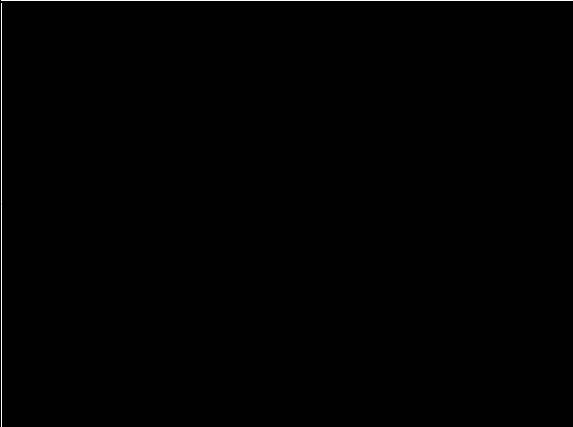
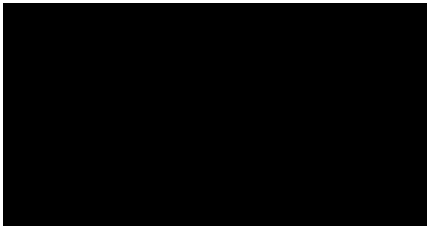
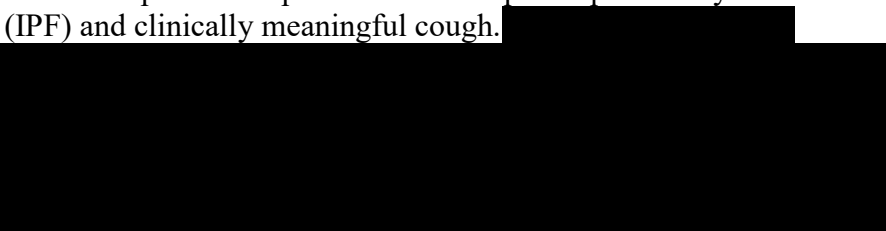


Clinical Trial Protocol

Document Number:		c43433838-03
EU Clinical Trial No.	EU clinical trial number: 2023-510249-79-00	
Universal Trial Number	Universal trial number: U1111-1301-1311	
Trial Sponsor	Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173 55216 Ingelheim am Rhein Germany	
Boehringer Ingelheim Trial No.	1490-0004	
Boehringer Ingelheim Investigational Medicinal Product	BI 1839100	
Title	A Phase IIa/IIb, randomised, double blind, placebo-controlled, parallel-group dose-finding study to examine the efficacy and safety of BI 1839100 administered orally over a 12-week treatment period in patients with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis with clinically meaningful cough	
Lay Title	A study to test whether BI 1839100 improves cough in people with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis	
Clinical Phase	Phase IIa/IIb	
Clinical Trial Leader		
Coordinating Investigator		
Current Version and Date	Version 2, 22 Aug 2024	
Original Protocol Date	19 Feb 2024	Page 1 of 145
Proprietary confidential information. © 2024 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.		

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	19 Feb 2024
Boehringer Ingelheim trial number EU CT number Universal Trial Number	BI trial number: 1490-0004 EU CT number: 2023-510249-79-00 Universal trial number: U1111-1301-1311
Title of trial	A Phase IIa/IIb, randomised, double blind, placebo-controlled, parallel-group dose-finding study to examine the efficacy and safety of BI 1839100 administered orally over a 12-week treatment period in patients with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis with clinically meaningful cough
Coordinating Investigator	
Trial site(s)	200 trial sites, up to 30 countries
Clinical phase	Phase IIa/IIb
Trial rationale	The purpose of this trial is to characterize the dose-response curve and evaluate the treatment effect of different doses of BI 1839100 relative to placebo in patients with idiopathic pulmonary fibrosis (IPF) and clinically meaningful cough. 

Benefit-risk assessment and ethical considerations	Considering the unmet medical need, anticipated benefit of BI 1839100, and currently available nonclinical and clinical information, the benefit-risk evaluation of BI 1839100 is favourable. Patients with IPF or PPF who receive treatment with BI 1839100 [REDACTED] improving symptoms, and improving quality of life (QoL) over a long-term period. There are no identified risks for BI 1839100 based on the toxicology program and clinical trials to date. The inclusion of a placebo arm within this trial is necessary to ensure the reliability of trial results. Participants will be allowed to continue their standard antifibrotic (AF) therapy.
Trial objective(s)	IPF cohort Phase IIa: - Primary objective: To demonstrate a meaningful reduction from baseline in 24-h cough frequency (defined as the cough counts (CC) measured over 24 h and averaged per hour, i.e. CC/h) in the highest dose group of BI 1839100 compared with placebo after 4 weeks of treatment. Geometric means and mean ratios will be the summary measures of treatment effect for the change from baseline in each group and differences between treatment groups - Secondary objective: To evaluate the efficacy by comparing the change from baseline in Cough Severity Numerical Rating Scale (NRS) score and Cough Severity Visual Analog Scale (VAS) after 4 weeks of treatment between the BI 1839100 highest dose group and the placebo group Phase IIb: - Primary objective: To demonstrate a non-flat dose-response curve with respect to change from baseline in 24-h cough frequency after 12 weeks of treatment and characterize the dose-response relationship within the therapeutic range of BI 1839100 regarding efficacy and safety. The mean changes from baseline for each treatment group, based on the log transformed CC/h, will be the summary measures of treatment effect for the analysis of dose-response - Secondary objectives: - To evaluate the efficacy of BI 1839100 by assessing cough responder status, defined as a $\geq 30\%$ 24-h cough frequency reduction (CC/h) from baseline after 12 weeks - To evaluate the efficacy by comparing the absolute change from baseline in forced vital capacity (FVC, mL) after 12 weeks of treatment between BI 1839100 dose groups and the placebo group

	To evaluate the efficacy by comparing the change from baseline in Cough Severity NRS, Cough Severity VAS, Leicester Cough Questionnaire (LCQ) physical domain, and Living with Pulmonary Fibrosis (L-PF) symptom cough domain after 12 weeks of treatment between BI 1839100 dose groups and the placebo group PPF cohort
Trial endpoints	IPF cohort Primary endpoints: - Phase IIa: change from baseline in 24-h cough frequency (CC/h) at Week 4 - Phase IIb: change from baseline in 24-h cough frequency (CC/h) at Week 12 Secondary endpoints: - Phase IIa: - Absolute change from baseline in Cough Severity NRS score at Week 4 - Absolute change from baseline in Cough Severity VAS score (mm) at Week 4 - Phase IIb: - Cough responder status, defined as a $\geq 30\%$ 24-h cough frequency reduction (CC/h) from baseline at Week 12 - Absolute change from baseline in FVC (mL) at Week 12 - Absolute change from baseline in Cough Severity NRS score at Week 12 - Absolute change from baseline in Cough Severity VAS score (mm) at Week 12 - Absolute change from baseline in L-PF symptom cough domain score at Week 12 - Absolute change from baseline in LCQ physical domain score at Week 12 PPF cohort Primary endpoints: Not applicable Secondary endpoints: Not applicable
Trial design	A randomised, multi-centre, multi-national, placebo-controlled, parallel-group, double-blind (double-dummy technique) clinical trial using a seamless Phase IIa/IIb design comparing 3 doses () of BI 1839100 to placebo over 12 weeks for the IPF cohort. A positive outcome at Week 4 interim analysis of IPF cohort will allow for the inclusion of an

	PPF cohort assessing 1 dose () of BI 1839100 compared with placebo over 4 weeks.
Total number of trial participants randomised	IPF cohort: approximately 180 PPF cohort: approximately 50
Number of trial participants per treatment group	IPF cohort: - Placebo: approximately 60 : approximately 30 : approximately 30 : approximately 60 PPF cohort: - Placebo: approximately 25 : approximately 25
Diagnosis, main inclusion and exclusion criteria	Diagnosis - IPF cohort: diagnosed with IPF according to the 2022 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thorax Association (ALAT) Guideline and confirmed with central review of chest high-resolution computed tomography (HRCT) scan - PPF cohort: fibrosing lung disease affecting more than 10% of lung volume on HRCT and have a diagnosis of PPF (i.e. meeting any of the following criteria in the 24 months prior to screening visit: relative decline in the FVC of at least 10% of the predicted value, relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms OR an increased extent of fibrosis on HRCT, worsening of respiratory symptoms and an increased extent of fibrosis) Main inclusion criteria - IPF and PPF cohorts - IPF or PPF diagnosis - Chronic cough (>8 weeks) due to IPF or PPF, refractory to treatment - Cough Severity VAS ≥ 30 mm at Visit 1 and Visit 2B - FVC $\geq 45\%$ of predicted normal at Visit 1 - Diffusing capacity of the lungs for carbon monoxide (DLCO) $\geq 25\%$ of predicted normal at Visit 1 - On stable therapy or not on therapy with nintedanib (IPF and PPF cohorts) or pirfenidone (IPF cohort) for ≥ 12 weeks prior to Visit 1

	• PPF cohort only ○ If receiving immunomodulatory therapy (i.e. tacrolimus, mycophenolate mofetil, azathioprine) for interstitial lung disease (ILD), on stable dose for 12 weeks prior to Visit 1 Main exclusion criteria • IPF and PPF cohorts ○ Acute exacerbation of IPF/PPF within 12 weeks prior to Visit 1 ○ Forced Expiratory Volume in 1 second (FEV1)/FVC <0.7 at Visit 1 ○ Known reversible airflow obstruction/response to bronchodilators ○ Other clinically significant pulmonary abnormalities ○ Upper or lower respiratory tract infection within 4 weeks prior to Visit 1 ○ Ongoing chronic pulmonary infection ○ Current smokers (tobacco use within the 6 months prior to Visit 1) ○ Initiation or change in supplemental oxygen requirement during 4 weeks prior to Visit 1 ○ Oral corticosteroids or prednisone >15 mg/day or equivalent ○ Initiation or change in dose within 4 weeks prior to Visit 1 of angiotensin converting enzyme (ACE) inhibitors, inhaled corticosteroids, inhaled bronchodilators, proton pump inhibitor or histamine type-2 receptor blockers ○ Use within 4 weeks of Visit 1: opiate/opioids, baclofen, gabapentin, pregabalin, thalidomide, amitriptyline, inhaled cromolyn or related products, gefapixant ○ Use of following herbal remedies within 4 weeks of Visit 1: schisandra extract, alkaloid berberine, ginseng (Asian), goldenseal, supplements containing turmeric, ginger, and/or atractylenoide • IPF cohort only ○ Treated with immunomodulatory medications (other than prednisone ≤15 mg/day or equivalent) for respiratory or pulmonary reasons • PPF cohort only ○ Acute or chronic pleuritis ○ Use of pirfenidone, cyclophosphamide, cyclosporine, tocilizumab, methotrexate, and/or leflunomide within 4 weeks or 5 half-lives (whichever is longer) prior to Visit 1
--	--

	○ Use of rituximab or other specific B-cell depleting therapies within 6 months of Visit 1
Trial intervention and test product	BI 1839100
Dose and mode of administration	IPF cohort: [REDACTED] PPF cohort: [REDACTED]
Comparator product(s)	Placebo
Dose and mode of administration	[REDACTED]
Duration of treatment	IPF cohort: 12 weeks PPF cohort: 4 weeks
Statistical methods	Phase IIa: The primary endpoint is the change from baseline in 24-h cough frequency at Week 4 in the IPF population. Restricted maximum likelihood estimation based on a mixed-effect model for repeated measures will be used to obtain adjusted means for the treatment effects. This model will include discrete fixed effects for treatment at each visit and AF treatment (Yes, No), and continuous fixed effects for baseline at each visit. The primary treatment comparisons will be the contrast between treatments at Week 4. Phase IIb: The primary trial objective includes demonstration of proof of concept (PoC) with respect to a non-flat dose-response curve and characterization of the dose-response relationship within the therapeutic range of BI 1839100, and selection of the dose range for Phase III development. The primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCP-Mod), whereby several possible dose-response models (patterns) will be evaluated, while keeping full control of the type I error at 5.0%, 1-sided to identify the best-fitting model or subset of model. To account for the repeated nature of the data and the covariates in the model, mixed model with repeated measurements (MMRM) analysis will be carried out for the 12-week endpoint. For both Phase IIa/IIb, all statistical analyses will be based on the log-transformed CC/h. However, to ease the interpretation of the clinical effect, the results will be displayed using values back-transformed to the original scale and presented as geometric means

	and geometric mean ratios (representing the proportional differences in change from baseline between treatment groups).
--	---

SCHEDULE OF ASSESSMENTS

IPF cohort

Trial periods	Screening		Treatment				Follow up
Visit	1	2A ¹	2B	3	4	5 EoT ²	6 EoS
Trial week	- 4	-1	-	4	8	12	13
Trial day	-14 to -28	-3 to -1	1	29	57	85	EoT+7
Visit window (days)	n.a.	n.a.	V1 + 14 to 28 d	± 3	± 3	+ 3	± 3
Informed consent	X						
Review of in-/exclusion criteria	X		X				
Demographics	X						
Smoking status/history	X						
Medical history	X						
Pregnancy test	X		X	X	X	X	
Height	X						
Weight	X		X	X	X	X	X
Physical exam	X		X	X	X	X	X
Vital signs ³	X		X	X	X	X	X
Pulse oximetry	X		X	X	X	X	X
ECG ⁴	X		X	X	X	X	X
Chest HRCT central review ⁵	X						
Spirometry	X		X	X	X	X	X
DLCO	X					X	

IPF cohort

Trial periods	Screening		Treatment				Follow up
Visit	1	2A ¹	2B	3	4	5 EoT ²	6 EoS
Trial week	- 4	-1	-	4	8	12	13
Trial day	-14 to -28	-3 to -1	1	29	57	85	EoT+7
Visit window (days)	n.a.	n.a.	V1 + 14 to 28 d	± 3	± 3	+ 3	± 3
Cough Severity NRS ⁶	X		X	X	X	X	X
Cough Severity VAS ⁶	X		X	X	X	X	
L-PF ⁶			X			X	
LCQ ⁶			X	X		X	
Safety labs	X		X	X	X	X	X
PK sampling ⁷			X	X	X	X	
Biomarker sampling ⁸			X	X	X	X	
Optional sampling for biobanking ⁹			X	X		X	
Distribute & provide instruction on cough monitor ¹⁰	X						
24-h cough recording ¹¹	X	X		X	X	X	
Return of cough monitor							X
Distribute & provide instruction on activity monitoring ¹²	X						
14-day activity monitoring	X→ ¹³				X→ ¹⁴		

IPF cohort

Trial periods	Screening		Treatment				Follow up
Visit	1	2A ¹	2B	3	4	5 EoT ²	6 EoS
Trial week	- 4	-1	-	4	8	12	13
Trial day	-14 to -28	-3 to -1	1	29	57	85	EoT+7
Visit window (days)	n.a.	n.a.	V1 + 14 to 28 d	± 3	± 3	+ 3	± 3
Return of activity monitor						X	
IRT transaction	X		X	X	X	X	
Randomisation			X				
Treatment start			X				
Dispense trial medication ¹⁵			X	X	X		
Administer trial medication at the site ¹⁶			X	X	X		
Treatment end						X	
Compliance check				X	X	X	
All AEs/SAEs/AESIs	X		X	X	X	X	X
Concomitant therapy	X		X	X	X	X	X
Trial participant surveys							X
Completion of trial participation							X

¹ At the discretion of the investigator, Visit 2A can be performed at the clinic or by the participant at home. Please see Section [6.2.1.2](#) for more details.

² Trial participants who prematurely discontinue IMP should still follow the trial schedule, if possible. Please see Section [3.3.4](#).

³ Measurements of vital signs should precede blood sampling.

⁴ 12-lead ECG measurements to be completed in triplicate.

⁵ Chest HRCT obtained within 1 year prior to the screening visit will be accepted. If not available or not of acceptable quality, chest HRCT can be performed during screening period.

⁶ Self-administration of PROs should precede other trial procedures.

⁷ Pre-dose plasma PK samples will be taken just before drug administration on Day 1 (Visit 2B), Day 29 (Visit 3), and Day 57 (Visit 4); post-dose plasma PK samples will be taken (at least 1 h after drug administration) on Day 1 (Visit 2B), Day 29 (Visit 3), and anytime on Day 85 (Visit 5). Please refer to Section [10.7](#) for more details.

- ⁸ The biomarker samplings will be plasma and serum. Biomarker samples will be taken just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF.
- ⁹ Trial participants are required to sign a separate informed consent for biobanking. One sample for DNA biobanking will be taken, preferably at Visit 2B. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid. No biobanking samples will be taken in China. No DNA samples are taken in Japan.
- ¹⁰ Cough monitoring kit will be given to trial participants after it is confirmed that the participant is eligible based on the inclusion/exclusion criteria that can be assessed during Visit 1. Trial participants will be given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure.
- ¹¹ 24-h cough recording should be initiated at the end of the visit. At Visit 2A, participant can be brought to the clinic to initiate recording or participant can perform it at home.
- ¹² Activity monitoring kit will be given to trial participants after it is confirmed that the participant is eligible based on the inclusion/exclusion criteria that can be assessed during the Visit 1. Trial participants will be given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure.
- ¹³ Activity monitoring will be initiated at the end of Visit 1 and trial participant must wear the watch for at least 2 weeks. Accordingly, the Visit 2B should be scheduled about 2 weeks after the Visit 1. Trial participants must continue wearing the watch after Visit 1 together with cough monitoring for the first 24 h.
- ¹⁴ Activity monitoring will be initiated at the end of Visit 4 and trial participants must wear the watch for at least 2 weeks after the visit. For the first 24 h trial participants will be wearing the watch together with cough monitoring.
- ¹⁵ Trial participants should be instructed not to take trial medication before coming to the clinic for Visit 3 and Visit 4 as they will be dosed at the clinic.
- ¹⁶ Trial medication should be administered after blood sampling.

