumption of methylxanthine-containing drinks or food was lifted: ~~Patients should refrain from consuming Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) in the 24 h preceding each on site visit.~~ Patients should ~~also~~ refrain **from** drinking grapefruit juice during the duration of the trial.
Rationale for change		Caffeine, theobromine, and theophylline are the most well-known compounds of the family of methylxanthines. They are predominantly metabolized by CYP1A2. Since BI 1015550 is not a CYP1A2 substrate and also does not modulate CYP1A2, an interaction between BI 1015550 and methylxanthine-containing drinks or food is not expected.
Section to be changed		Section 4.2.2.3 Contraception requirements
Description of change		The following sentence was deleted: ~~Of note, oral hormonal contraceptives are not considered highly effective due to a potential CYP3A4 drug interaction of BI 1015550 in the gastrointestinal tract. Non-oral hormonal contraception is permissible as described below.~~ And the following was added to the list of acceptable highly effective methods of contraception: **• Oral hormonal contraceptives together with one barrier method (e.g. condom) to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhea. In case of vomiting or diarrhea, instructions in the label of the OC should be followed in addition. In case of prolonged (>48h) or repeated vomiting/diarrhea, the use of an alternative**

		highly effective contraceptive measure should be considered
Rationale for change		Based on the results of a drug-drug interaction trial on the PK of midazolam, OCs are now allowed as highly effective measure of contraception in WOCBP, associated with one barrier method to prevent the risk of potentially reduced efficacy of the OCs in case of severe vomiting and diarrhea (also see change to Section 1.4.2).
Section to be changed		Section 5.1.1 FVC
Description of change		Addition of the following sentence: **In case unacceptable results for FVC/FEV1 at V1 or FVC at V10 are obtained after the review, the patient must be reassessed.**
Rationale for change		These instructions are in the spirometry guidance document but it was considered important to emphasize to the sites.
Section to be changed		Section 5.1.5.3 Patient's Global Impression of Severity (PGIS) of Cough, Shortness of Breath, and Fatigue (also Section 5.1.5)
Description of change		The description of the questionnaire assessing the severity of the patient's fatigue was added (the actual questionnaire was added in Appendix 10.2.4).
Rationale for change		The assessment of fatigue severity will be implemented in all countries where the setup is completed and translated questionnaire available.
Section to be changed		Section 5.1.6 DLCO
Description of change		The section was updated to clarify that the correction for Hb was applied to **predicted** DLCO values. It was also clarified that the site has to enter the unadjusted **predicted** DLCO result without Hb correction in the eCRF. The first formula (one for each gender) was for predicted DLCO corrected for Hb (and not percent predicted DLCO corrected for Hb) and the unit of Hb was clarified (g·dL-1) A second formula was added for **percent predicted DLCO corrected for Hb:** **Percent predicted DLCO corrected for Hb = (Mean value of two DLCO measurements, expressed in mmol/min/kPa) / Predicted DLCO corrected for Hb) * 100** DLCO ~~should always~~ **must** be performed after spirometry on the same day.