PPF cohort

Trial periods	Screening		Treatment		Follow up
Visit	1	2A ¹	2B	3 EOT ²	4 EOS
Trial week	- 4	-1	-	4	5
Trial day	-7 to -28	-1 to -3	1	29	36
Visit window (days)	n.a.	n.a.	V1 + 7 to 28 d	+3	± 3
Informed consent	X				
Review of in-/exclusion criteria	X		X		
Demographics	X				
Smoking status/history	X				
Medical history	X				
Pregnancy test	X		X	X	
Height	X				
Weight	X		X	X	X
Physical exam	X		X	X	X
Vital signs ³	X		X	X	X
Pulse oximetry	X		X	X	X
ECG ⁴	X		X	X	X
Chest HRCT central review ⁵	X				
Spirometry	X		X	X	X
DLCO	X				
Cough Severity NRS ⁶	X		X	X	X

PPF cohort

Trial periods	Screening		Treatment		Follow up
Visit	1	2A ¹	2B	3 EOT ²	4 EOS
Trial week	- 4	-1	-	4	5
Trial day	-7 to -28	-1 to -3	1	29	36
Visit window (days)	n.a.	n.a.	V1 + 7 to 28 d	+3	± 3
Cough Severity VAS ⁶	X		X	X	
L-PF ⁶			X	X	
LCQ ⁶			X	X	
Safety labs	X		X	X	X
PK sampling ⁷			X	X	
Biomarker sampling ⁸			X	X	
Optional sampling for biobanking ⁹			X	X	
Distribute & provide instruction on cough monitor ¹⁰	X				
24-h cough recording ¹¹	X	X		X	
Return of cough monitor					X
IRT transaction	X		X	X	
Randomisation			X		
Treatment start			X		
Dispense trial medication			X		
Administer trial medication at the site ¹²			X		
Treatment end				X	
Compliance check				X	

PPF cohort

Trial periods	Screening		Treatment		Follow up
Visit	1	2A ¹	2B	3 EOT ²	4 EOS
Trial week	- 4	-1	-	4	5
Trial day	-7 to -28	-1 to -3	1	29	36
Visit window (days)	n.a.	n.a.	V1 + 7 to 28 d	+3	± 3
All AEs/SAEs/AESIs	X		X	X	X
Concomitant therapy	X		X	X	X
Trial participant survey					X
Completion of trial participation					X

¹ At the discretion of the investigator, Visit 2A can be performed at the clinic or by the participant at home. Please see Section [6.2.1.2](#) for more details.

² Trial participants who prematurely discontinue IMP should still follow the trial schedule, if possible. Please see Section [3.3.4](#).

³ Measurements of vital signs should precede blood sampling.

⁴ 12-lead ECG measurements to be completed in triplicate.

⁵ Chest HRCT obtained within 1 year prior to the screening visit will be accepted. If not available or not of acceptable quality, chest HRCT can be performed during screening period.

⁶ Self-administration of PROs should precede other trial procedures.

⁷ Pre-dose plasma PK samples will be taken just before drug administration on Day 1 (Visit 2B); post-dose plasma PK samples will be taken (at least 1 h after drug administration) on Day 1 (Visit 2B) and anytime during the visit on Day 29 (Visit 3). Please refer to Section [10.7](#) for more details.

⁸ The biomarker samplings will be plasma and serum. Biomarker samples will be taken just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF.

⁹ Trial participants are required to sign a separate informed consent for biobanking. One sample for DNA biobanking will be taken, preferably at Visit 2B. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid. No biobanking samples will be taken in China. No DNA samples are taken in Japan.

¹⁰ Cough monitoring kit will be given to trial participants after it is confirmed that the participant is eligible based on the inclusion/exclusion criteria that can be assessed during Visit 1. Trial participants will be given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure.

¹¹ 24-h cough recording should be initiated at the end of the visit. At Visit 2A, participant can be brought to the clinic to initiate recording or participant can perform it at home.

¹² Trial medication should be administered after blood sampling.

TABLE OF CONTENTS

TITLE PAGE	1
CLINICAL TRIAL PROTOCOL SYNOPSIS	2
SCHEDULE OF ASSESSMENTS	9
TABLE OF CONTENTS	16
ABBREVIATIONS AND DEFINITIONS	21
1. INTRODUCTION.....	28
1.1 MEDICAL BACKGROUND	28
1.2 DRUG PROFILE	29
1.3 RATIONALE FOR PERFORMING THE TRIAL	31
1.4 BENEFIT - RISK ASSESSMENT.....	32
1.4.1 Benefits.....	32
1.4.2 Risks	32
1.4.3 Discussion.....	36
2. TRIAL OBJECTIVES AND ENDPOINTS.....	37
2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS.....	37
2.1.1 Main objectives.....	37
2.1.2 Primary endpoints.....	38
2.1.3 Secondary endpoints	38
2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS	39
2.2.1 Further objectives	39
2.2.2 Further endpoints	40
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION	43
3.1 OVERALL TRIAL DESIGN.....	43
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)	44
3.3 SELECTION OF TRIAL POPULATION	46
3.3.1 Main diagnosis for trial entry	46
3.3.2 Inclusion criteria	47
3.3.3 Exclusion criteria	49
3.3.4 Discontinuation of trial participants from treatment or assessments.....	50
3.3.4.1 Discontinuation of trial treatment	51
3.3.4.2 Withdrawal of consent to trial participation	52
3.3.4.3 Discontinuation of the trial by the sponsor	52
4. TREATMENTS.....	53
4.1 INVESTIGATIONAL TREATMENTS	53
4.1.1 Identity of the Investigational Medicinal Products.....	53

4.1.2	Selection of doses in the trial and dose modifications.....	53
4.1.3	Method of assigning trial participants to treatment groups	54
4.1.4	Drug assignment and administration of doses for each trial participant	54
4.1.5	Blinding and procedures for unblinding.....	55
4.1.5.1	Blinding.....	55
4.1.5.2	Emergency unblinding and breaking the code	56
4.1.6	Packaging, labelling, and re-supply.....	57
4.1.7	Storage conditions	57
4.1.8	Drug accountability.....	57
4.2	OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS	58
4.2.1	Other treatments and emergency procedures	58
4.2.1.1	Auxiliary medicinal products	58
4.2.1.2	Emergency procedures	58
4.2.2	Restrictions	59
4.2.2.1	Restrictions regarding concomitant treatment	59
4.2.2.2	Restrictions on diet and lifestyle	60
4.2.2.3	Contraception requirements	60
4.3	TREATMENT COMPLIANCE	61
5.	ASSESSMENTS.....	62
5.1	ASSESSMENT OF EFFICACY	62
5.1.1	Cough monitoring	62
5.1.2	Forced vital capacity (spirometry)	62
5.1.3	Diffusing capacity of the lungs for carbon monoxide	63
5.1.4	Clinical outcome assessments.....	64
5.1.4.1	Cough Severity Numerical Rating Scale	64
5.1.4.4	Cough Severity Visual Analog Scale.....	65
5.1.4.6	Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire	65
5.1.4.7	Leicester Cough Questionnaire	66
5.1.4.8	eCOA handling	66
5.1.5	Activity measurement.....	66
5.1.6	Composite outcome	67
5.2	ASSESSMENT OF SAFETY	68
5.2.1	Physical examination	68
5.2.2	Vital signs.....	68
5.2.3	Pulse oximetry	68
5.2.4	Safety laboratory parameters	68
5.2.5	Electrocardiogram	71
5.2.6	Other safety parameters.....	71
5.2.7	Assessment of adverse events.....	71

5.2.7.1	Definitions of AEs	71
5.2.7.1.1	Adverse event.....	71
5.2.7.1.2	Serious adverse event.....	72
5.2.7.1.3	AEs considered ‘Always Serious’.....	72
5.2.7.1.4	Adverse events of special interest.....	72
5.2.7.1.5	Intensity (severity) of AEs	73
5.2.7.1.6	Causal relationship of AEs.....	74
5.2.7.2	Adverse event collection and reporting	74
5.2.7.2.1	AE collection.....	74
5.2.7.2.2	AE reporting to the sponsor and timelines.....	75
5.2.7.2.3	Pregnancy.....	75
5.3	DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS	76
5.3.1	Assessment of pharmacokinetics	76
5.3.2	Methods of sample collection	76
5.3.3	Analytical determinations	76
5.3.3.1	Analytical determination of BI 1839100 plasma concentration	76
5.3.3.2	Analytical determination of nintedanib plasma concentration	76
5.3.3.3	Analytical determination of pirfenidone plasma concentration	77
5.3.4	Pharmacokinetic - pharmacodynamic relationship.....	77
5.4	ASSESSMENT OF BIOMARKER(S)	77
5.4.1	Exploratory biomarkers	77
5.5	BIOBANKING	78
5.5.1	Methods and timing of sample collection.....	78
5.6	OTHER ASSESSMENTS.....	79
5.6.1	Chest high-resolution computed tomography	79
5.7	APPROPRIATENESS OF MEASUREMENTS	79
6.	INVESTIGATIONAL PLAN.....	80
6.1	VISIT SCHEDULE.....	80
6.2	DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS	80
6.2.1	Screening period(s)	81
6.2.1.1	Visit 1	81
6.2.1.2	Visit 2A	83
6.2.2	Treatment period(s)	83
6.2.3	Follow-up period and trial completion.....	84
7.	STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	87
7.1	NULL AND ALTERNATIVE HYPOTHESES	87
7.2	PLANNED ANALYSES.....	88
7.2.1	General considerations	88
7.2.1.1	Analysis overview.....	88
7.2.1.2	Analysis set definitions	88

7.2.2	Handling of intercurrent events.....	89
7.2.3	Primary objective analyses.....	90
7.2.3.1	Main analyses.....	90
7.2.3.2	Sensitivity analyses.....	93
7.2.3.3	Subgroup analyses.....	93
7.2.3.4	Supplementary analyses.....	93
7.2.4	Secondary objective analyses.....	93
7.2.5	Further objective analyses.....	94
7.2.6	Safety analyses.....	94
7.2.7	Other analyses.....	95
7.2.8	Interim analyses.....	95
7.3	HANDLING OF MISSING DATA.....	96
7.4	RANDOMISATION.....	96
7.5	DETERMINATION OF SAMPLE SIZE.....	97
8.	INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE.....	101
8.1	TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT	101
8.2	DATA QUALITY ASSURANCE.....	102
8.3	RECORDS.....	102
8.3.1	Source documents.....	102
8.3.2	Direct access to source data and documents.....	104
8.3.3	Storage period of records.....	104
8.4	EXPEDITED REPORTING OF ADVERSE EVENTS.....	104
8.5	STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY.....	105
8.5.1	Collection, storage, and future use of biological samples and corresponding data.....	106
8.6	TRIAL MILESTONES.....	107
8.7	ADMINISTRATIVE STRUCTURE OF THE TRIAL.....	107
8.7.1	Sponsor.....	107
8.7.2	Coordinating Investigator.....	107
8.7.3	Data Monitoring Committee.....	108
8.7.4	Development Decision Committee.....	108
8.7.5	Investigators.....	108
8.7.6	Trial management and performance.....	108
9.	REFERENCES.....	110
9.1	PUBLISHED REFERENCES.....	110
9.2	UNPUBLISHED REFERENCES.....	112
10.	APPENDICES.....	113

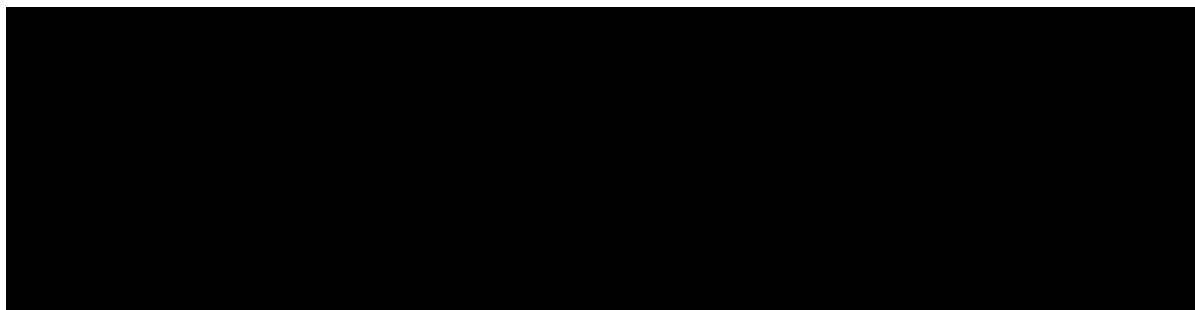
10.1	ELIGIBILITY CONFIRMATION OF IDIOPATHIC PULMONARY FIBROSIS DIAGNOSIS	113
10.2	ELIGIBILITY CONFIRMATION FOR PROGRESSIVE PULMONARY FIBROSIS DIAGNOSIS	115
10.3	EQUIVALENT DOSES OF CORTICOSTEROIDS.....	116
10.4	DEVICE PROFILE	117
10.5	SPIROMETRY: BRONCHODILATOR WASHOUT RECOMMENDATIONS.....	118
10.6	PATIENT REPORTED OUTCOMES	119
10.6.1	Cough Severity Numerical Rating Scale.....	119
10.6.4	Cough Severity Visual Analog Scale	122
10.6.6	Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire	124
10.6.7	Leicester Cough Questionnaire.....	136
10.7	TIME SCHEDULE FOR PHARMACOKINETIC BLOOD SAMPLING	137
10.8	TRIAL PARTICIPANT FEEDBACK	138
11.	DESCRIPTION OF GLOBAL AMENDMENT	139
11.1	GLOBAL AMENDMENT 1	139

ABBREVIATIONS AND DEFINITIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse event of special interest
AF	Antifibrotic
ALAT	Asociación Latinoamericana de Tórax (Latin American Thorax Association)
ALT	Alanine amino transferase
AP	Alkaline phosphatase
API	Application programming interface
aPTT	Activated partial thromboplastin time
AST	Aspartate amino transferase
ATS	American Thoracic Society
AUC	Area under the curve
AUC ₀₋₂₄	Area under the plasma concentration-curve over the time interval from 0 to 24 h
AUC _{0-inf}	Area under the plasma concentration-curve over the time interval from 0 extrapolated to infinity
AUC _{0-tau}	Area under the plasma concentration-curve over the time interval from 0 to time tau
AUC _{12,ss}	Area under the plasma concentration-curve at steady state up to 12 h after dosing
AUC _{tau,ss}	Area under the plasma concentration-curve at steady state over the dosing interval tau
BAL	Bronchoalveolar lavage



BI Boehringer Ingelheim



CARE-PF Canadian Registry for Pulmonary Fibrosis

$C_{avg,ss}$	Average plasma concentration at steady state
CC	Cough count
CDE	Centre for Drug Evaluation
CDMS	Clinical data management system
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	Creatine kinase myocardial band
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady state
$C_{min,ss}$	Minimum concentration at steady state
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID	Coronavirus disease
CRA	Clinical Research Associate
CRE	Clinical reporting environment
CRF	Case Report Form
CRO	Contract Research Organization
CT	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450 isozymes
DBL	Data base lock
DDC	Development Decision Committee
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DLCO	Diffusing capacity of the lungs for carbon monoxide

DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
$dP/dt_{\max}$	Maximum derivative of left ventricular pressure (maximal rate of rise of left ventricular pressure)
dx	Diagnosis
EC	Ethics committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
eDC	Electronic data capture/collection
EDT	Electronic data transfer
EDTA	Ethylenediamine tetraacetic acid
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoS	End of study
EoT	End of treatment
ePRO	Electronic patient reported outcome
ERS	European Respiratory Society
EU-IPFF	European Idiopathic Pulmonary Fibrosis and Related Disorders Federation
FAS	Full analysis set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FTP	File transfer protocol
FVC	Forced vital capacity
GCP	Good clinical practice
GERD	Gastroesophageal reflux disease
GGT	Gammaglutamyl transferase
GLI	Global Lung Initiative
gMean	Geometric mean
GMP	Good manufacturing practice
HA	Health authority

Hb	Haemoglobin
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
IA	Interim analysis
IB	Investigators Brochure
IC ₅₀	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation (formerly the International Conference on Harmonisation)
ICH-GCP	International Conference of Harmonization-Good Clinical Practice
IDMS	Isotope dilution mass spectrometry
IEC	Independent ethics committee
ILD	Interstitial lung disease
IMP	Investigational medical product
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator Site File
ISO	Organisation for Standardisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JRS	Japanese Respiratory Society
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LCQ	Leicester Cough Questionnaire
L-PF	Living with Pulmonary Fibrosis

LPLT	Last patient last treatment
MARSI	Medical adhesive-related skin injuries
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCP-Mod	Multiple comparison procedure – modelling
MCT	Multiple comparison test
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
MMRM	Mixed model with repeated measurements
MRD	Multiple rising dose
MVPA	Moderate to vigorous physical activity
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse event level
NRI	Nonresponse imputation
NRS	Numerical rating scale
OPU	Operating Unit
PD	Pharmacodynamics
PF	Pulmonary fibrosis
PI	Principle Investigator
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics
PMDA	Pharmaceuticals and Medicinal Devices Agency

PoC	Proof of concept
PoCP	Proof of clinical principle
PPF	Progressive pulmonary fibrosis
PPS	Per protocol set
PRO	Patient reported outcome
PSPV	Patient Safety Pharmacovigilance
PT	Prothrombin time
QoL	Quality of life
QTc	Corrected QT interval
RA	Regulatory authority
RBC	Red blood cell
RDW	Red blood cell distribution width
REML	Restricted maximum likelihood
REP	Residual effect period
RNA	Ribonucleic acid
RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
SoA	Schedule of assessments
SOP	Standard operating procedure
SRD	Single rising dose
SUSAR	Suspected unexpected serious adverse reactions
t _{1/2}	Half-life
T3	Triiodothyronin
T4	Thyroxine

TBLC	Transbronchial lung cryobiopsy
TdP	Torsades de Pointes
TGFβ1	Transforming growth factor beta 1
t _{max}	Time after dosing when C _{max} occurs
t _{max,ss}	Time after dosing when C _{max} occurs at steady state
TMF	Trial Master File

TS	Treated set
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid stimulating hormone
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cells
WOCBP	Women of childbearing potential

Terms synonymous with those used in this CTP are listed below.

Term	Synonymous term
Trial participant <i>or</i> participant	Subject <i>or</i> patient
End of study	End of trial
Investigational medicinal product	Trial medication (<i>or</i> medication), <i>or</i> trial drug (<i>or</i> drug), <i>or</i> trial treatment (<i>or</i> treatment), <i>or</i> trial intervention, <i>or</i> intervention, <i>or</i> investigational product

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

IPF is the most well-known form of fibrosing ILD with a progressive phenotype, with a median survival of 2-3 years after diagnosis. Cough is amongst the most problematic symptoms in IPF, manifesting as a chronic cough in 49-89% of patients, with cough frequency rates of approximately 200 to 500 per 24 h, [[R12-1608](#), [R21-1708](#), [R21-1709](#)]. In other PPFs, cough also develops as the disease progresses, with cough prevalence ranging from 21-95% [[R17-2148](#), [R21-1710](#)].

In persons with PF, including IPF, worse cough-specific QoL (as measured by the LCQ), has been associated with higher risk of death, lung transplantation, and respiratory-related hospitalization [[P22-05773](#)]. Additionally, patients with IPF or PPF, and cough report poorer HRQoL, higher rates of depression, and increased loss of workplace productivity.

Cough-induced mechanical stress may give rise to micro-injuries in the lungs of patients with IPF or PPF. Lung micro-injury and aberrant epithelial repair are currently discussed as major drivers of lung fibrotic disease [[P15-05871](#), [P15-01629](#)]. Cough has been reported to predict prognosis in IPF [[R12-1608](#)] and the lung injury biomarker SP-D predicts survival in IPF [[R20-3564](#), [R15-4125](#)].

[REDACTED]

[REDACTED] Studies utilizing the P2X3 inhibitor, gefapixant, and inhaled cromolyn did not achieve therapeutic effects. Ifenprodil was studied in a single arm PoC study for patients with IPF and chronic cough, though further development has been discontinued. Orvepitant, nalbuphine, and morphine sulphate are being investigated for chronic cough associated with IPF. These agents function in part through centrally acting mechanisms for cough suppression; orvepitant and nalbuphine have manifested CNS related side effects in early trials, such as fatigue and lethargy. Supportive therapies for cough are largely ineffective.

[REDACTED]

By targeting [REDACTED] BI 1839100 has the potential prospect to [REDACTED]

[REDACTED] providing multiple therapeutic benefits [REDACTED]

1.2 DRUG PROFILE

Mode of action

[REDACTED]

Key PK characteristics

Non-clinical

[REDACTED]

Clinical

[REDACTED]

[REDACTED]

Drug interactions

[REDACTED]

Residual Effect Period

There are limited *in vivo* data from humans [REDACTED]

[REDACTED]

Data from non-clinical studies

Pharmacology, safety pharmacology, and toxicity

[REDACTED]

[REDACTED] were the selected species for nonclinical safety profiling of BI 1839100. The nonclinical program of BI 1839100 includes repeat-dose toxicity studies up to [REDACTED]

[REDACTED]

[REDACTED]

Data from clinical studies

As of February 2024, BI 1839100 was investigated in healthy volunteers in 2 SRD trials with oral doses of [REDACTED] and in 1 MRD trial with [REDACTED]

Overall, BI 1839100 was considered safe and well tolerated by healthy male subjects.

For a more detailed description of the BI 1839100 profile, please refer to the current IB [REDACTED]

1.3 RATIONALE FOR PERFORMING THE TRIAL

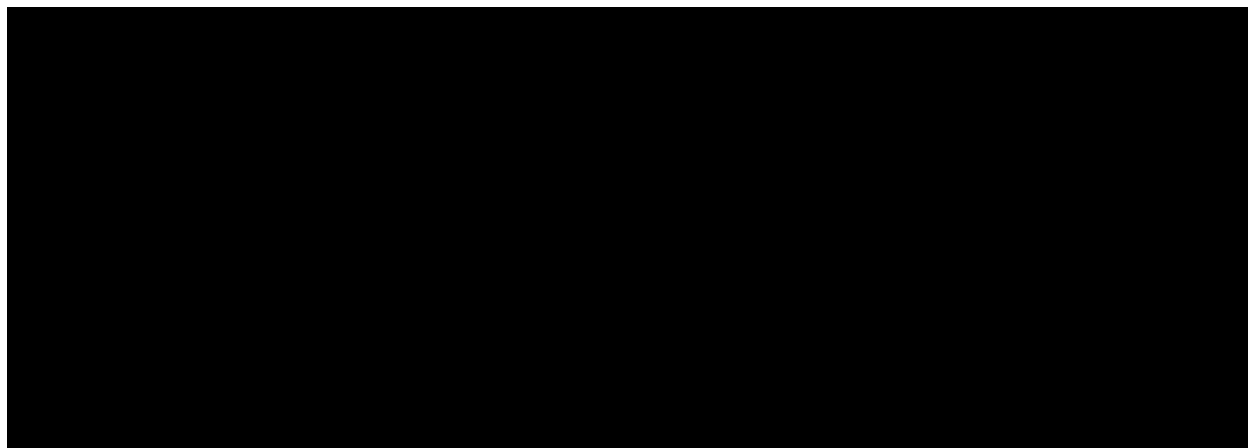
Health authority interactions and patient consultations helped guide the design of this trial (see Section [3.2](#)).

In this Phase IIa/IIb trial, we will characterise the dose-response curve and evaluate the treatment effect of different doses of BI 1839100 relative to placebo in participants with IPF and clinically meaningful cough. [REDACTED]

[REDACTED] The primary endpoints will be the change from baseline in objective 24-h cough frequency (defined as the cough counts measured over 24 h and averaged per hour, i.e. CC/h) at 4 and 12 weeks of treatment with BI 1839100 in Phase IIa and Phase IIb, respectively. Additionally, we will assess change from baseline in lung function as measured by FVC, change from baseline in patient-relevant outcomes, including cough-specific QoL and HRQoL, and measures of daily levels of physical activity over the trial period. [REDACTED]

In addition to efficacy, this trial will address the safety and tolerability of BI 1839100 in participants with IPF or PPF.

The results of this Phase IIa/IIb trial will be used to guide the design and dosing in the Phase III trial.



1.4 BENEFIT - RISK ASSESSMENT

Based on the mode of action, the pharmacological target, and the non-clinical toxicology data, BI 1839100 is not considered a high-risk compound for clinical studies.

1.4.1 Benefits

IPF and PPF are serious debilitating conditions characterised by worsening symptoms and QoL, and progressive loss of lung function which can ultimately result in respiratory failure and early death.

[REDACTED] and approved AF treatments have limitations; they do not impact symptoms and cannot stop or reverse fibrosis (i.e. the disease trajectory).

Nonclinical studies have shown that targeting [REDACTED]

1.4.2 Risks

Apart from risks related to trial procedures, the risks shown in [Table 1](#) are hypothetical in nature. The hypothetical risks are derived from general safety considerations based on the mechanism of action of BI 1839100 and nonclinical data in studies with BI 1839100.

There are no identified risks (side effects) for BI 1839100 based on any clinical trials conducted for this IMP to date. For specifics on clinical data, including adverse events reported during clinical trials with BI 1839100, please refer to the current IB [REDACTED]

Table 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 1839100		
DILI	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow up of laboratory alterations in selected liver laboratory parameters to ensure trial participants' safety. Increased awareness and expedite reporting (AESI).
Cardiovascular risks		
Inadvertent cough suppression		

Table 1 (cont'd) Overview of trial related risks

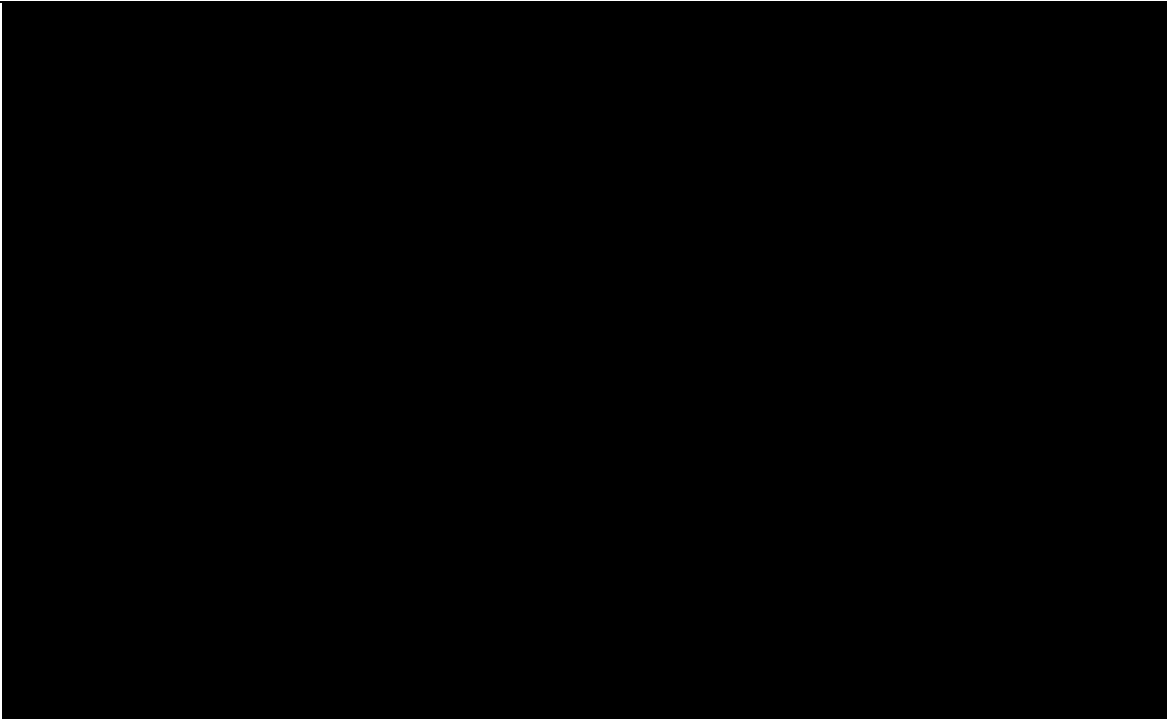
Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1839100		
		
Trial procedures		
Blood sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black 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 sensations (paraesthesia), impaired sensation of touch, and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as: • Close clinical monitoring for AEs • Selection of experienced sites and site staff

Table 1 (cont'd) Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures (cont'd)		
Chest HRCT	The more radiation is received over the course of a life, the greater risk of having cancerous tumours or of inducing changes in genes. The changes in genes could possibly 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: • Close clinical monitoring for AEs • 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: • Close clinical monitoring for AEs • Selection of experienced sites and site staff • Training from vendor to conduct procedure correctly
Wearing the cough monitor	Potential for skin irritation (i.e. MARSI) caused by acrylic-based adhesive used to apply the device to the chest wall.	Not anticipated; if present not expected to be severe. Irritation mitigation agents (i.e. 3 M™ Cavilon™) which establish a skin barrier are available for reducing the risk of skin irritation. Collection of AEs.

Table 1 (cont'd) Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures (cont'd)		
Participant burden of cough monitoring and activity monitoring	CC/h endpoint requires the use of cough monitors for assessment over 24-h time period. MVPA and non-sedentary time endpoints requires the use of activity monitors over a 2-week time period.	Clear explanation to participants regarding the use of the equipment during their day-to-day activities.

Privacy insights

Continuous audio recordings may raise concern for privacy breaches and/or inadvertent recording of conversations. The cough monitor biosensor data is fully encrypted on device and in transit to prevent unauthorized access to health information. Cough monitor device does not contain an open-air microphone and is not designed to acquire speech or other sounds from a participant's mouth. The cough monitor device is designed with passive noise filtering and a directional microphone optimizing the sensitivity to internal lung sounds and reducing sounds from the ambient environment. It is intended to acquire sounds of the lungs and airways including cough sounds, wheeze sounds, and normal breath sounds. Files are broken up into short <60 s segments and randomly distributed to annotators to reduce the risk further of any file containing discernible speech over a long enough period of time to capture private conversations and information.

1.4.3 Discussion

Treatment with BI 1839100 has the potential to provide significant benefits to patients with IPF and PPF [REDACTED] QoL and slowing lung function decline.

Based on the toxicology program and clinical trials to date for BI 1839100, there are no identified risks. Hypothetical risks stemming from general safety considerations and risks related to trial procedures, have been reviewed and mitigation strategies put in place.

Considering the unmet medical need, anticipated benefit of BI 1839100, and currently available nonclinical and clinical information, the benefit-risk evaluation of the compound is favourable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

IPF cohort

Phase IIa:

The aim of Phase IIa is to explore the efficacy of BI 1839100 in comparison with placebo in trial participants with IPF and clinically meaningful cough. An IA will be performed to determine whether to continue to Phase IIb or terminate the trial.

Primary objective:

- To demonstrate a meaningful reduction from baseline in 24-h cough frequency (defined as the cough counts measured over 24 h and averaged per hour, i.e. CC/h) in the highest dose group of BI 1839100 compared with placebo after 4 weeks of treatment. Geometric means and mean ratios will be the summary measures of treatment effect for the change from baseline in each group and differences between treatment groups

Secondary objective:

- To evaluate the efficacy by comparing the change from baseline in Cough Severity NRS score and Cough Severity VAS after 4 weeks of treatment between the BI 1839100 highest dose group and the placebo group

Phase IIb:

The aim of Phase IIb is to characterize the dose-response curve and evaluate the treatment effect of different doses of BI 1839100 relative to placebo in trial participants with IPF and clinically meaningful cough.

Primary objective:

- To demonstrate a non-flat dose-response curve with respect to change from baseline in 24-h cough frequency after 12 weeks of treatment and characterize the dose-response relationship within the therapeutic range of BI 1839100 regarding efficacy and safety. The mean changes from baseline for each treatment group, based on the log transformed CC/h, will be the summary measures of treatment effect for the analysis of dose-response

Secondary objectives:

- To evaluate the efficacy of BI 1839100 by assessing cough responder status, defined as a $\geq 30\%$ 24-h cough frequency reduction (CC/h) from baseline after 12 weeks
- To evaluate the efficacy by comparing the absolute change from baseline in FVC (mL) after 12 weeks of treatment between BI 1839100 dose groups and the placebo group

- To evaluate the efficacy by comparing the change from baseline in Cough Severity NRS, Cough Severity VAS, LCQ physical domain, and L-PF symptom cough domain after 12 weeks of treatment between BI 1839100 dose groups and the placebo group

For both Phase IIa and IIb, a treatment policy approach will be used as the primary approach to the handling of intercurrent events associated with the primary and secondary objectives, i.e. the primary treatment comparisons will be made for randomised participants analysed by the treatment the participant was assigned, regardless of changes of background AF therapy or background medication used for cough, treatment discontinuation or interruption, or start of restricted medication.

PPF cohort

no primary or secondary objectives are defined.

2.1.2 Primary endpoints

IPF cohort

- Phase IIa: change from baseline in 24-h cough frequency (CC/h) at Week 4
- Phase IIb: change from baseline in 24-h cough frequency (CC/h) at Week 12

Note that, for each participant, the change from baseline will be calculated as the change in CC/h after the values have been log-transformed. More details are described in Section [7.2](#).

PPF cohort

- Not applicable

2.1.3 Secondary endpoints

IPF cohort

Key secondary endpoint(s)

- Not applicable

Secondary endpoints

- Phase IIa:
 - Absolute change from baseline in Cough Severity NRS score at Week 4
 - Absolute change from baseline in Cough Severity VAS score (mm) at Week 4
- Phase IIb:
 - Cough responder status, defined as a $\geq 30\%$ 24-h cough frequency reduction (CC/h) from baseline at Week 12
 - Absolute change from baseline in FVC (mL) at Week 12
 - Absolute change from baseline in Cough Severity NRS score at Week 12

- Absolute change from baseline in Cough Severity VAS score (mm) at Week 12
- Absolute change from baseline in L-PF symptom cough domain score at Week 12
- Absolute change from baseline in LCQ physical domain score at Week 12

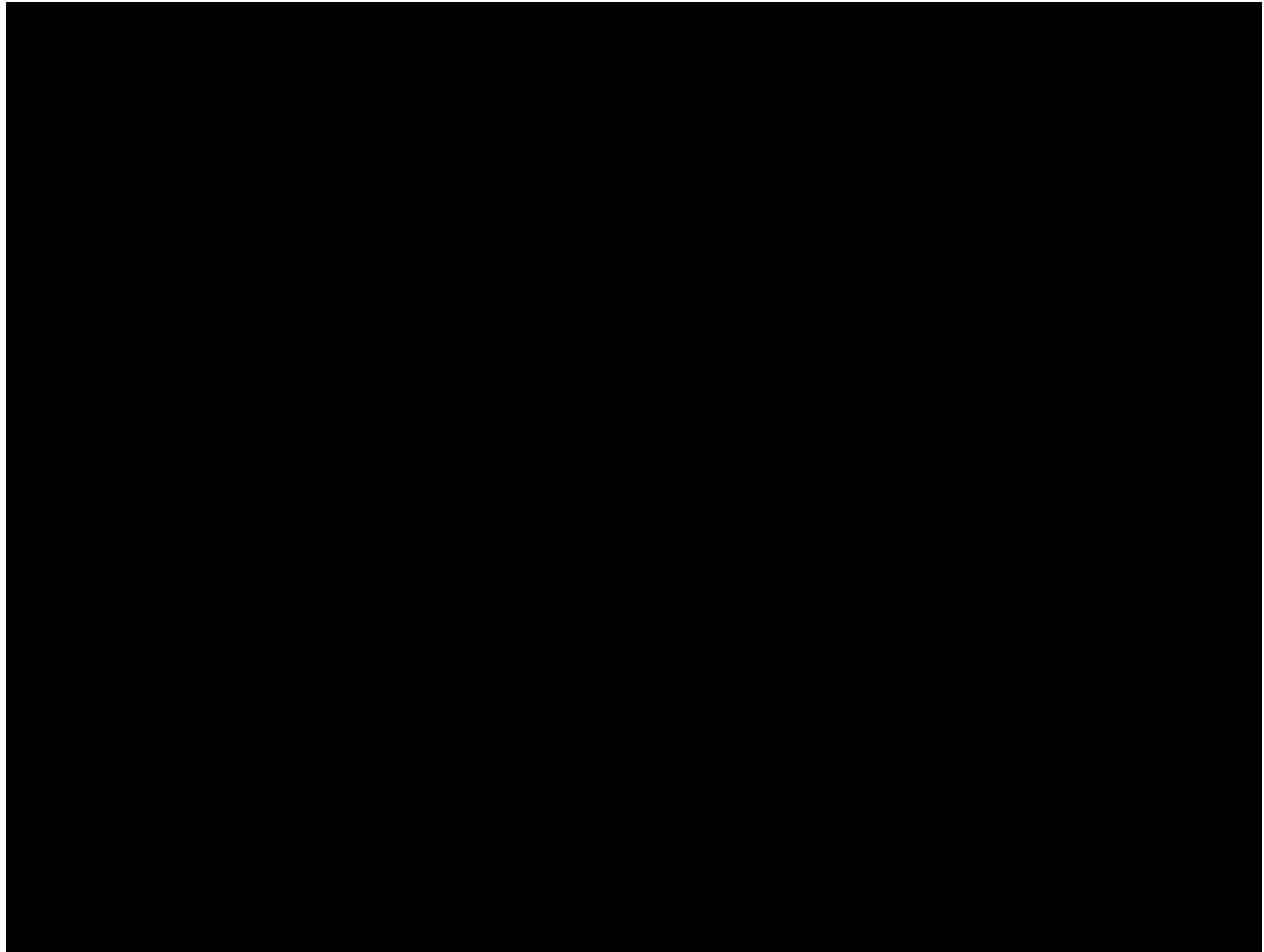
PPF cohort

- Not applicable

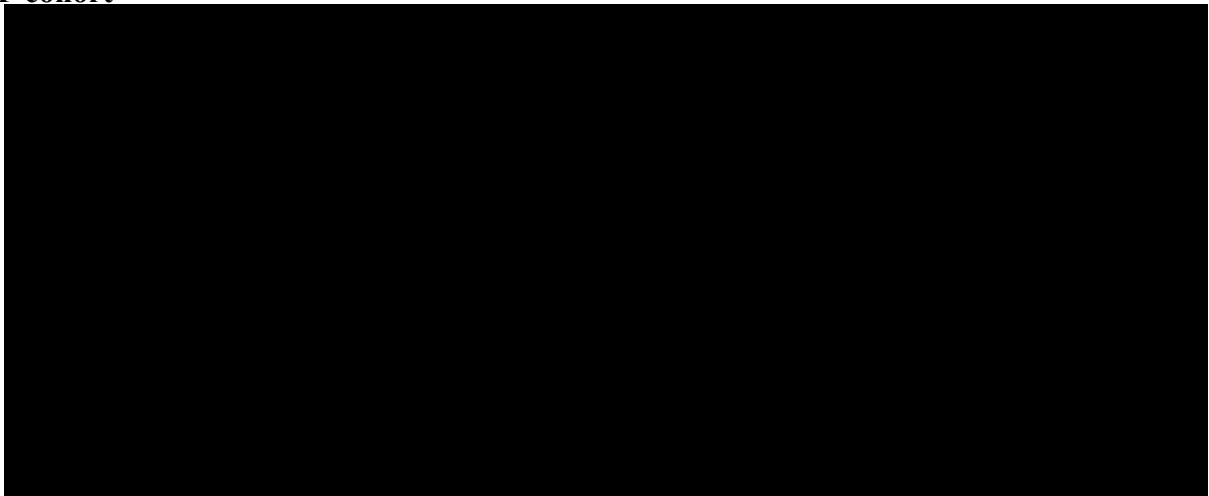
2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