Rationale for change		Clarification of the correction of predicted DLCO for Hb and revision/addition of formulas to calculate 1) predicted DLCO corrected for Hb, and 2) percent predicted DLCO corrected for Hb. Clarification of the timing of DLCO relative to spirometry.
Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		The ESR test was removed from the routine safety lab test panel (Section 5.2.3.1) and the test for cryoglobulins was removed from the vasculitis lab test panel (Section 5.2.3.3). Note: the mention of ESR test in Section 5.2.6.1.4 (Adverse Events of Special Interest) was also removed.
Rationale for change		Local workup is crucial for the reliability of the results, but sites are not familiar with the sample handling and procedures. Therefore test results are often inconclusive.
Section to be changed		Section 5.2.3.1 Routine safety lab tests (Table 5.2.3.1: 1)
Description of change		The type and timing of the pregnancy tests were clarified. At screening (V1), a serum pregnancy test is to be performed (no IMP taken at that time) whereas at V2 (and following visits), urine dipstick pregnancy test is to be performed (if positive, urine dipstick test should be followed by serum test for confirmation).
Rationale for change		The use of "Day -1" in the table was confusing; visit numbers were used instead.
Section to be changed		Section 5.2.3.2 Infection serology
Description of change		Wording was updated as follows: In case of positive **TB test** ~~Screening Test~~**,** further diagnostic work up to confirm/exclude the diagnosis of latent or active is needed (documentation on respective eCRF page).
Rationale for change		Clarification that further diagnostic work up to confirm/exclude the diagnosis of latent or active TB is to be done for any positive TB test (not just at screening)
Section to be changed		Section 5.2.3.3 Immunological vasculitis markers
Description of change		Addition of the following paragraph: **Due to stability matter during storage, ANCA markers (MPO-ANCA and PR3-ANCA) from Visit 2 and Visit 10 are analyzed upon receipt, but investigators will not receive these results as it could influence their judgement regarding a suspected vasculitis. The rest of the analysis of immunological vasculitis markers is performed if an unscheduled "Vasculitis event" is collected. In this situation, the site will receive the result for all vasculitis markers previously performed (from**

		V2 and V10 if already done) and from the unscheduled "Vasculitis event" kit. These results are shared by the trial team to the site via the CRA.
Rationale for change		The timing and conditions of analysis of ANCA markers and communication of results to the site were clarified due to stability matter during storage.
Section to be changed		Section 5.2.6.3 Independent safety monitoring and adverse events with additional information collection
Description of change		Wording was updated as follows: Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse event 'Diarrhea/gastrointestinal events', the adverse events in the Standard MedDRA Query (SMQ) 'vasculitis' and in case of positive **TB tests** ~~tuberculosis screening~~ **(see Section 5.2.3.2)**.
Rationale for change		Clarifications that additional details should be collected in the eCRF for any positive TB test (not just at screening).
Section to be changed		Section 5.6.1 Chest HRCT assessment (repetition of HRCT)
Description of change		The following sentence was deleted: ~~HRCT should not be repeated for eligibility if previous scan was taken within the past 3 months.~~
Rationale for change		The possibility to repeat the HRCT for eligibility and the allowed timeframe between scans will be left up to the investigator's decision, based on local guidance.
Section to be changed		Section 5.6.1 Chest HRCT assessment (patient eligibility)
Description of change		The sentence about patient eligibility was modified as follows: Eligible patients will have fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing**,** with disease extent of >10%. The following sentence about patients with PF-ILD was edited as follows: The following co-existing features will be accepted as other fibrotic patterns **(but not limited to)**: ground glass opacity, upper lung or peribronchovascular predominance, mosaic attenuation, air trapping, and centrilobular nodules.
Rationale for change		A comma was added before "with disease extent of >10%" to be consistent with the main diagnosis for trial entry in Section 3.3.1. Patients with PF-ILD may still be eligible if all these fibrotic patterns are not met (except if they met these two

		patterns: widespread consolidation or progressive massive fibrosis).
Section to be changed		Section 6.1 Visit Schedule
Description of change		The following sentence was amended: The patient will be randomized at Visit 2 if all inclusion **criteria (**including positive HRCT review **and acceptable spirometry measurements)** and none of the exclusion criteria (lab exclusion criteria referring to Visit 1 results) are fulfilled.
Rationale for change		The conditions for randomization were clarified (also see the change in Section 5.1.1)
Section to be changed		Section 6.2 Details of trial procedures at selected visits
Description of change		The following edits were made: Regarding patients' questionnaire: **At the latest, the patients' questionnaires must be completed prior to the pulmonary function tests** Regarding the pulmonary function tests: FVC (spirometry) ~~should~~ **must** be performed before DLCO Regarding IRT call and IMP dosing/dispensing: IRT call and IMP dosing/dispensing should always be done as the last procedure after all visit assessments**, except at Visit 1 where the IRT call may be done earlier during the patient's visit**.
Rationale for change		The order of procedures was clarified.
Section to be changed		Section 6.2.1 Screening period
Description of change		Sentence amended: If a patient is re-screened and there are valid screening determinations from patient's previous participation in the trial, like for example safety labs, performed within ~~28 days~~ **8 weeks** prior to randomization (Visit 2), these do not need to be repeated.
Rationale for change		This is to align the timeframe with the regular allowed screening phase of 8 weeks without repetition of V1 laboratory tests.
Section to be changed		Section 6.2.2.1 Conduct of a regular site visit
Description of change		The need for supervision during administration was clarified: Each patient will receive the first dose of BI 1015550 or placebo at the end of Visit 2 (Day 1) **under direct supervision of the investigator or designee**. Patients will take trial medication twice daily (bid) orally from that timepoint onwards. **On the day of any further**~~At~~ clinic visit~~s~~, **supervision of administration is not required** but

		trial medication will **preferably** be administered to the patient during the visit (as the last procedure, see Section 6.2) ~~taken under direct supervision of the investigator or [redacted] designee~~.
Rationale for change		Supervision remains mandatory during the first administration but is not mandatory for any of the following administrations including further clinic visits. Simplified for facilitation of scheduling the visits.
Section to be changed		Section 6.2.3 Follow-up period and trial completion
Description of change		Specification about the design of the extension trial ("open-label") was removed (also applied in Section 3.1). The procedures in case of temporary vs. permanent discontinuation of trial treatment were aligned with the changes made in Section 3.3.4.1. It was clarified that the abnormal values to monitor are those collected at the last study visit (EOS).
Rationale for change		The extension trial design is not finalized and might also contain a double-blind start until the decision about the dose that could be given as an open-label treatment is taken. Alignment of procedures in case of temporary vs. permanent discontinuation of trial treatment with Section 3.3.4.1.
Section to be changed		Section 7.2.1 General considerations (and Sections 7.2.3 and 7.2.4)
Description of change		Addition of the Full Analysis Set (FAS) as the primary population for the efficacy analysis, and modification of the definition of the Treated Set (TS), which will be the primary population for the safety analysis (but not the efficacy analysis). Inclusion of the analysis strategy in the definition of the analysis sets. Deletion of the following sentence: ~~For efficacy and safety analyses, patients will be analysed according to their planned treatment group.~~ Deletion of the Per Protocol Set (PPS). Sections 7.2.3 and 7.2.4 were updated to reflect the fact that the FAS will be the efficacy set.
Rationale for change		Efficacy and safety analyses will be conducted with different analysis strategy. Patients will be analyzed as randomized in the efficacy analysis, whereas they will be analyzed as treated in the safety analysis. The PPS was deleted as post-randomization events will be handled via estimands (based on ICH E9 addendum), as described in the TSAP.

Section to be changed		Section 7.2.1 General considerations (important protocol deviations)
Description of change		The sentence was updated as follows: ~~Specifications for~~ **Definitions and handlings of important** protocol deviations **(IPDs)** ~~leading to exclusion from PPS~~ will be ~~provided in the trial Integrated Quality and Risk Management Plan (IQRMP)~~ **included in the DV domain specifications and will be stored within the trial master file (TMF) in the electronic document management system (EDMS). All potential important protocol deviations will be discussed during trial oversight meetings and report planning meetings.** ~~and a~~**A**ll **final** decisions concerning IPDs will be made before un-blinding.
Rationale for change		Clarification on handling, documentation and review of IPDs.
Section to be changed		Section 7.2.3.1 Sensitivity analyses Section 7.2.4.1 Analysis of key secondary endpoint
Description of change		Sentence amended: On-treatment ~~analyses~~, **while-compliant-to-protocol** analyses ~~in the PerProtocol Set~~ and models with modified sets of covariates will be conducted as further sensitivity analyses
Rationale for change		Deletion of the PPS.
Section to be changed		Section 7.2.4.1 Analysis of key secondary endpoint Section 7.2.4.2 Analysis of other secondary endpoints
Description of change		For all time-to-event endpoints, the start date considered when calculating the time to event of interest (and the time to censoring) was changed from ‘randomization date’ to ‘first drug intake date’.
Rationale for change		There may be a few days gap between the randomization date and the first drug intake date. For the purpose of time-to-event analyses, the actual time at risk starts with the first drug intake.
Section to be changed		Section 7.2.8 Interim analyses (and synopsis)
Description of change		The following sentences were added: **If the 9 mg dose is considered futile, the patients on that treatment arm will be re-assigned to the 18 mg dose in a blinded manner (see Section 4.1.5.1) at their next scheduled visit.** A shorter version of this new paragraph was added to the synopsis.
Rationale for change		The management and handling of patients and data in case the dose of 9 mg bid is considered as futile were clarified.