IPF cohort

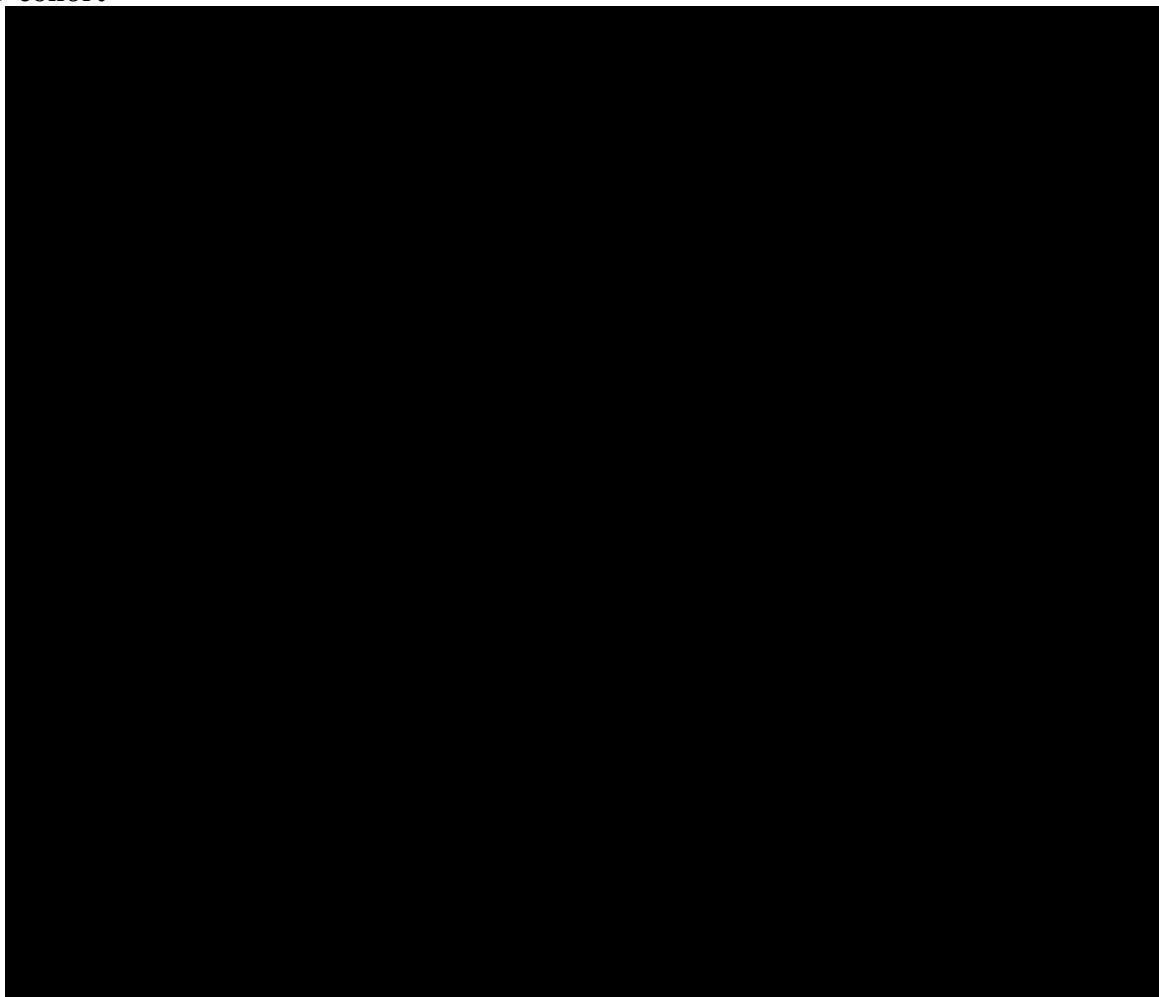


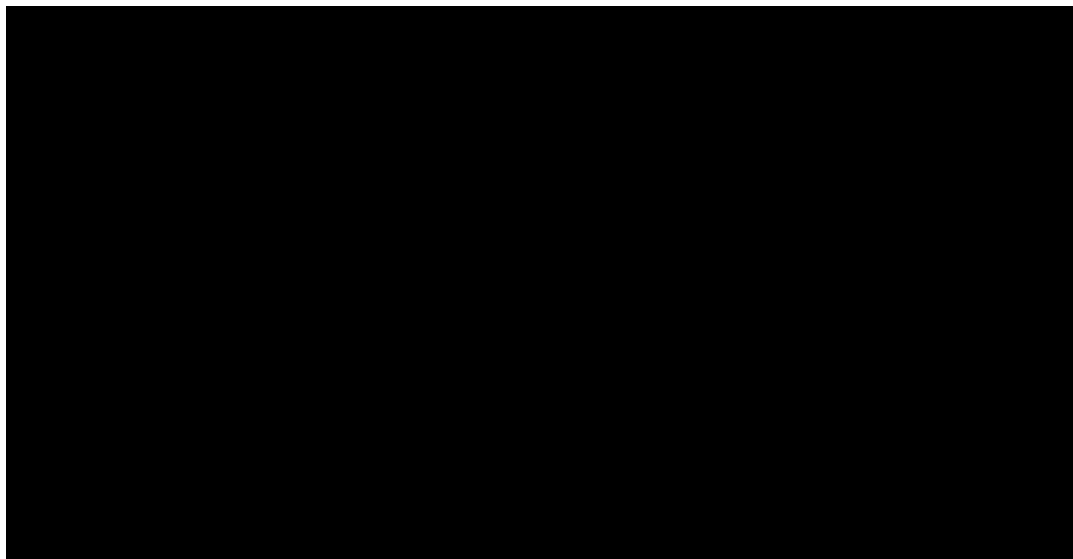
PPF cohort



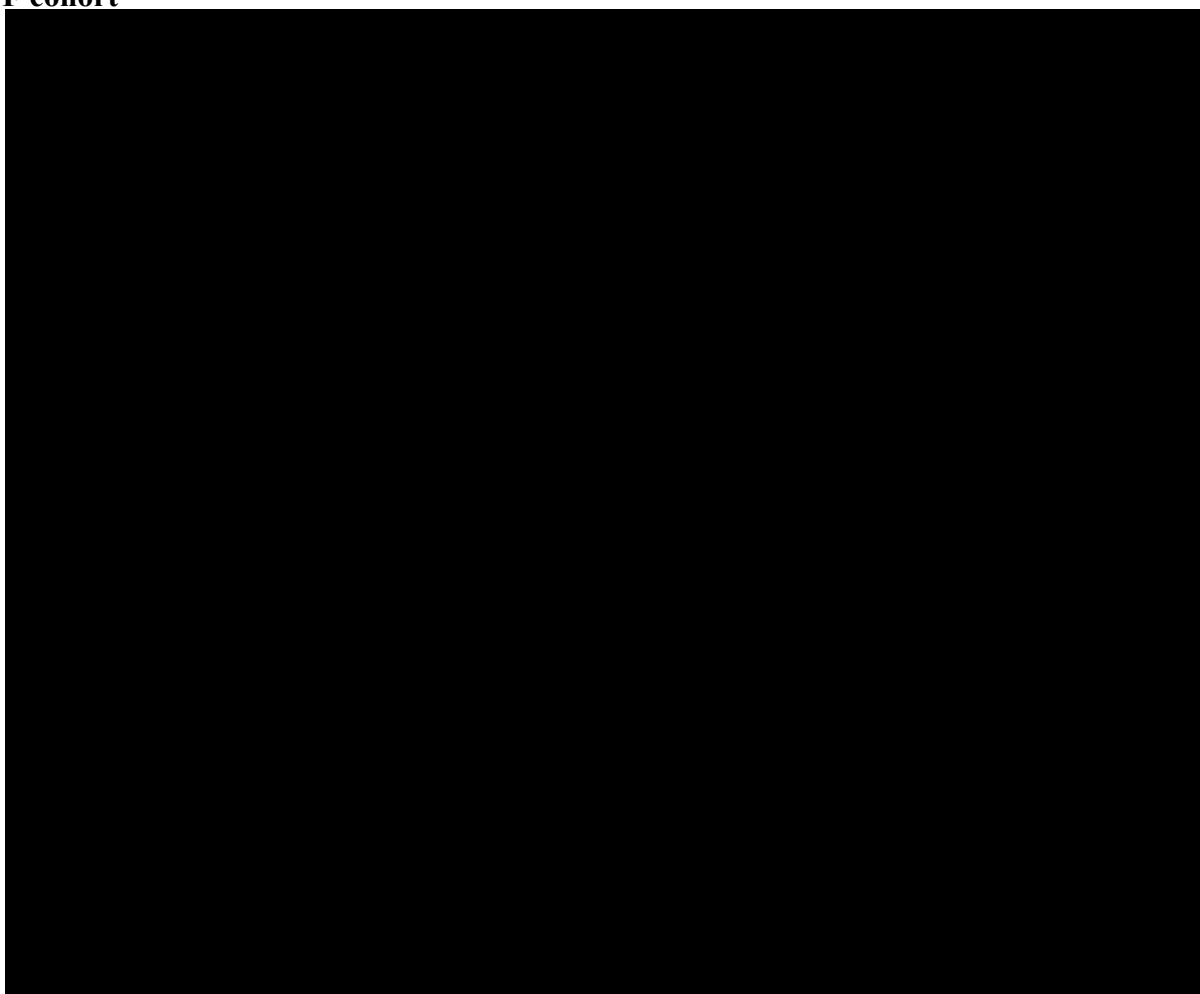
2.2.2 Further endpoints

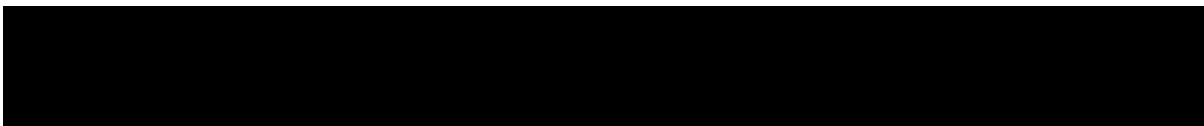
IPF cohort



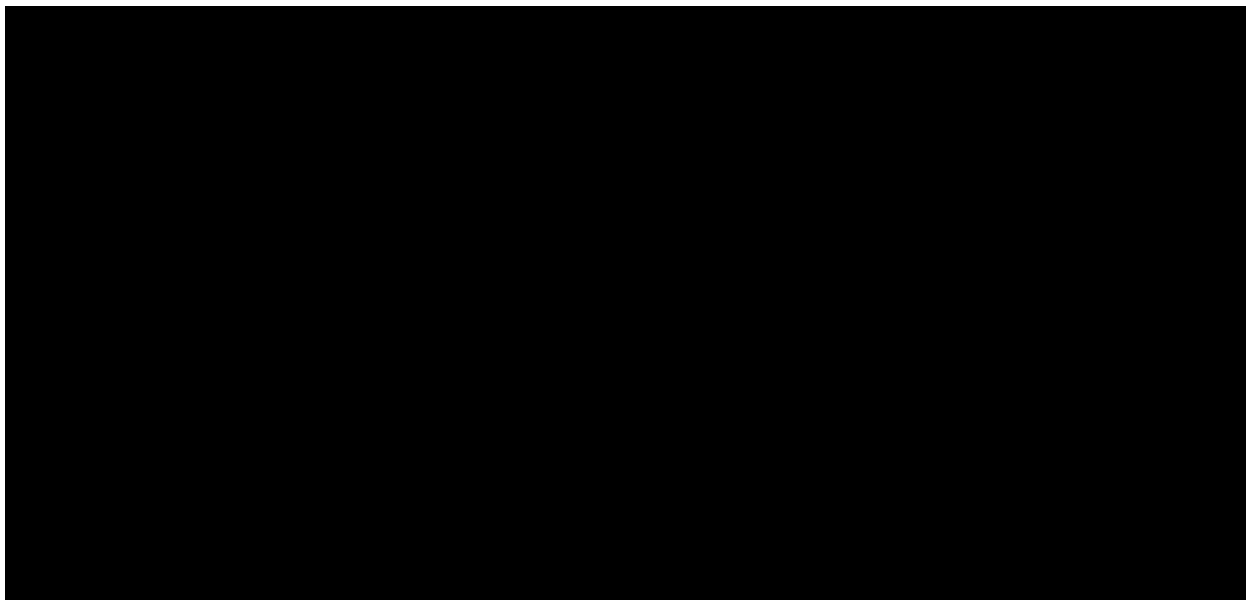


PPF cohort





IPF and PPF cohort



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The overall trial design is a randomised, multi-centre, multi-national, placebo-controlled, parallel-group, double-blind (double-dummy technique) clinical trial using a seamless Phase IIa/IIb design ([Figure 1](#)).

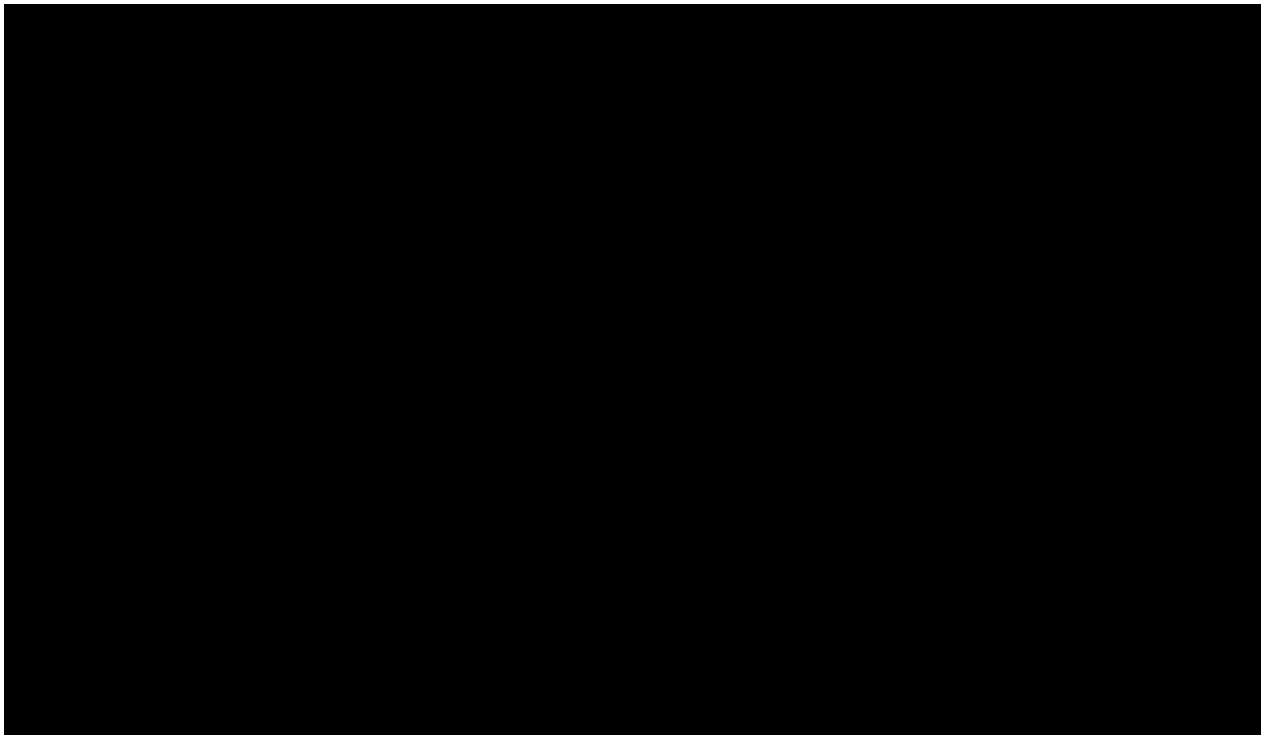


Figure 1 Trial design

S-screening, R-randomisation.

Patients with IPF or PPF (in a separate cohort) with clinically meaningful cough (Cough VAS ≥ 30 mm), with background AF treatment on stable dose (for >12 weeks) or without AF treatment will be eligible to enrol.

The overall sample size is approximately 180 participants for the IPF cohort (up to completion of Phase IIb). The eligible IPF patients will be randomised in the trial in a 2:1:1:2 ratio (placebo, [REDACTED] Patient randomisation will be stratified by the presence of background treatment with AF (AF group versus non-AF group).

The planned duration of treatment is 12 weeks for the IPF cohort and 4 weeks for the PPF cohort.

An IA, i.e. the primary analysis for Phase IIa part, will be performed when approximately 25 trial participants in each of the [REDACTED] and placebo groups in the IPF cohort complete 4 weeks

of treatment (Section [7.2.8](#) and [8.7.4](#)). Enrolment will continue during the IA analysis. If the outcome of the IA is negative, the trial will be halted. Further recruitment will be stopped and treatment for all the participants will be discontinued at the next scheduled visit. If the outcome of the IA is positive, enrolment in IPF dose groups will proceed as planned. In addition, enrolment in the PPF cohort will begin. An additional 50 patients are planned to be randomised into the [REDACTED] PPF cohort in a 1:1 ratio (placebo, [REDACTED]). Patient randomisation in the PPF cohort will also be stratified by background treatment with AF.

The final DBL will be done once all participants (IPF and PPF) complete the trial. If the PPF cohort is still in progress when completion of the IPF cohort occurs, a snapshot will be taken to perform an IA (i.e. the primary analysis of the Phase IIb in IPF cohort) when all IPF participants have either completed 12 weeks of treatment or discontinued.

The Follow-up Visit will be conducted [REDACTED] after treatment completion and is the last planned visit for trial participants. In case of early treatment discontinuation, the participants will be encouraged to follow the trial schedule of visits and assessments as per protocol. Completion of EoS assessments by the last participant randomised will constitute the end of the trial.

Change in 24-h cough frequency observed for IPF trial participants treated with placebo, [REDACTED] in a parallel-group design will be used to characterise the dose-response.

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

IPF cohort

[REDACTED]
[REDACTED] a
randomised controlled trial [REDACTED] to establish efficacy and safety of BI 1839100 in [REDACTED]
[REDACTED] Randomisation and inclusion of the placebo group ensures the scientific interpretability of results.

A treatment period of 12 weeks has been selected for the Phase IIa/IIb trial for the following reasons:

- This period will allow evaluation of whether BI 1839100 maintains a sustained effect on cough reduction

- A recent study examining NMDA receptor antagonist ifenprodil in 20 patients with IPF utilised a similar approach, employing co-primary endpoints of CC reduction and FVC 'responder' or 'non responder' status at 12 weeks [[P23-01135](#)]

- Recent meta-analysis demonstrated that FVC treatment effect could be observed as early as 3 months utilizing either absolute change (mL) or relative percent change in FVC [P22-00512]
- In a recent trial evaluating the safety and efficacy of BI 1015550 in persons with IPF, a significant treatment effect based on FVC change (mL) was observed at 12 weeks in patients with IPF regardless of background therapy [P22-03537]

A 2:1:1:2 randomisation ratio was selected to optimize the opportunity to assess treatment differences between the high dose and placebo groups while still allowing for dose range finding by including the intermediate and low dose groups.

The primary and secondary endpoints were selected because they assess the effect of BI 1839100 on objective cough measures, cough symptoms and QoL, and lung function. They are common endpoints evaluated in cough studies and address important medical and QoL aspects of the disease.

PPF cohort

Evaluation of the PPF cohort is [REDACTED]. A 1:1 randomisation ratio including BI 1839100 [REDACTED] and placebo is selected [REDACTED]
[REDACTED]

Trial guidance and insights

An external DMC will be involved in the evaluation of safety data (and if requested, efficacy data) during the trial (see Section [8.7.3](#)).

This trial will include an option for participants to complete 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 analysed as part of the clinical data for the trial (see Appendix [10.8](#)).

Early interactions have been held with 4 major health authorities (FDA, EMA, PMDA, and CDE). All have accepted the overall trial rationale, design, duration, and endpoints.

Patient consultation was solicited early in the development and design of the Phase II program. Consultations included a dedicated patient advisory board focused on cough monitoring devices, consultation with the EU-IPFF, 2 PF patient advisory boards, 2 meetings with the early PF patient steering committee, and an online exchange around various trial-related topics. These interactions date back to the summer of 2021 and have continued through the fall of 2023. Patient and patient advisory group input was sought on benefits and trade-offs around specific cough devices, cough endpoints of clinical relevance to patients, the inclusion of digital device monitoring, including activity monitoring and PRO measures.

3.3 SELECTION OF TRIAL POPULATION

The trial will randomise approximately 180 patients in the IPF cohort and an additional 50 patients in the PPF cohort. There are expected to be 200 trial sites in up to 30 countries involved in the trial.

If enrolment is delayed, additional sites may be recruited. To avoid differential centre influence on trial results, permission to randomise more than 10 patients per site must be obtained from the sponsor. This will only be allowed after a careful review of the enrolment status and of the site.

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

A participant who fails screening may be rescreened for the trial only once based on investigator judgment and prior permission from the sponsor.

A log of all participants enrolled in the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether or not IMP was administered to the participant.

The following information, at minimum, will be collected, including for participants who are determined to be ineligible for enrolment: participant number, visit date, demographics, eligibility criteria, information on AEs (if applicable), concomitant treatment relevant for the AE, reason(s) for screening failure.

If retrospectively it is found that a trial participant has been randomised in error (i.e. did not meet all inclusion criteria or met 1 or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made as to whether continued trial participation is possible.

3.3.1 Main diagnosis for trial entry

IPF cohort

Patient must be diagnosed with IPF according to the 2022 ATS/ERS/JRS/ALAT Guideline [[P22-03204](#)] and confirmed by centrally reviewed chest HRCT scan taken within 12 months of Visit 1. 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.

A 'UIP' or 'probable UIP' HRCT pattern consistent with the clinical diagnosis of IPF must be confirmed by central review prior to Visit 2B. Patients with an 'indeterminate' HRCT finding are eligible if a clinical diagnosis of IPF can be confirmed locally based on (historical) surgical lung biopsy or TBLC demonstrating a 'UIP' or 'probable UIP' histopathology pattern ([Table 10](#)). Patients with an 'alternative diagnosis' HRCT finding are eligible if a clinical diagnosis of IPF

can be confirmed locally based on (historical) surgical lung biopsy or cryobiopsy demonstrating a 'UIP' histopathology pattern ([Table 10](#)).

See Appendix [10.1](#) for additional information on confirmation of IPF diagnosis.

Numerous observational studies were reviewed to assess optimal criteria to enrich the trial population to enrol IPF patients with clinically meaningful cough. The Cough Severity VAS was used in the Australian IPF registry [[P17-02366](#)] as well as the CARE-PF registry [[R18-0482](#)] to assess cough. In both real-world registries, Cough VAS was able to be administered at scale across multiple centres. In the former, elevated Cough VAS was associated with higher risk of mortality, which informed its use for inclusion. The additional inclusion and exclusion criteria are in line with prior interventional studies in this patient population.

PPF cohort

Patient must have fibrosing lung disease affecting more than 10% of lung volume on HRCT, as confirmed by central review, and have a diagnosis of progressive lung fibrosis, according to INBUILD criteria [[P19-08802](#)]. Patients must meet at least 1 of the following criteria within 24 months before the screening visit, despite treatment with unapproved medications used in clinical practice to treat ILD, as assessed by the investigator:

- Relative decline in the FVC of at least 10% of the predicted value
- Relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms OR an increased extent of fibrosis on HRCT
- Worsening of respiratory symptoms and an increased extent of fibrosis

See Appendix [10.2](#) for additional information regarding HRCT requirements for PPF.

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

Patients will be eligible if they meet all the following inclusion criteria at screening:

IPF cohort

1. Diagnosis of IPF (see Section [3.3.1](#))
2. Chronic cough (>8 weeks prior to Visit 1) attributed to IPF and refractory to treatment for known causes (PI assessment)
3. Cough Severity VAS ≥ 30 mm at Visit 1 and Visit 2B
4. FVC $\geq 45\%$ of predicted normal at Visit 1
5. DLCO $\geq 25\%$ of predicted normal at Visit 1
6. Patients may be either:

- On stable therapy with nintedanib or pirfenidone for ≥ 12 weeks prior to Visit 1 and are planning to stay on this background treatment for the whole trial duration. Combination of nintedanib plus pirfenidone will not be allowed
 - Not on therapy with nintedanib or pirfenidone for ≥ 12 weeks prior to Visit 1 (either AF-treatment naïve or previously discontinued) and do not plan to start or re-start AF treatment during the trial. It is not permitted to delay nintedanib or pirfenidone therapy for the purpose of participating in this trial
7. Patients aged ≥ 40 years when signing the informed consent
 8. Male or female participants
 - WOCBP¹ must be willing and able to use 1 highly effective method of birth control. Please refer to Section [4.2.2.3](#) for additional details
 9. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

PPF cohort

13. Diagnosis of PPF (see Section [3.3.1](#))
14. Chronic cough (> 8 weeks prior to Visit 1) attributed to PPF, refractory to treatment for known causes (PI assessment)
15. Cough Severity VAS ≥ 30 mm at Visit 1 and Visit 2B
16. FVC $\geq 45\%$ of predicted normal at Visit 1
17. DLCO $\geq 25\%$ of predicted normal at Visit 1
18. If receiving immunomodulatory therapy for ILD, allowed medications include tacrolimus, mycophenolate mofetil, or azathioprine (stable dose for 12 weeks prior to Visit 1)
19. Patients may be either:
 - On a stable therapy with nintedanib for ≥ 12 weeks prior to Visit 1 and are planning to stay on this background treatment for the whole trial duration
 - Not on a therapy with nintedanib for ≥ 12 weeks prior to Visit 1 (either AF-treatment naïve or previously discontinued) and do not plan to start or re-start AF treatment during the trial. It is not permitted to delay nintedanib therapy for the purpose of participating in this trial
20. Patients aged > 18 years when signing the informed consent
21. Male or female participants
 - WOCBP¹ must be willing and able to use 1 highly effective method of birth control. Please refer to Section [4.2.2.3](#) for additional details

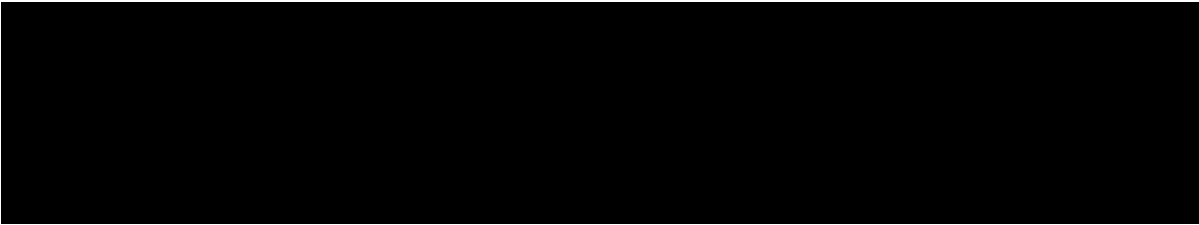
¹ A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Please note that tubal ligation is NOT accepted as a method of permanent sterilisation and therefore a woman who underwent tubal ligation is still considered as WOCBP. However, tubal ligation is considered as a method of highly effective birth control.

22. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

Patients will NOT be eligible if they meet any of the following exclusion criteria:

IPF and PPF cohorts

1. Acute exacerbation of IPF/PPF within 12 weeks prior to Visit 1
2. FEV1/FVC <0.7 at Visit 1
3. Known reversible airflow obstruction/response to bronchodilators
4. In the opinion of the Investigator, other clinically significant pulmonary abnormalities, including primary bronchitic and bronchiectatic disorder
5. Upper or lower respiratory tract infection within 4 weeks prior to Visit 1
6. Ongoing chronic pulmonary infection (e.g. mycobacterial or fungal disease)
7. Current smokers (tobacco use within the 6 months prior to Visit 1)
8. Initiation or change in supplemental oxygen requirement during 4 weeks prior to Visit 1
9. Oral corticosteroids or prednisone >15 mg/day or equivalent (Appendix [10.3](#), [Table 12](#))
10. Initiation or change in dose within 4 weeks prior to Visit 1 of the following medication: ACE inhibitors, inhaled corticosteroids, inhaled bronchodilators, proton pump inhibitors or histamine type-2 receptor blockers
11. Use of the following drugs within 4 weeks of Visit 1: opiate/opioids (e.g. codeine, morphine), baclofen, gabapentin, pregabalin, thalidomide, amitriptyline, inhaled cromolyn or related products, gefapixant
12. 
13. Any of the following:
 - Severe hypertension (uncontrolled under treatment $\geq 160/100$ mmHg at multiple occasions) within 3 months of Visit 1
 - Myocardial infarction within 6 months of Visit 1
 - Unstable cardiac angina within 6 months of Visit 1
14. QTcF interval >450 ms in males or >470 ms in females (confirmed by repeat ECG recording) at Visit 1 or a history of additional risk factors for TdP (such as hypokalaemia or family history of Long QT Syndrome)
15. Patients with underlying chronic moderate to severe liver disease (Child Pugh B or C hepatic impairment)

16. AST and/or ALT >1.5x ULN at Visit 1
17. eGFR ≤ 30 mL/min/1.73 m² at Visit 1 (CKD-EPI formula or Japanese version of CKD-EPI for Japanese patients)
18. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix
19. Life expectancy <12 months
20. Major surgery (major according to the investigator's assessment) performed within 6 weeks prior to randomisation or planned during the trial, e.g. hip replacement
21. Participants taking any of the restricted medications (see Section [4.2.2.1](#)) or any drug considered likely to interfere with the safe conduct of the trial
22. Women who are pregnant, breastfeeding, or plan to become pregnant while in the trial
23. The patient is currently enrolled in another investigational device or drug trial, or their Visit 1 occurs <30 days or 5 half-lives (whichever is longer) after completing a previous investigational device or drug trial or receiving other investigational treatment(s)
24. Previous treatment in this trial
25. Participants 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 participant an unreliable trial participant)
26. Any condition not covered by any of the other exclusion criteria which, in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol
27. Any vulnerable person (defined as: pregnant or breastfeeding women; persons deprived of their liberty; minors; persons that may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests; or unable to explicitly give consent), as per local regulation

IPF cohort only

28. Treated with immunomodulatory medications (other than prednisone ≤ 15 mg/day or equivalent) for respiratory or pulmonary reasons

PPF cohort only

29. Patients with acute or chronic pleuritis (per PI assessment)
30. Use of pirfenidone, cyclophosphamide, cyclosporine, tocilizumab, methotrexate and/or leflunomide within 4 weeks or 5 half-lives (whichever is longer) prior to Visit 1
31. Use of rituximab or other specific B-cell depleting therapies within 6 months of Visit 1

3.3.4 Discontinuation of trial participants from treatment or assessments

Trial participants may discontinue trial IMP 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](#).

Measures to control the withdrawal rate include careful trial participant 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 IMP or withdraw consent to trial participation and the reason (if provided) must be documented in the trial participant files and CRF. If applicable, consider the requirements for AE collection and reporting (see Section [5.2.7.2](#)).

3.3.4.1 Discontinuation of trial treatment

An individual trial participant will discontinue trial IMP if:

- The trial participant wants to discontinue trial IMP. The trial participant will be asked to explain the reasons but has the right to refuse to answer
- The trial participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the trial participant cannot be guaranteed as he/she is not willing or able to adhere to the trial requirements in the future
- The trial participant needs to take restricted medication
- The trial participant can no longer receive trial IMP for serious or severe drug induced liver injury attributable to the trial IMP (see Section [5.2.7.1.4](#))
- The trial participant can no longer receive trial IMP for medical reasons such as surgery, AEs, other diseases, or pregnancy. See Section [5.2.7.2.3](#) regarding follow up in case of pregnancy
- The trial participant experienced QTcF increase of >60 ms from baseline (Visit 2B) or absolute QT or QTcF >500 ms, as confirmed by a repeat ECG recording
- The trial participant has ≥ 2 instances of treatment interruption each lasting for ≥ 7 days

In case of a temporary reason, trial IMP should be restarted if medically justified; please see Section [4.1.4](#).

Data of the trial participants who discontinue IMP prematurely will be collected and reported in the clinical trial report until last trial participant last visit and that any events thereafter will be reported in the BI pharmacovigilance database.

Additional participants may be recruited to replace participants who discontinue participation early for non-safety related reasons (e.g. unable to attend the protocol defined visits for personal reason) or trial disruption (e.g. force majeure or other disrupting circumstance).

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

Even if the IMP is discontinued, the trial participants will remain in the trial and, given their agreement, undergo the procedures for early treatment discontinuation and follow up as outlined in the [SoA](#) and Section [6.2.3](#). Participants may choose to re-start the IMP at any time during their planned treatment period as long as there is no safety concern, in the opinion of the investigator.

3.3.4.2 Withdrawal of consent to trial participation

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

If a trial participant wants to withdraw consent, the investigator should be involved in the discussion with the trial participant and explain the difference between IMP discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow up after IMP discontinuation (see Section [3.3.4.1](#) and [6.2.3](#)).

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 see 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 trial participants affected will occur as described in Section [3.3.4.1](#).

The investigator/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 trial medication (BI 1839100 and placebo) will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the IMP and placebo are given below in [Table 2](#) and [Table 3](#), respectively.

Table 2 Characteristics of BI 1839100

Substance:	BI 1839100
Pharmaceutical formulation:	[REDACTED]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[REDACTED]
Posology:	[REDACTED]
Mode of administration:	[REDACTED]

Table 3 Characteristics of placebo treatment

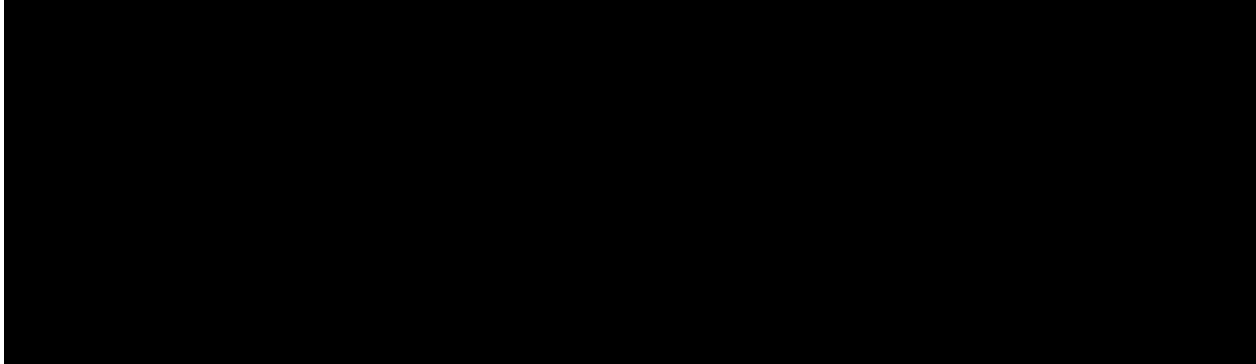
Substance:	Placebo [REDACTED] [REDACTED] of BI 1839100
Pharmaceutical formulation:	[REDACTED]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	[REDACTED]
Mode of administration:	[REDACTED]

4.1.2 Selection of doses in the trial and dose modifications

Doses of BI 1839100 planned for the IPF cohort are [REDACTED]
as determined based on [REDACTED]

(C_{max})
(C_{min,ss})

dosing



of BI 1839100.

The

IMP dose modifications and/or reductions are not possible due to blinded design. Participants who are not able to tolerate the treatment must be discontinued from the trial medication.

Temporary treatment interruption is allowed to manage adverse events per investigators judgment.

4.1.3 Method of assigning trial participants to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible trial participant will be randomised to a treatment group at Visit 2B according to a randomisation plan (see Section [7.4](#)). Randomisation codes will be generated through a validated software and kept blinded to the trial team, sites, and trial participants. Access to the codes will be controlled and documented. An IRT system will be used to create a participant number, assign IMP (medication number), manage initial and re-supply ordering of IMP supplies, and handle emergency unblinding.

4.1.4 Drug assignment and administration of doses for each trial participant

At Visit 2B, after randomisation, trial participants will receive their first IMP supply. The first dose of IMP will be taken at the trial site under supervision of the investigator or site staff. Additional IMP will be distributed to the trial participants as indicated in the [SoA](#). At each dispensing visit, participants will receive 5 medication kits for IMP supply for 5 weeks of treatment. One medication kit will include medication for 1 week. Medication kits can be taken in any order. The last dose of IMP will be the evening before the EoT Visit.

Trial participants should be instructed not to take IMP in the morning of visits, since they will be dosed at the site after pre-dose blood sampling. Trial participants should also be instructed not to take IMP in the morning of EoT visit. Trial participants who take the IMP the morning of their scheduled visits should have their visit rescheduled to as soon as possible, ideally on the following day.