Section to be changed		Section 7.2.8 Interim analysis (and synopsis)
Description of change		The description of the interim analysis to detect early signs of substantial efficacy was adjusted and remains to be confirmed: […] an interim analysis for efficacy ~~will~~ **may** be performed by the DMC. This interim analysis ~~is planned to~~ **may** be conducted ~~when a minimum of 450 patients (150 patients per arm) have reached the Week 52 FVC assessment~~ **approximately 52 weeks after 450 patients (150 patients per arm) have started treatment** and 26 weeks after the last patient has started treatment.
Rationale for change		The previous wording excluded patients who died or who were lost to follow-up from the count of 450 because these patients would not reach the Week 52 FVC assessment. The new wording does include the patients who died or who were lost to follow-up in the count of 450. The exact timing of this analysis remains to be confirmed.
Section to be changed		Section 7.4 Randomization (futility analysis)
Description of change		The following sentence was added: **For patients to be enrolled and randomized after a potential futility stop of the low dose level (9 mg; see Section 7.2.8), the randomization ratio will be 1:1 (BI 1015550 18 mg bid vs. Placebo).**
Rationale for change		The randomization ratio in case the dose of 9 mg bid is considered as futile were clarified.
Section to be changed		Section 7.5 Determination of sample size
Description of change		Calculations were performed using **"rpact" package version 3.0.4 in R Version 4.0.2** ~~SAS® Version 9.4 (or later version)~~.
Rationale for change		The SAS® software was not used in the end. The switch to a new software led to very minor change in power values (<1%) as shown in Table 7.5:1.
Section to be changed		Section 10.1 Spirometry: Bronchodilator Washout Recommendations
Description of change		The title of table was amended to clarify that the washout timeframes presented were **minimal** timeframes
Rationale for change		Washout timeframes for bronchodilators before spirometry may be longer than those presented in the table.
Section to be changed		Section 10.2.4 Patient's Global Impression of Severity (PGIS) for Cough, Shortness of Breath, and Fatigue
Description of change		Addition of the questionnaire on fatigue severity

Rationale for change		See change to Section 5.1.5.3
Section to be changed		Section 10.6 Trial participant feedback
Description of change		This new section describes the conditions of implementation of the optional participant and caregiver feedback questionnaires.
Rationale for change		To identify where improvements can be made in the clinical trial process, the sponsor wants to collect the participants' and caregivers' feedback on their clinical trial experience.
Section to be changed		Throughout the CTP
Description of change		Typographical errors and minor formatting issues amended
Rationale for change		To increase readability

11.3 GLOBAL AMENDMENT 3

Date of amendment		21 September 2023
EudraCT number		2022-001134-11
BI Trial number		1305-0023
BI Investigational Medicinal Product		BI 1015550
Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)
Global Amendment due to urgent safety reasons		
Global Amendment (substantial changes)		X
Section to be changed		Synopsis
Description of change		The paragraphs on futility and efficacy interim analyses were deleted, and a new paragraph added to the statistical methods: ~~An interim analysis assessing futility of the 9 mg dose vs. placebo will be conducted after approximately 300 patients have reached the Week 12 primary endpoint assessment. If the 9 mg dose is considered futile, the patients will be re-assigned to the 18 mg dose.~~ ~~An interim analysis for a potentially earlier regulatory submission may be conducted approximately 52 weeks after 450 patients (150 patients per arm) have started treatment and 26 weeks after the last patient has started treatment in order to detect early signs of substantial efficacy. The interim analysis will be implemented within a group sequential design with the aim to decide whether or not efficacy of BI 1015550 can be claimed early on in a confirmatory manner.~~ **Once the last randomized patient**