IMP is self-administered by the trial participant at home. IMP

3.3.4.1

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war [see Section 6]), physical visits to the sites may not be feasible or may need to be restricted to ensure participant safety. In such cases, based on a thorough assessment of the benefits and risks, the investigator may decide to continue IMP administration. Where permitted by local law and regulations, trial IMP may be shipped directly to a participant's home.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In order to maintain double-blinding in regard to each dose group, each dose will contain ██████████ in a double-dummy design, as shown in [Table 4](#), taken ██████████ Placebo ██████████

██████████ as needed in each dose group to maintain the blinding.

Table 4

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

Access to the randomisation codes will be kept restricted until its documented release at the time of database lock per sponsor SOP.

Randomisation codes will be provided to the bioanalytics during the trial to allow PK samples taken from participants receiving placebo to be excluded from the analyses. In preparation for data transfer and bioanalytical report writing, the trial bioanalyst may receive unblinded data after the last trial participant has completed the last visit but prior to official unblinding of the analysis database. The bioanalytics will not disclose the randomisation codes or bioanalytical results until the trial is unblinded after DBL.

The IA, the primary analysis for Phase IIa part, (see Sections [7.2.8](#) and [8.7.4](#)) will be performed by an unblinded team independent of the trial team. The trial team will remain blinded throughout the IA process.

Details regarding access and handling of the unblinded data will be described in the Data Logistics Plan and Results Access Plan.

The final DBL will be performed when all participants complete the trial. In case that IPF cohort completes before the PPF cohort, an IA (i.e. the primary analysis of Phase IIb in IPF cohort) will be performed once all participants in the IPF cohort have either completed 12 weeks of treatment or discontinued. A snapshot for this analysis will be done and treatment of IPF cohort will be unblinded to trial and project team members. The final DBL will then be done when all PPF cohort participants complete the trial and treatment of PPF cohort will be unblinded.

In addition, the selected members of the trial/project team will receive access to the treatment information of the enrolled participants prior to the database lock to allow for early PK assessment for project planning. Only personnel involved in the analysis of these data will be granted access to the unblinded data before the DBL. Results will be presented at the treatment-group level without individual treatment data. Some trial team members involved in the project decision may see the results, but this is unlikely to lead to unblinding. Details regarding access and handling of the unblinded data will be described in the Data Logistics Plan and Results Access Plan.

4.1.5.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the investigator via emergency service. It must be used only in an emergency when the identity of the trial IMP must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The treatment allocation should not be disclosed to the sponsor unless this is explicitly requested. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report SUSARs, it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual trial participants during trial conduct. The access to the code will only be given to authorised PSPV representatives for processing in the Pharmacovigilance database and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The IMP will be provided by Boehringer Ingelheim or a designated CRO. The IMP will be packaged and labelled in accordance with the principles of GMP.

The label will be prepared according to EU Regulation No. 536/2014, Annex 6, Section D.8., omitting certain particulars with the following justifications:

- The investigator name is omitted from the label due to the IRT system
- The visit number is not relevant for this clinical trial due to the straightforward trial design (no crossover, different dosages in a blinded sequence, or similar). The visit number is included in the drug accountability form, and additionally, the Med. No. on the label allows correct traceability and documentation of the corresponding IMP administration cycle

Should local regulations outside the EU require these particulars, they will be added to the country-specific label text.

Initial study drug supplies will be sent to the site after the first participant is screened at the site. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

For site-to-participant shipments, the IMP will be assigned at the site via the IRT/regular kit allocation process and taken from the stock at the site.

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, immediately contact the CRA (as provided in the list of contacts) and follow the procedures for assessing and reporting temperature excursions provided in the ISF.

The site is responsible for maintaining documentation for site to participant shipments. In case of temperature excursions during the shipment, immediately contact the CRA, and follow the procedures for assessing and reporting temperature excursions provided in the ISF.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB/ethics committee
- 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 PI
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the PI
- Availability of FDA Form 1572 (if applicable)

The IMP is not allowed to be used outside the context of this protocol and must not be forwarded to other investigators or clinics. Trial participants should be instructed to return unused IMP, which may include shipment to the site.

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

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the IMP and trial participants. The investigator or designee will maintain records that adequately document that trial participants were provided the doses specified by this clinical trial protocol and reconcile all IMPs received from the sponsor. At the time of return to the sponsor the investigator or designee must verify that all unused or partially used IMP supplies have been returned by the trial participant and that no remaining IMP supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Auxiliary medicinal products

Not applicable.

4.2.1.2 Emergency procedures

In the case of acute IPF/PPF exacerbation, participants must be treated according to local SoC. If the participant requires a restricted medication to treat the exacerbation, the IMP must be discontinued according to Section [3.3.4.1](#).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

1. While enrolled in this trial, trial participants must not participate in another investigational drug or device trial or receive other investigational treatment(s)
2. Restricted medications
 - a. Systemic corticosteroids (>15 mg daily prednisone or equivalent) for the treatment of IPF or PPF or cough are not allowed during the screening and/or treatment period (see Appendix [10.3](#), [Table 12](#)). Escalations in steroid dose during the trial, whether for non-IPF/PPF or non-pulmonary indications must be recorded in source documentation
 - b. AF therapy
 - Ongoing stable doses of nintedanib or pirfenidone are allowed as background therapy in the IPF cohort. Ongoing stable doses of nintedanib are allowed as background therapy in the PPF cohort. Combination of nintedanib and pirfenidone is not allowed. For participants who have not received nintedanib or pirfenidone in the 12 weeks prior to trial entry, these medications are not allowed during the screening or treatment period
 - In the PPF cohort, pirfenidone is not allowed during the screening or treatment period
 - c. Immunomodulatory medications
 - IPF cohort only: administration of immunomodulatory medications (other than prednisone 15 mg/day or equivalent) should not be started for respiratory or pulmonary indications during the screening or treatment period
 - PPF cohort only: use of cyclophosphamide, cyclosporine, tocilizumab, methotrexate, leflunomide, rituximab, or other specific B-cell depleting therapies is not allowed during the screening or treatment period
 - d. Use of the following drugs is not allowed during the screening or treatment period: opiates/opioids (e.g. codeine, morphine), baclofen, gabapentin, pregabalin, thalidomide, amitriptyline, inhaled cromolyn or related products, gefapixant
 - e.
 - f.
 - g.

h.

- i. Use of drugs that are known to be associated with QT/QTc prolongation such as antiarrhythmics (e.g. sotalol), macrolides (e.g. azithromycin), fluoroquinolones (e.g. levofloxacin), antifungals (e.g. fluconazole), antipsychotics (e.g. haloperidol), antidepressants (e.g. citalopram), and antiemetics (e.g. ondansetron), is not allowed during the screening or treatment period
- j. ACE inhibitors, inhaled corticosteroids, inhaled bronchodilators, proton pump inhibitors or histamine type-2 receptor blockers medications dose should not be changed or started during screening and treatment period

4.2.2.2 Restrictions on diet and lifestyle

In general, participants should keep their usual habits throughout the trial for diet and exercise, as well as alcohol and caffeine intake. These habits should be within acceptable daily amounts, at the discretion of the investigator, and should not be drastically changed throughout the trial.

Participants do not have to fast prior to trial visits.

Restrictions regarding cough monitor

During the 24-h monitoring period, participants are advised against using the cough monitor during a bath or swimming as the device is not waterproof. The cough monitor is water resistant, however, participants are advised not to submerge or expose the device to a significant amount of water. Should the device be used during a shower, participants will be asked to ensure that the Tegaderm™ is intact, fully covering the cough monitor device and additional precautions are taken (as outlined in training instructions) to avoid prolonged exposure to water.

Restrictions regarding activity monitor

Activity monitor watch must be worn at all times during the 2-week assessment periods, including during sleep. Activity monitor watch can be worn during showering and swimming.

4.2.2.3 Contraception requirements

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal 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.

During the treatment period and until the end of the trial ([REDACTED]), WOCBP must use 1 highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of <1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- IUD or IUS
- Bilateral tubal occlusion

Or:

- Complete abstinence (refraining from heterosexual intercourse) is considered a highly effective method of contraception only if it is in line with the preferred and usual lifestyle of the trial participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to trial IMP, and withdrawal are not acceptable methods of contraception

Women who are breast-feeding, and children under the age of 18 years should not participate in trials with BI 1839100.

4.3 TREATMENT COMPLIANCE

Trial participants are requested to bring all remaining trial IMP, including empty package material, with them when attending visits.

Based on [REDACTED] treatment compliance will be calculated as shown in the formula below.

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Cough monitoring

BI/vendor will provide the cough monitoring device(s) (includes device(s), charging station, and mobile phone (with the corresponding app)).

The cough monitor utilizes a proprietary algorithm to analyze recordings of respiratory and cough sounds. Data will be uploaded via Bluetooth interface from the biosensor to the mobile app and subsequently from the mobile app to the cloud. Cough data analyses as well as cough reports in which audio and spectrographic recordings are manually read, will be available.

The participants are provided with the device and appropriate training at Visit 1 after it is confirmed that participant meets eligibility criteria that can be assessed during the Visit 1. Participants will be given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure and is not returning to the site.

The cough monitoring device is worn for 24 h at 5 time points in the trial as defined in the [SoA](#). The device is attached to the participant's chest using self-adhesive Tegaderm™.

Participants should bring the device to each visit since device will be reattached at the end of the visit to initiate the next 24-h recording. Participants must charge the device overnight before the trial visit. If the participant brings an uncharged device to the trial visit, sites may use an extra cough monitor charger to charge the device in parallel to other trial procedures, enabling recording to be started before the participant leaves the site. After the 24-h monitoring period, participants must remove the device and place it on the charging cradle, adjacent to the study provisioned mobile phone (also connected to charger). This will initiate data transfer from the device.

Device must be returned at the end of the trial.

Data from the cough recording, including source audio files, may be used by BI or the vendor for further analyses, including, but not limited to, device performance validation or development of further cough-related endpoints.

See Appendix [10.4](#) for additional information on the cough monitor device.

5.1.2 Forced vital capacity (spirometry)

Spirometry measurements will be performed onsite according to ATS/ERS 2019 guideline [[R20-2419](#)]. FVC will be assessed using standardised spirometry equipment which will be provided by BI/vendor centrally with supplies of precalibrated disposable flow sensors. These

sensors meet ISO 26782 standards, but with a maximum permissible accuracy error of $\pm 2.5\%$, in accordance with the ATS/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 participant in a seated position. It is preferable that the same trained individual performs the PFTs for a given participant. The best of 3 efforts will be defined as the highest FVC obtained on any of 3 blows meeting the 2019 ATS/ERS criteria (with a maximum of 8 attempts). Predicted normal values will be calculated according to GLI.

Efforts should be made to schedule the spirometry measurements at approximately the same time of day, at least within the same half-day (morning vs. afternoon), with reference to baseline measurement (Visit 2B). On days of trial visits, participants should be encouraged to refrain from vigorous activity within 1 h of pulmonary function testing. If treated with bronchodilators, washout according to Appendix [10.5 \(Table 13\)](#) 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 at Visits 1 to 5 are obtained after the review, the participant must be reassessed.

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

5.1.3 Diffusing capacity of the lungs for carbon monoxide

The site will use its own DLCO equipment and conduct all measurements. In the case that several devices are available at the site, it is recommended to have all measurements for an individual participant performed with the same DLCO equipment. 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 [SoA](#). Both acceptable DLCO measurements will be recorded. Manoeuvres will be demonstrated before beginning of the test, and the participant will be carefully instructed.

Predicted DLCO value will be corrected for Hb. The site has to enter the unadjusted predicted DLCO result without Hb correction in the eCRF. At Visit 1, the most recent Hb value (ideally on the same day or within 15 days) 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 in 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: $\text{DLCO predicted for Hb} = \text{DLCO predicted} \times [1.7 \text{ Hb} / (10.22 + \text{Hb})]$
- Females: $\text{DLCO predicted for Hb} = \text{DLCO predicted} \times [1.7 \text{ Hb} / (9.38 + \text{Hb})]$

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

$\text{Percent predicted DLCO corrected for Hb} = (\text{Mean value of two DLCO measurements, expressed in mmol/min/kPa} / \text{Predicted DLCO corrected for Hb}) \times 100$

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

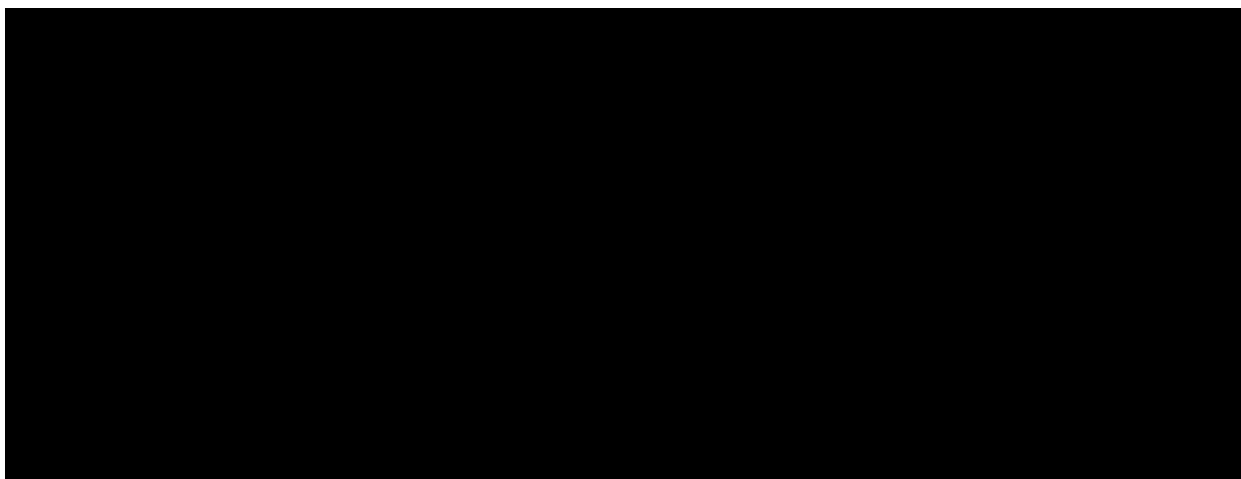
5.1.4 Clinical outcome assessments

The participant will complete PRO measures electronically, preferably according to the prespecified order defined in Section [6.2](#).

5.1.4.1 Cough Severity Numerical Rating Scale

The Cough Severity NRS is a single-item PRO measure to assess cough severity on a 11-point numerical rating scale ranging from 0 (no cough) to 10 (worst possible cough) with a recall period of the past 7 days. Higher scores indicate higher severity of cough.

The Cough Severity NRS (Appendix [10.6.1](#)) will be administered during the visits as specified in the [SoA](#). The Cough Severity NRS should take <1 min to complete.



5.1.4.4 Cough Severity Visual Analog Scale

The Cough Severity VAS is a PRO measure assessing cough severity. It is a single-item measure with a visual analogue scale as response option and a recall period ‘in the past week’. Participants will mark on the scale with a 100 mm line anywhere between the 2 ends corresponding to the overall severity of the cough in the past week, ranging from no cough to the worst possible cough. The Cough Severity VAS is scored according to the distance between no cough (0) and the mark set by the participant, higher distance indicating higher severity of cough.

The Cough Severity VAS (Appendix [10.6.4](#)) will be administered during the visits as specified in the [SoA](#). The Cough Severity VAS should take <1 min to complete.

5.1.4.6 Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire

L-PF is a 44-item PRO measure with 2 modules: Symptoms (23 items) and Impacts (21 items). The Symptom module assesses 3 domains: dyspnea (items 1-12), cough (items 13-18), and fatigue (items 19-23) in the past 24 h. The Impact questionnaire assesses impact related to dyspnea (items 1-6), cough (items 7-11), energy (items 13-14), and global (items 15-21) within the last week. Both modules have a 5-point Likert scale (numeric rating scale) with varying response options. For the Symptoms module a total Symptom score as well as Symptoms domain scores (dyspnoea, cough, and fatigue) are generated. 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 symptom module domain and total scores as well as the L-PF impact module total score ranges from 0-100, with higher scores indicating a greater impairment.

There are 5 additional questions pertaining to oxygen use at the end of the Symptoms module to serve interpretation of the L-PF scores.

The L-PF (Appendix [10.6.6](#)) will be administered during the visits as specified in the [SoA](#). The L-PF should take about approximately 10 min to complete.

5.1.4.7 Leicester Cough Questionnaire

LCQ is a 19-item PRO measure that assesses the impact of cough on various aspects of QoL. The LCQ is divided into 3 domains (physical, social and psychological). Each domain is scored with a 7-point Likert response scale (1 to 7). The total score is calculated using the sum of the means of each subdomain, and ranges from 3 to 21. A higher score indicates better cough specific QoL.

The LCQ (Appendix [10.6.7](#)) will be administered during the visits as specified in the [SoA](#). The LCQ should take approximately 5 min to complete.

5.1.4.8 eCOA handling

Administration of eCOAs will be handled according to guidance documents from regulatory authorities and international societies (e.g. ISPOR). Participants are to complete ePRO assessments on their own in a quiet area/room at the frequency specified in the [SoA](#), without being influenced by the investigator or other members of the trial team. ePROs should be completed in the order specified in Section [6.2](#). ePRO assessments are to be completed by the participant in the same language the participant provided written consent for the trial and without any help from or interpretation/translation by other people. If this is not possible, the ePRO assessments are not to be done.

Adequately trained and qualified site staff are to be available at any time for general questions and to support the participant, as well as to ensure ePRO completion compliance.

Whether the participant was able to complete the ePRO assessment him/herself will be documented.

ePROs will be completed electronically on the on the tablets supplied by the vendor. A web-based PROs will be available to collect data when the tablet is unavailable. ePRO data will be electronically transferred to the ePRO vendor database.

The data flow for eCOA is described in the Vendor Data Management Plan.

5.1.5 Activity measurement

IPF cohort

BI/vendor will provide the activity monitoring device (includes watch, charging station, and data hub).

The activity monitoring kit is given to participants at Visit 1 after it is confirmed that the participant meets eligibility criteria that can be assessed during the Visit 1. Participants will be

given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure and is not returning to the site.

Activity monitoring watch must be worn for at least 2 weeks:

- After Visit 1 through Visit 2B (between screening and randomisation visit) and continuing for 24 h after Visit 2B. For the first 24 h after Visit 1 and Visit 2B, both cough monitoring device and activity watch will be worn together
- After Visit 4 (Week 8). For the first 24 h after Visit 4, both cough monitoring and activity watch will be worn together

Activity monitoring watch must be worn at all times, including during sleep. Device may need to be recharged during the measurement period.

The device must be returned at the end of the trial.

PPF cohort

Activity monitoring will not be performed in the PPF cohort.

5.1.6 Composite outcome

This composite outcome consists of the occurrence of acute exacerbation, respiratory hospitalization, and/or death up to Week 12.

The most recent definition of acute IPF exacerbation will be used [[P16-06899](#)].