		completes the Week-52 assessment, the main analysis of the trial will be carried out by the sponsor, who will be unblinded to assess the benefit-risk of the two doses of BI 1015550 compared with placebo. Patients will remain on their randomized blinded treatment until the sponsor has reviewed the efficacy and safety data from the main analysis and communicated the end of the trial. Once this trial ends, a final analysis based on all data will be carried out.
Rationale for change		1) To reflect that the futility and efficacy interim analyses will not be conducted. The reasons the futility analysis will not be conducted: • The futility analysis was defined as non-binding in the DMC charter. Recruitment of this trial will be completed by the time of the previously planned futility analysis. Outliers observed from trial 1305-0014 in FVC changes from baseline among early recruited patient cohort increased the concern that the point estimate for the futility decision may not be robust • 9 mg was deemed not futile in the parallel trial 1305-0014 by the DMC • No safety concern was observed by the DMC in 1305-0014 or 1305-0023 • Consistency of treatment groups and analyses between trial 1305-0014 and 1305-0023 will facilitate the interpretation of results across different patient populations The sponsor's decision not to conduct the efficacy interim analysis was based on Health Authority feedback and shifting trial timelines with fast recruitment, which make the time advantage in conducting the interim analysis limited 2) To specify the main analysis and the final analysis
Section to be changed		Flow chart
Description of change		The following footnotes were revised: (1) Following completion of V10 patients will continue to have study visits every 12 weeks until **the start of EoT visits is announced. The global study will be completed after all patients have performed the EoT visit and the EoS visit (if not continuing in the separate extension trial)**~~the last patient randomized has reached Week 52. If the patient will complete EOT at 52 weeks (study completion phase), V10 is replaced by the EOT visit~~.

		(8) Assisted home spirometry will be offered at selected centres where every patient should have a training and measurement with the device **ideally** at Visits 2 or 3. **If the requirement to use the iSpiro appears later in the trial, then this timepoint can be shifted.** Remote measurement can be performed as per investigator's judgement but should not replace the on-site FVC measurement.
Rationale for change		1) Clarification 2) To allow flexibility in training of iSpiro
Section to be changed		Section 1.4.1 Benefits
Description of change		The following sentence was revised: Patients with IPF **and other forms of progressive pulmonary fibrosis** who receive treatment with BI 1015550 have the potential benefit of slowing lung function decline, improving symptoms, and improving quality of life over a long-term period.
Rationale for change		Correction
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.1 Overall trial design
Description of change		The following paragraphs were added or revised: **The main analysis of this study will be performed once the last randomized patient reaches the Week-52 visit (Visit 10 at the end of Part A). At that time, a first database lock (DBL1; Figure 3.1: 1) will occur and all data will be unblinded to the sponsor. Efficacy and safety analyses will be performed on the data from Part A of the trial to assess the benefit-risk of BI 1015550 over 52 weeks. In addition, data collected in Part B of the trial (after 52 weeks) and available at the time of data cut-off for the main analysis will be reported together with data from Part A (i.e. over the whole trial).** **Trial 1305-0023 Part B, will continue until all patients have completed the EOT visit and the EOS visit as applicable. A final database lock (DBL2; Figure 3.1: 1) will then occur and a final analysis based on the data over the whole trial will be carried out.**

		Depending on the results of the evaluation based on DBL1 and determination of the BI 1015550 dose with the more favorable benefit-risk profile, patients receiving trial medication until the end of Part B will be eligible for open-label treatment with BI 1015550 in a separate extension trial. ~~Around the time the last randomized patient reaches 52 weeks of treatment,~~ **After review of the efficacy and safety data available at DBL1, the sponsor will communicate the end of the trial and** all patients still on blinded study treatment will perform an End of Treatment (EOT) visit and an End of Study (EOS) visit if applicable. The trial ends when all patients complete these visits. Details on follow-up and rollover to the extension trial are given in Section 6.2.3. "Figure 3.1: 1 Trial design overview **at patient level (upper panel) and trial level (lower panel)**" was updated according to the revised text.
Rationale for change		To specify the main analysis and the final analysis
Section to be changed		Section 3.2 Discussion of trial design, including the choice of control group(s)
Description of change		The following sentences were added: **The additional data collected while patients remain on blinded treatment beyond 52 weeks will provide supportive long-term efficacy and safety data on the effect of BI 1015550 in a controlled manner. Due to the varying length of follow-up in Part B of the trial, the efficacy analyses incorporating data from Part A and Part B will focus on time-to-event endpoints.**
Rationale for change		To add the rationale on conducting Part B
Section to be changed		Section 4.1.5.1 Blinding
Description of change		The following paragraphs were added or revised: **At the main analysis database lock (DBL1; see Section 3.1), the sponsor will be unblinded to assess the benefit-risk of both doses of BI 1015550 vs placebo and select the dose with the more favorable benefit-risk profile for the open-label extension trial. Patients, investigators, and other site personnel will remain blinded to the randomized treatment assignment until the end of the trial.**

		The trial medication is identified by a medication code number and packaging is identical. The color, size, and shape of the respective 9 mg and 18 mg BI 1015550 and the matching placebo tablets will be indistinguishable. The access to the randomization code will be kept restricted until its release for analysis at **DBL1**. Further details regarding the timepoint of unblinding the database for analysis is documented in the TSAP. The randomization codes will be provided to bioanalytics before ~~the last patient completed the trial~~ **DBL1** to exclude placebo or comparator samples from the PK analysis. Bioanalytics will not disclose the randomization code or the results of their measurements until ~~the database lock~~ **DBL1**. **A dedicated database snapshot (not a partial DBL) will be generated prior to DBL1, after all patients have completed the last PK visit (i.e. Week-26 visit), to allow for development and refinement of the population PK model (for "fast-track" PK analysis). Details of the analysis will be defined in the PK/PD analysis plan. In addition, the data will be used for front-loading of descriptive analysis for PK. Only personnel involved in the population PK and descriptive analyses will be granted access to the unblinded PK data before DBL1, whereas the trial team and all other functions not involved in the population PK and PK descriptive analyses will remain blinded (details will be provided in a separate logistics and access plan). The analysis plan for the population PK analysis will be finalized and signed prior to this dedicated database snapshot.** **No formal interim report will be generated for the population PK analysis. The final PK and PK/PD analyses will be reported separately from the clinical trial report (CTR) after DBL1.** The external DMC will review unblinded data upon request ~~and for the interim analyses as described in Section 7.2.8~~, and only under conditions that ensure that patients, investigators, everyone involved in trial conduct or analysis, and anyone with any other participation in this double-blind trial will remain blinded. ~~If the 9 mg dose is considered futile based on the respective interim analysis (see Section 7.2.8), the patients will be re-assigned to the 18 mg dose in a blinded manner and the 18 mg dose will be given at the next scheduled visit.~~ ~~In case the interim analyses result in the recommendation for a preliminary report preparation, a respective team~~

		~~("shadow team") independent of the main trial team will be formed to conduct the necessary data cleaning, analysis, and reporting steps and ensure to maintain the blind and restrict access to the randomization codes from the main trial team. Details of data transfer, timelines and involved trial functions during this process will be described in a separate logistics plan which will also specify details on data access.~~
Rationale for change		1) To explain that unblinding of the sponsor will occur at the main analysis (DBL1); 2) To add that to front-load, personnel involved in the PK analyses will use unblinded PK data before DBL1; 3) To reflect that the futility and efficacy interim analyses will not be conducted
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		The following sentence was revised: Prednisone >15 mg/day or equivalent can be prescribed during the treatment period in case of (suspected) acute ~~IPF~~**ILD** exacerbation. Treatment with non-selective PDE inhibitors as well as ~~PDE1, PDE3,~~ PDE4~~, and PDE10~~ inhibitors is not allowed. "Table 4.2.2.1: 1 Restrictions regarding concomitant treatment" was updated according to the revised text above, and footnotes 4 and 5 were corrected: 4. Prednisone >15mg/day or equivalent can be prescribed during the treatment period in case of (suspected) acute ~~IPF~~**ILD** exacerbation 5. After 6 months from randomization, changes ~~in immunomodulatory treatment~~ are allowed for the management of worsening of the underlying disease as medically indicated.
Rationale for change		1) Clarification on prednisone use; 2) To narrow restricted PDE inhibitors down to those that specifically interfere with PDE4
Section to be changed		Section 5.1.1 FVC
Description of change		The following sentence was revised: Training of the patients on the use of the iSpiro device and App ~~should~~ **can** be done at **any visit, ideally at** Visit 2 or Visit 3 together with a first recording.
Rationale for change		To allow flexibility in training of iSpiro