Such events 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 <1 month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
- 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 IPF exacerbation but fail to meet all diagnostic criteria above due to missing computed tomography data must be reported as ‘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.

Adjudication of acute exacerbations is not planned for this trial. Acute exacerbations will be reported as per the principal site investigator’s assessment.

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

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the [SoA](#). This examination includes, at a minimum, general appearance, neck, lungs, cardiovascular system, abdomen, neurological, extremities, and skin.

Measurement of height and body weight will be performed at the time points specified in the [SoA](#).

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the [SoA](#), prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 min) in a seated position after 5 min of rest. The results must be included in the source documents available at the site.

5.2.3 Pulse oximetry

Pulse oximetry will be evaluated at the time points specified in the [SoA](#), prior to blood sampling. The results must be included in the source documents available at the site.

5.2.4 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in [Table 5](#). Sampling time points are shown in the [SoA](#).

Trial participants do not have to fast for the blood sampling for safety laboratory tests. Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the laboratory manual in the ISF.

All analyses will be performed by a central laboratory, and the respective reference ranges will be provided 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 AEs (refer to Section [5.2.7.1](#)).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (see Section [5.2.7.1.4](#) and the DILI Checklist provided in the ISF. The amount of blood taken from the trial participant concerned will be increased due to this additional sampling. Tests to be performed at each visit will be defined in the Laboratory Manual.

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

Table 5 Safety laboratory tests

Functional laboratory group	Test name
Haematology	Haematocrit
	Haemoglobin
	RBC
	WBC
	Platelet count
	MCV
	MCH
	MCHC
	RDW
Automatic WBC differential (relative and absolute)	Neutrophils total
	Lymphocytes total
	Eosinophils
	Basophils
	Monocytes
	Lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils, eosinophils, basophils, monocytes, lymphocytes
Coagulation	aPTT
	PT
	INR
Enzymes	AST
	ALT
	AP
	GGT
	CK [CK-MB in cases of elevated CK]
	Lipase
	Amylase
Hormones	TSH
	Free T3
	Free T4

Table 5 (cont'd) Safety laboratory tests

Functional laboratory group	Test name
Substrates	Glucose Creatinine, enzymatic Urea nitrogen Uric acid Total bilirubin Direct bilirubin Total protein Albumin Globulin Albumin/globulin ratio Total cholesterol
Electrolytes	Calcium Sodium Potassium Chloride Phosphate
Serum pregnancy test (only for female participants of childbearing potential) at screening, and if urine pregnancy test is positive	Human serum chorionic gonadotropin
Urinalysis (qualitative determination)	Urine nitrite Urine protein Urine glucose Urine ketone Urine bilirubin Urine haemoglobin (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 participants of childbearing potential) ¹	Human chorionic gonadotropin in the urine

¹ Completed locally on-site using kits provided by central laboratory.

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

5.2.5 Electrocardiogram

The 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded at the timepoints shown in the [SoA](#) by a qualified technologist. ECGs will be recorded after subjects have rested for at least 5 min in a supine position. Triple ECGs will be recorded at all time points. Each ECG must be at least 10 s duration, and all 3 ECGs must be recorded within 180 s. ECGs may be repeated for quality reasons and the repeated recording used for analysis. If necessary, additional ECGs may be recorded for safety reasons.

The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. The digital ECG recordings will be transmitted to a vendor for central evaluation, and the results will be reported to the site. Decisions on eligibility for the trial or further treatment, if needed due to abnormal ECG, is at investigator's discretion. Clinically relevant abnormal findings will be reported either as baseline conditions (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the participant's medical file if there is no validated and certified e-medical record for ECG data.

5.2.6 Other safety parameters

Not applicable.

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of AEs

5.2.7.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a trial participant 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 unfavourable 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 on the appropriate eCRF(s) and Boehringer Ingelheim SAE form (if applicable):

- Worsening of the underlying disease (including acute IPF and PPF exacerbation) or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination findings, and/or laboratory test results, if 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.

5.2.7.1.2 Serious adverse event

An SAE is defined as any AE that fulfils at least 1 of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the participant 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 hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the participant and may require medical 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 hospitalisation 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.

5.2.7.1.3 AEs considered ‘Always Serious’

In accordance with the EMA 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 in Section [5.2.7.2.1](#). The latest list of ‘Always Serious AEs’ can be found in the Clinergize 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 [5.2.7.2](#).

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section [5.2.7.2](#), subsections ‘AE Collection’ and ‘AE reporting to sponsor and timelines’.

5.2.7.1.4 Adverse events of special interest

The term 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; see Section [5.2.7.2.2](#).

The following is considered as AESI:

Potential severe DILI

A potential severe DILI that requires follow up is defined by any of the following alerts (alterations) of hepatic laboratory parameters that occur after the first dose of IMP:

1. AST or ALT elevation $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ measured at the same visit, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation $\geq 3 \times \text{ULN}$ and INR $\geq 1.5 \times \text{ULN}$ measured at the same visit, or in samples drawn within 30 days of each other, OR
3. AST or ALT elevation $\geq 3 \times \text{ULN}$ with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$), OR
4. AST or ALT elevation $\geq 5 \times \text{ULN}$

These laboratory findings constitute a hepatic injury alert, and participants showing any of these laboratory abnormalities need to be followed up according to the DILI Checklist provided in the ISF.

In case of clinical signs or symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, 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.

Additionally, with participants having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥ 3 -fold and $< 5 \times \text{ULN}$ requires repeat testing within 72 h. DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4.

The following events should lead to immediate discontinuation of the IMP:

- Hepatic injury alert numbers 1, 2, or 3
- Hepatic injury alert number 4, if persists > 2 weeks
- AST or ALT elevation $> 8 \times \text{ULN}$

Following completion of the DILI Checklist, if the IMP cannot be excluded as a possible cause of the DILI event, discontinuation should be made permanent without rechallenge. If an alternate causality, e.g. acute viral hepatitis, is confirmed by the DILI Checklist evaluation, IMP may be re-started, if warranted.

5.2.7.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the CRF according to the CTCAE Version 5.0.

5.2.7.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the AE and the Boehringer Ingelheim IMP, 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 a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the IMP
- 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 IMP exposure
- Evidence that the event is reproducible when the IMP is reintroduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or comedications)
- 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 no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of IMP exposure is evident (e.g. pretreatment cases, diagnosis of cancer or chronic disease within days/weeks of IMP administration, an allergic reaction weeks after discontinuation of the IMP concerned)
- Continuation of the event despite the withdrawal of the IMP, 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 IMP concerned
- Disappearance of the event even though trial IMP treatment continues or remains unchanged

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 AE collection

The investigator shall maintain and keep detailed records of all AEs in the participant files.

Per default, SAEs/AESIs should be reported via the eCRF in the eDC system. If the eDC system is not or no longer available (e.g. after DBL), the Boehringer Ingelheim paper SAE form should be used; see Section [5.2.7.2.2](#). The following must be collected and documented:

- From signing the informed consent onwards until the individual participant's end of trial (usually the EoS Visit; please see Section [6.2.3](#)):
all AEs (serious and non-serious) and all AESIs
- After the individual participant's end of trial:
the investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer, IMP-related SAEs and IMP-related AESIs of which the investigator may become aware by any means of communication, e.g. phone call

5.2.7.2.2 AE reporting to the sponsor and timelines

The investigator must report immediately (within 24 h of becoming aware of the event): SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE eCRF pages triggering a data transfer to the safety database as applicable. The country-specific process will be described in the ISF. On specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

With receipt of any further information on these events, follow-up reports must be provided. For follow-up information, the same rules and timelines apply as for initial information. All AEs/SAEs, including those persisting after an individual participant'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 h, reporting must occur via the Boehringer Ingelheim paper SAE forms.

5.2.7.2.3 Pregnancy

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

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

The ISF will contain the Pregnancy Monitoring Form for Studies (Parts 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 Studies is to be completed. However, an SAE and/or AESI associated with the pregnancy must be reported as described in Section [5.2.7.2.2](#).

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood samples will be collected for the assessment of PK. The date and clock times of drug administration on the [REDACTED] before sample collection ([REDACTED] and, if applicable, nintedanib or pirfenidone) and PK sampling will be recorded in the eCRF. The actual sampling times will be used for determination of PK parameters. In addition, a population PK analysis will be performed, which will be reported separately.

5.3.2 Methods of sample collection

For quantification of BI 1839100 concentrations and for the determination of nintedanib or pirfenidone concentrations, if applicable, venous blood will be collected from a forearm vein in EDTA anticoagulant blood drawing tubes at the time points indicated in the [SoA](#) and Appendix [10.7](#), [Table 14](#). Plasma samples will be stored frozen at about -20°C and should be shipped on dry ice to the central laboratory preferable on the same day of collection. Details regarding the sample collection, sample handling, storage, and shipments are specified in the laboratory manual.

[REDACTED] will be generated by these additional investigations. The samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of BI 1839100 plasma concentration

BI 1839100 concentrations in plasma will be determined by a validated LC-MS/MS assay. All details of the analytical method will be available prior to the start of sample analysis.

The analysis will be performed at [REDACTED]

5.3.3.2 Analytical determination of nintedanib plasma concentration

Nintedanib concentrations in plasma will be determined by a validated LC-MS/MS assay. All details of the analytical method will be available prior to the start of sample analysis.

The analysis will be performed at [REDACTED]

5.3.3.3 Analytical determination of pirfenidone plasma concentration

Pirfenidone concentrations in plasma will be determined by a validated LC-MS/MS assay. All details of the analytical method will be available prior to the start of sample analysis.

The analysis will be performed at [REDACTED]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

5.4 ASSESSMENT OF BIOMARKER(S)

5.4.1 Exploratory biomarkers

Samples can be analysed in a staged approach, and decisions for further analysis may depend on the results of prior analyses. This may also imply that not all collected samples will be analysed, especially in case of termination of the project/trial.

The trial samples will be discarded after completion of any investigations, but not later than 2 years after the final trial report has been signed. Any leftover samples or derived material from prespecified analyses (e.g. RNA, DNA, and blood) may be used for method development/validation but will be destroyed no later than 2 years after the final trial report has been signed. Exceptions are remainders of trial samples for which a participant has voluntarily accepted a biobanking option and has provided a signed ICF (see Section [5.5](#)).

Detailed instructions on sampling, preparation, processing, and shipment of the samples are provided in the laboratory manual. For sampling timepoints, see the [SoA](#). Sampling timepoints and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK/PD data), including addition or reduction of samples and visits. Such changes would be implemented via non-substantial CTP amendments.

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 signed in accordance with local ethical and regulatory requirements. DNA samples will be taken preferably at Visit 2B or, if not possible, at any subsequent visit until EoT. Serum and plasma samples will be taken at Visit 2B (baseline), Visit 3 (Week 4) and Visit 5 (Week 12) (see [SoA](#)). Biobanking samples will not be taken in China and DNA samples will not be taken in Japan.

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 the [SoA](#).

Separate blood samples will be drawn for DNA (8.5 mL), plasma (10 mL), and serum (8.5 mL) banking purposes.

5.6 OTHER ASSESSMENTS

5.6.1 Chest high-resolution computed tomography

Screening chest HRCT will be used in all patients to determine trial eligibility.

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 UIP or probable UIP HRCT pattern (for detailed specifications see Appendix [10.1](#)) prior to randomisation. Confirmation of eligibility must be available prior to randomisation Visit 2B.

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 addition to central reading of the HRCT scans, there is the potential 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.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way. Therefore, the appropriateness of all measurements applied in this trial is a given.

Additionally, patients, patient advocacy groups, and health authorities were consulted during the development and design of this Phase II program (see Section [3.2](#)).

Information about race should be obtained from all trial participants as allowed by local regulations. It is necessary to collect these data to assess consistency of treatment effects across different patient populations.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstance (e.g. pandemic, war), the execution of the investigational plan as per this protocol may not be feasible. With the consent of the participant, 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-participant shipments of IMP, direct-from-participant shipments of IMP, or biological sample pick up from the participant's home. The implementation of these measures will depend on the participant's consent, operational feasibility, and local laws and regulations. Such alternative measures will be described in the participant information. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

The trial visit schedule is presented in the [SoA](#) for each cohort.

All participants have to adhere to the visit schedule as specified in the [SoA](#). Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Unscheduled visits will be possible at the discretion of the investigator at any time in order to check the safety of the trial participant or to perform safety laboratory assessments.

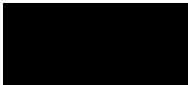
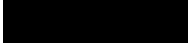
In the event of force majeure or other disrupting circumstance, physical visits to the sites may not be feasible for participants or may need to be restricted to ensure participant safety. Based on a thorough assessment of the benefits and risks by the PI, the participant may be contacted by phone. The phone call should include, at minimum, assessment of AEs and concomitant medications.

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

Trial procedures to be performed at each visit are listed in the [SoA](#). Additional details regarding visit procedures are provided below.

Only the trial procedures listed below must follow the specific order during the visit:

- Self-administration of PRO measures should precede other trial procedures. PRO measures should be completed in the following order:
 1. Cough Severity NRS
 2. 
 3. 
 4. Cough Severity VAS

5. [REDACTED]
 6. L-PF
 7. LCQ
- Measurements of vital signs should precede blood sampling
 - Drug should be administered after blood sampling

Spirometry measurements have to be performed at approximately same time of day at each visit, at least within the same half-day (morning vs. afternoon; reference time determined at Visit 2B). If treated with bronchodilators or inhaled corticosteroids, drug washout should occur before spirometry (see Appendix [10.5](#), [Table 13](#)).

Additional specifics regarding performing trial procedures can be found in Section [5](#).

6.2.1 Screening period(s)

6.2.1.1 Visit 1

Visit 1 procedures may be extended to more than one physical visit, if needed. Screening period may be extended to 6 weeks with approval from the sponsor.

Informed consent for trial participation

All participants must sign an Informed Consent consistent with ICH-GCP guidelines prior to any trial specific procedures. Please refer to Section [8.1](#) for details.

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

Demographics

During the screening visit, demographics information will be collected. This includes:

- Age (in years) on the day of informed consent
- Sex (male or female, in order to describe the trial participant's sex at birth)
- Gender identity (male, female, non-binary, not answered, or other in order to describe how the trial participant self-identifies, regardless of their genotypic or phenotypic sex) if 1) locally accepted (i.e. based on HA/EC/IRB acceptance, independent of acceptance by investigators or participants), 2) investigators are willing to ask, and 3) participants are willing to reply
- For women of 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, and to support the calculation of the kidney function via the CKD-EPI formula unless not acceptable according to local regulations

- Primary language spoken by the participant will be collected. This may be used for validation of the cough monitoring device algorithms

Medical history

In order to collect previous medical reports to keep records of exact dates/diagnoses of relevant medical history or prior medication, up to 3 attempts at different days should be made and documented.

Chest HRCT

If no historical HRCT is available, an HRCT may be performed after consent to determine eligibility.

IRT

All patients who are screened must be registered with IRT. If the screening results in a screen failure, patient must be recorded as screen failure in IRT as soon as possible and within the 4-week screening period. Details of IRT procedures can be found in the IRT Manual filed in the ISF.

24-h cough monitoring

The trial participants are provided with the device and appropriate training at Visit 1 after it was confirmed that participant meets eligibility criteria that can be assessed during the Visit 1. Device will be attached to the participant's chest and recording will be started. Trial participants should be reminded to remove the device after at least 24 h and initiate data transfer through the app. If issues with data transfer occur, the data can be collected from the cough monitor device at the end of the trial. Trial participants will be given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure and is not returning to the site.

Baseline 24 h CC is defined as the measurement from Visit 2A. If the baseline CC is missing, the screening CC measurement (Visit 1; see Section [6.2.1.2](#)) will be used as the baseline value instead.

Activity monitoring (IPF cohort only)

The trial participants are provided with the device and appropriate training at Visit 1 after it was confirmed that participant meets eligibility criteria that can be assessed during the Visit 1. The trial participant will begin wearing the activity monitor before leaving the site. Trial participants will be given shipping supplies to ship the device back to site if the participant is later determined to be a screen failure and is not returning to the site.

Retesting

Screening evaluations may be repeated once during the screening period.

Rescreening

Rescreening of patients may be done only once based on investigator judgement and prior permission from the sponsor. Patient who are re-screened need to be re-consented and will be given a new patient number. All the trial procedures for screening (Visit 1) must be repeated.

6.2.1.2 Visit 2A

Visit 2A should be performed after it is confirmed that the participant meets eligibility criteria. Visit 2A can be performed at the clinic or by the participant at home, at the discretion of the investigator.

If performed in the clinic, the 24-h cough monitoring device will be attached to the participant's chest and recording will be started. If performed at home, the site should call the participant and guide the participant through the steps of attaching the device and starting the recording.

Trial participants should be reminded to remove the device after at least 24 h and initiate data transfer through the app. The cough count recording should be completed prior to the start of Visit 2B.

6.2.2 Treatment period(s)

General

After all the screening procedures have been completed and eligibility of screened participants is confirmed, Visit 2B can be conducted including randomisation via IRT. Randomisation in the IRT system should not be performed in advance of Visit 2B until eligibility is fully confirmed, as randomisation of a patient cannot be reversed.

Sites should contact participants prior to the next scheduled visit to confirm the next visit and remind participants to:

- Bring unused IMP and empty blisters
- Record the time and date for administration of IMP and, if applicable, nintedanib or pirfenidone, for [REDACTED] prior to the visit
- Charge the cough monitoring device overnight prior to the visit and bring it to the visit
- For Visit 4 (IPF cohort only), charge the activity monitoring device overnight prior to the visit and bring it to the visit

If the cough monitoring device and activity monitoring device are not fully charged, the recording cannot be started.

Pharmacokinetic blood sampling

The PK blood sampling times are given in Appendix [10.7](#). The actual date/time of drug administration and blood samplings must be recorded in the eCRF.

Visit 2B (Randomisation)

At the start of Visit 2B, it should be ensured that all Visit 1 procedures have been successfully completed and eligibility has been confirmed. Reconfirmation of Cough Severity VAS ≥ 30 mm is required at Visit 2B for trial eligibility.

Randomisation should not be performed in the case of a positive pregnancy test.

Upon randomisation via the IRT, medication kit will be dispensed. The first dose should be taken at the clinic after all Visit 2B assessments are completed.

Samples for optional plasma/serum and DNA biobanking will be collected if Informed Consent is provided. A sample for DNA biobanking is preferentially collected at Visit 2B but can be collected at another time point thereafter.

Visit 3 and Visit 4 (IPF cohort only)

Trial participants should not take trial medication before coming to the clinic. This is because participants will be dosed at the clinic.

Trial participants should be instructed to bring all trial medication (used and unused kits/packaging including blisters) with them to these clinic visits.

24-h cough monitoring device will be attached to the trial participant at the end of each visit and recording will be started. When the participant is contacted to schedule subsequent visit, the trial participant should be reminded to charge the device overnight prior to the visits. If device is not charged, recording cannot be started during the visit.