Section to be changed		Section 5.2.6.1.1 Adverse event
Description of change		The following paragraph was added: **<u>Adverse event report for depression and anxiety</u>** **AE reporting based on the Hospital Anxiety and Depression Scale (HADS): new onset of moderate depression, defined as HADS subscore of >10, has to be reported as AE; new onset of moderate anxiety, defined as HADS subscore of >10, has to be reported as AE. HADS subscore of ≤10 should only be reported as an AE if clinically relevant. See Section 5.2.6.1.4 for reporting of AESI based on HADS.**
Rationale for change		To clarify AE reporting based on HADS
Section to be changed		Section 6.2.2.3 End of treatment visit
Description of change		The following sentence was revised: As described in Section 3.1, ~~around the time the last randomized patient reaches 52 weeks of treatment (Visit 10)~~**after the confirmation of the benefit-risk evaluation for a potential start of the extension trial based on the main analysis**, all patients still on blinded study treatment will perform an EOT visit. ~~It will occur either at the regular timepoint of Visit 10 (52 weeks) if it falls within this timeframe (e.g. if patient is still in Treatment Period A) or at a convenient timepoint in this timeframe if the patient already had performed Visit 10 previously (e.g. if the patient had already started Treatment Period B).~~ ~~The start of these EOT visits will be communicated when the last patient is randomized and thus, the timepoint of the anticipated last patient at 52 weeks visit is known.~~
Rationale for change		Clarification
Section to be changed		Section 7.1 Null and alternative hypotheses
Description of change		A paragraph was added: **The hypothesis testing of the key secondary endpoint is based on data collected up to the main analysis (all data up to DBL1; see Figure 3.1: 1). A supplementary analysis of the key secondary endpoint using all data collected over the whole trial will be performed after DBL2.** The following paragraphs were deleted:

		~~If the 9 mg bid arm is considered futile at the futility interim, the remaining tests for 18 mg bid arm will be tested sequentially for primary and key secondary endpoint with α level of 0.04 and 0.02 as depicted in Figure 7.1: 1.~~ ~~The tests for the primary endpoint comparing each dose vs. placebo within the graphical testing procedure will include one interim analysis for potential efficacy claim using a group sequential design. The alpha level at interim analysis and final analysis will be adjusted accordingly, see Section 7.2.8.~~
Rationale for change		1) To clarify that the hypothesis testing of the key secondary endpoint will be done at the main analysis; 2) To reflect that the futility and efficacy interim analyses will not be conducted
Section to be changed		Section 7.2.1 General considerations
Description of change		A paragraph was added: **All planned efficacy and safety analyses, including for the primary and key secondary endpoints will be carried out at DBL1 (Figure 3.1: 1) and the statistical hypotheses described in Section 7.1 will be tested. After DBL2, analyses of the efficacy endpoints defined as "over the duration of the trial" and all safety analyses will be repeated to include all data collected until the end of the trial.**
Rationale for change		To describe at a high level what will be analyzed at the main and the final analysis
Section to be changed		Section 7.2.3.3 Supplementary Analyses
Description of change		The following sentence was revised: **Further details will be specified in the TSAP**~~Not applicable for this trial~~.
Rationale for change		Clarification
Section to be changed		Section 7.2.8 Interim analyses
Description of change		The content of this section was deleted and replaced by "**Not applicable**"
Rationale for change		To reflect that the futility and efficacy interim analyses will not be conducted
Section to be changed		Section 7.4 Randomization
Description of change		The following sentence was deleted: ~~For patients to be enrolled and randomized after a potential futility stop of the low dose level (9 mg; see Section 7.2.8),~~

		~~the randomization ratio will be 1:1 (BI 1015550 18 mg bid vs. Placebo).~~
Rationale for change		To reflect that the futility analysis will not be conducted
Section to be changed		Section 7.5 Determination of sample size
Description of change		The following paragraphs were revised: An effective sample size of 336 patients per group will detect a treatment effect of 71 mL with ~~90~~**91**% power under ~~two-stage group sequential design with Wang-Tsiatis alpha spending function (delta=0.25) and cumulative~~ two-sided alpha of 5%. With 336 patients per arm and a two-sided type I error rate of 0.05, a treatment effect size of 80, 65, 55, and 45 can be detected for each of the primary endpoint with 96%, 85%, 72%, and 55% power respectively. Simulation results as presented in Table 7.5: 2 suggest that with 336 effective sample size per arm, there is at least ~~93~~**94**% power to detect an effect size of 71 mL in FVC change from baseline at Week 52 for at least one dose is significant (Scenario #1). Regardless of effect size of the 9 mg bid arm, probability of detecting a significant FVC effect of 71 mL in the 18 mg bid arm is between ~~88~~**89**% to ~~93~~**90**%. Furthermore, if 18 mg bid arm has an effect of 71 mL in primary endpoint and HR of 0.6 in key secondary endpoint, the probability of rejecting both H_01 and H_03 is between ~~69~~**70**% to ~~77~~**78**% depending on relative effect size of the 9 mg bid arm. The simulation results also show a well-controlled type-I error under the null hypothesis (Scenario #5) with the proposed testing strategy. Additional simulation results, which are not displayed here, also show that the transition weight from H_01 to H_02 ranging from 0.5 to 0.7 does not impact the marginal power for the primary and key secondary efficacy endpoints much. Hence we choose 0.5 as the transition weight given the desirable success probabilities of ~~88~~**89**% to ~~93~~**94**% for primary endpoint and ~~69~~**70**% to ~~77~~**78**% for key secondary endpoint 18 mg bid arm under various conditions. "Table 7.5: 2 Multiplicity adjusted probabilities of success for each hypothesis~~,~~ **and** positive study ~~and interim success~~ under different scenarios of effect sizes from simulations" was revised to update the numbers without the efficacy interim analysis, to delete 5 lines with "~~probability of rejecting at least one dose primary endpoint at interim~~", and to delete a footnote "~~Multiplicity adjusted for interim analysis using group sequential design with Wang-Tsiatis alpha spending function (delta = 0.25).~~".

Rationale for change		To reflect that the efficacy interim analysis will not be conducted
Section to be changed		Section 8.7 Administrative structure of the trial
Description of change		The following sentence was revised: The DMC will evaluate safety data on a regular basis~~ and perform the interim analysis~~.
Rationale for change		To reflect that no interim analysis will be conducted
Section to be changed		Appendix 10.4.3 Restricted PDE inhibitors
Description of change		The table was revised to delete the lines of the following PDE inhibitors: ~~**PDE1**~~ ~~Vinpocetine (Cavinton)~~ **PDE3** ~~Cilostazol (Pletal, Ekistol)~~ ~~Olprinone (Coretec)~~ ~~Anagrelide (also inhibits phospholipase A2) (Agrylin, Xagrid)~~ ~~**PDE10A**~~ ~~Papaverine (Pavabid, Pavagen)~~
Rationale for change		To narrow restricted PDE inhibitors down to those that specifically interfere with PDE4

APPROVAL / SIGNATURE PAGE

Document Number: c37763552 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-1305-0023-version-04

Title: A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)

Signatures (obtained electronically)

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Verification-Paper Signature Completion		21 Sep 2023 17:01 CEST

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