Activity monitoring will be started at the end of the Visit 4. When the trial participant is contacted to schedule the Visit 4, the participant should be reminded to charge the activity monitor overnight prior to the visit. If device is not charged, recording cannot be started during the visit.

EoT Visit

EoT visit represents the end of the treatment period. Last IMP administration will be on the day before EoT visit.

For trial participants in the IPF cohort, the EoT visit is Visit 5 (Week 12). The overall duration of the treatment period (Randomisation to EoT) should not be less than 84 days; therefore, the EoT visit is scheduled at Day 85 with a visit window of up to +3 days. For trial participants in the PPF cohort, the EoT visit is Visit 3 (Week 4). The overall duration of the treatment period (Randomisation to EoT) should not be less than 28 days; therefore, the EoT visit is scheduled at Day 29 with a visit window of up to +3 days.

6.2.3 Follow-up period and trial completion

A trial participant is considered to have completed the trial if one of the following applies:

- Completion of planned follow-up period (i.e. EoS Visit completed)
- Lost to follow-up
- Refusal to be followed-up/consent withdrawal
- Death

If needed, in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

Abnormal assessments or laboratory values judged clinically relevant by the investigator will be monitored until they return to a medically acceptable level.

EoS Visit is the final scheduled trial visit.

If it is not possible for the trial participant to attend a Follow-up Visit at the trial site as scheduled, a visit outside of the visit window should be performed as soon as possible, for safety reasons.

In case of early IMP discontinuation, the trial participant should be encouraged to continue participating in the trial, by emphasising the importance of continuing trial participation and the value of collecting data for all randomised participants. Options to be discussed with the participant are presented in [Table 6](#). After early discontinuation, PK sample collection and activity measurements will not be conducted during trial visits. Teleconference visits should assess at a minimum, AEs and concomitant therapy.

Participants prematurely discontinuing trial drug

If the IMP needs to be permanently stopped for any reason prior to the scheduled EoT visit, the EoT visit will be completed instead of the planned treatment period visit as soon as possible after trial drug discontinuation. See below for further details regarding trial participant follow up after premature treatment discontinuation.

Table 6 Follow up of trial participants who prematurely discontinue the trial treatment

Option 1	Continue to attend regularly scheduled trial visits as per the SoA
<i>In case trial participant does not agree to option 1, then present</i>	Attend only planned EoT visit in clinic. For participants in the IPF cohort, this is Week 12 visit, and in this case, this will be called Visit 5 instead of EoT visit. For participants in the PPF cohort, this is Week 4 visit, and in this case, this will be called Visit 3 instead of EoT visit. Other visits can be replaced by teleconference visits.
Option 2	
<i>In case trial participant does not agree to option 2, then present</i>	Follow-up Visit in clinic must be performed for safety reasons.
Option 3	

When discussing the options for continued trial participation, investigators must present the first option outlined in [Table 6](#) to the trial participant and discuss this option thoroughly before presenting the next option for follow up. Trial participants should be encouraged to choose the

most rigorous follow-up schedule with which they are willing and able to comply. The investigators should inform these trial participants that they will be allowed to change this schedule later if needed. A retention guide will be provided in the ISF to assist investigators in discussing these options with the trial participant.

If the trial participant refuses any further follow up after treatment discontinuation, this will be considered as “withdrawal of consent” by the participant and must be recorded as such in the CRFs.

After completing the trial, participants can continue treatment according to the local standard of care.

Trial participants may choose to re-start the IMP at any time during their planned treatment period as long as there is no safety concern, in the opinion of the investigator. 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This trial combines PoCP (Phase IIa) and dose ranging (Phase IIb) in a seamless design to establish whether or not there is a relationship between dose of BI 1839100 and change from baseline in 24-h cough frequency in patients with IPF. An interim analysis (IA) will be conducted once Phase IIa is completed as described in Section [3.1](#) to determine whether the trial will continue or will be stopped. This IA will be considered the primary analysis for the Phase IIa part of the trial.

The primary efficacy analysis of the Phase IIb part will be based on all trial participants in the Full Analysis Set (FAS), including the trial participants randomised in the Phase IIa part. Safety analyses are based on the Treated Set (TS). Refer to Section [7.2.1.2](#) for definitions of trial participant analysis sets.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Phase IIa:

The primary endpoint is the change from baseline in 24-h cough frequency at Week 4.

In Phase IIa, no confirmatory hypothesis testing will be performed and hence no null and alternative hypotheses are defined. A justification of the sample size for this part of the trial is provided in Section [7.5](#).

Phase IIb part:

The primary endpoint is the change from baseline in 24-h cough frequency at Week 12.

The primary objective is to demonstrate there is a non-flat dose response curve based on the primary endpoint after 12 weeks of treatment in trial participants with IPF using 3 doses of BI 1839100 and a placebo control. For this purpose, the primary analysis will apply methodology for dose finding that employ both multiple comparison procedures and modelling techniques (MCP-Mod) [[R10-1424](#), [R15-4293](#)].

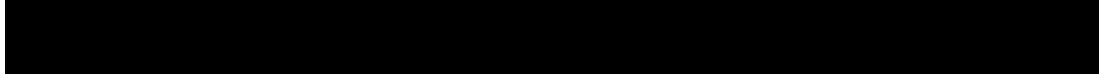
The null and alternative hypotheses are described below. Statistical testing will be performed based on 1-sided hypotheses with corresponding 1-sided p-values. Note that for publication purposes 2-sided p-values may also be derived if needed.

Null hypothesis: There is a flat dose response curve comparing the placebo and the BI 1839100 dose groups in trial participants with IPF.

Alternative hypothesis: There is a non-flat dose response curve indicating a benefit of BI 1839100 over placebo in trial participants with IPF.

The MCP-Mod approach allows for simultaneous evaluation of different potential dose-response curves whilst protecting the overall probability of Type I error. The pre-specified models and their parameters used for this test are outlined in Section [7.2.3](#).

A non-flat dose is established if at least 1 dose-response model curves is statistically significant at the 1-sided α of 0.05, rejecting the null hypothesis of a flat dose response curve indicating a benefit of BI 1839100 over placebo.



7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis overview

This trial combines PoCP (Phase IIa) and dose ranging (Phase IIb) in a seamless design.

Once the Phase IIa part is completed as outlined in Section [3.1](#), an analysis of the Phase IIa data will be performed to assess whether there is a meaningful reduction from baseline in 24-h cough frequency between the highest dose group of BI 1839100 compared with placebo after 4 weeks of treatment in trial participants with IPF. If a meaningful reduction is observed, the trial will continue, otherwise the trial will be stopped.

If the trial continues after demonstrating an early indication of efficacy based on reducing cough frequency in the Phase IIa part of the trial, all dose arms will continue enrolment into the Phase IIb portion of the trial. Once all trial participants complete 12 weeks of treatment and assessments, the final analysis will be done to establish whether or not there is a non-flat dose-response relationship between BI 1839100 and change in 24-h cough frequency after 12 weeks of treatment in participants with IPF.

In addition to the statistical analyses described below, descriptive summaries over time will be tabulated and standard descriptive statistics will be presented by visit for efficacy and safety data. The details below describe the analyses planned to address objectives for the Phase IIa and IIb parts of the trial in IPF patients. Similar analyses will be produced for the  PPF cohort. Further details will be included in the TSAP.

7.2.1.2 Analysis set definitions

The following analysis sets are defined for this trial:

- Randomised Set (RS): includes all participants who signed informed consent and were randomised into the trial, regardless of whether a participant was treated with trial medication. The RS will be used for the analyses of participant disposition

- Full Analysis Set (FAS): includes all randomised participants who received at least 1 dose of trial medication. The FAS will be used for baseline demographics and characteristics, protocol deviations, and all efficacy analyses, in which participants will be analysed as according to the treatment group to which they were randomised (i.e. planned treatment). This analysis set is meant to adhere closely to the intention-to-treat principal
- Treated Set (TS): includes all randomised participants who received at least 1 dose of study treatment. The TS will be used for all safety analyses, in which participants will be analysed according to the actual dose they received (e.g. according to actual treatment). Handling of cases where study treatment was incorrectly assigned or taken will be described in the TSAP

Other analysis sets, for example a Per Protocol Set (PPS), may be defined in the TSAP.

7.2.2 Handling of intercurrent events

The expected intercurrent events of interest in this trial are:

- Change in background AF therapy or AF dosage after randomisation
- Change in other background medication for cough after randomisation
- Start of a restricted medication other than background AF therapy or used as background medication for cough (see Section [4.2.2.1](#))
- Continuous treatment interruption ≥ 7 days or treatment discontinuation

The primary strategy for primary and secondary endpoints will handle intercurrent events using treatment policy approach.

Treatment policy: Estimating the effect of randomising trial participants to a treatment arm regardless of treatment actually being taken. For this, all intercurrent events will be handled according to the ‘treatment policy’ approach which uses the value of the endpoint(s) regardless of the occurrence of the intercurrent event.

The secondary strategy for primary and secondary endpoints will handle intercurrent events using the hypothetical approach.

Hypothetical approach: Estimating the effect of taking the randomised treatment as directed for the duration of the trial. In this approach, intercurrent events, except start of restricted medication, will be handled according to the ‘hypothetical approach’ where data collected after the occurrence of an intercurrent event will be considered missing. The intercurrent event of start of restricted medications will be handled according to the treatment policy approach.

Other intercurrent events and/or strategies will be decided based on blinded review and will be documented in the TSAP.

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.

7.2.3 Primary objective analyses

7.2.3.1 Main analyses

Phase IIa:

The primary endpoint is the change from baseline in 24-h cough frequency at Week 4, with baseline being defined as the closest measurement prior to randomisation. Due to the expected skewed distribution of the data, the raw CC over 24 h will be standardised to CC per hour, and then log-transformed (natural log). The resulting distribution of the log transformed data is expected to be approximately normal. All statistical analyses will be based on the log-transformed CC/h. However, to ease the interpretation of the clinical effect, the results will be displayed using values back-transformed to the original scale and presented as geometric means and geometric mean ratios (representing the proportional differences in change from baseline between treatment groups).

The primary analysis will be a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline of the log transformed values for CC/h after 4 weeks of treatment.

The analysis will include the fixed categorical effects of treatment at each visit, background AF treatment (Yes, No), and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-participant measurements. All data collected up to the time of the Phase IIa data cut will be included in the analysis.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The primary treatment comparison will be the contrast between the highest dose and placebo at the endpoint visit.

The estimated mean change from baseline (in log scale) with the associated standard errors will be presented for each treatment group along with the estimated treatment differences (each BI 1839100 dose group - placebo) and corresponding 95% confidence intervals (CIs). In addition, the geometric means of the 24-h CC/h will be presented by treatment group and by visit. The geometric mean ratios representing the proportional (i.e. percent) difference between the change from baseline in CC/h in the BI 1839100 groups compared with that of placebo and 95% CIs will be presented similarly. The percent difference in the change from baseline between each BI 1839100 treatment group and placebo will be estimated by $100 \cdot (e^{\text{diff}} - 1)$, where diff is the difference provided by the analysis of the log transformed variable.

Phase IIb:

The primary trial objective includes demonstration of PoC with respect to a non-flat dose-response curve and characterization of the dose-response relationship within the therapeutic range of BI 1839100, and selection of the dose range for Phase III development. For this purpose, the primary analysis uses methodology for dose finding employing MCP-Mod [R10-1424], whereby several possible dose-response models (patterns) will be evaluated, while keeping full control of the Type I error at 5.0%, 1-sided, to identify the best-fitting model or subset of models. As described for Phase IIa, the standardised CC per hour will log-transformed (natural log) for analysis so that the resulting distribution of the log transformed data is expected to be approximately normal. All statistical analyses will be based on the log-transformed CC/h and, for interpretation, the results will be displayed using values back-transformed to the original scale and presented as geometric means and geometric mean ratios (representing the proportional differences in change from baseline between treatment groups).

To account for the repeated nature of the data and the covariates in the model, MMRM analysis as described above for Phase IIa will be carried out for the 12-week endpoint. The covariate adjusted fixed effect estimates of average response for each dose group and the covariance matrix will be extracted from the fit and used for MCP-Mod analysis.

For the PoC testing and for the sample size calculation, the basic shape of each of the models to be tested must be pre-defined. The following model shapes have been selected as the candidate set of possible dose-response patterns based on current expectation of the dose-response shape and assuming that the following dose groups will be tested: placebo, [REDACTED]

[REDACTED] The following model assumptions have been selected to cover both a plausible and diverse range of dose-response patterns:

- Linear: no assumptions needed
- Emax 1: 40% of the maximum effect is achieved at [REDACTED]
- Emax 2: 80% of the maximum effect is achieved at [REDACTED]
- Exponential: 1% of the maximum effect is achieved at [REDACTED]
- Logistic: 5% of the maximum effect is achieved at [REDACTED] and 80% of the maximum effect is achieved at [REDACTED]

[REDACTED] (Figure 2). [REDACTED]

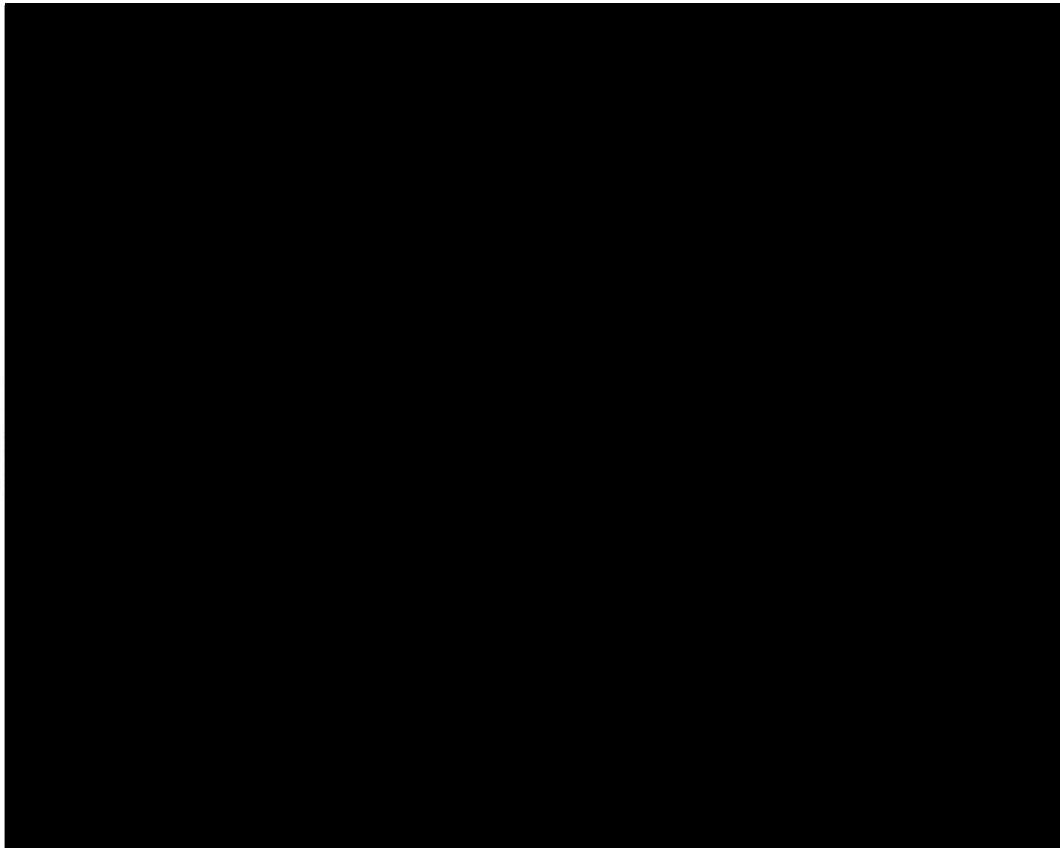


Figure 2

PoC is established if at least 1 model is statistically significant, rejecting the null hypothesis of a flat dose-response relationship over the log transformed CC/h, jointly for each of the candidate dose-response models with a contrast test controlled for the family-wise type I error rate at 1-sided $\alpha = 0.05$.

If PoC is established, the statistically significant (best fitting) model(s) from the candidate set will be refitted to the data to generate new estimates for all model parameters from the data. The target dose(s) can then be estimated from each significant model by incorporating information on the minimum clinically relevant effect and accounting for safety.

Once a non-flat dosing-response has been established in participants with IPF, then subsequently, the secondary objectives in participants with IPF and further objectives in participants with PPF will be evaluated based on primary and secondary endpoints by comparing the change of CC/h and FVC decline (in mL) from baseline after 12 weeks of treatment between BI 1839100 and placebo groups.

The primary analyses for both the Phase IIa and IIb parts of the trial will be performed using the FAS. Trial participants will be analysed 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 randomisation and is therefore consistent with regulatory guidance.

In the primary analysis, intercurrent events are handled with the treatment policy approach as described in Section [7.2.2](#).

7.2.3.2 Sensitivity analyses

For each study part, further sensitivity analyses may be performed using an alternative analysis set, i.e. the PPS, as well based on alternative approaches for the handling of missing data.

For Phase IIb, MCP-Mod may be repeated on the primary endpoint but with an extended set of shapes, including the original candidates, as well as additional shapes.

Details on sensitivity analyses will be included in the TSAP.

7.2.3.3 Subgroup analyses

The subgroups of interest include (but are not limited to):

- Background AF treatment (stratification factor)
- Demographic characteristics (such as age, sex)
- Geographical region
- GERD requiring proton pump inhibitors or histamine type-2 receptor blockers

The main purpose of these subgroup analyses is to check for the consistency of results across subgroups rather than to make inferences within a particular subgroup; therefore, only descriptive approaches will be used. Further subgroups of interest will be defined in the TSAP.

7.2.3.4 Supplementary analyses

Supplementary analyses will be performed using the same statistical model(s) described in Section [7.2.3.1](#) but using the hypothetical approach to handle ICEs as specified in Section [7.2.2](#).

Details on supplementary analyses will be described in the TSAP.

7.2.4 Secondary objective analyses

Phase IIa:

The secondary objectives for Phase IIa are to evaluate the efficacy by comparing the change from baseline in Cough Severity NRS score and Cough Severity VAS after 4 weeks of treatment between the BI 1839100 highest dose group and the placebo group.

The secondary endpoints will be analysed according to the same analysis method as the primary endpoint using REML-MMRM.

Phase IIb:

Secondary objectives:

- To evaluate the efficacy by assessing cough responder status, defined as a $\geq 30\%$ 24-h cough frequency reduction (CC/h) from baseline after 12 weeks of treatment between BI 1839100 dose groups and the placebo group
- To evaluate the efficacy by comparing the absolute change from baseline in FVC (mL) after 12 weeks of treatment between BI 1839100 dose groups and the placebo group (using the difference in mean FVC [mL] decline)
- To evaluate the efficacy by comparing the change from baseline in Cough Severity NRS, Cough Severity VAS, LCQ physical domain, and L-PF cough symptom domain after 12 weeks of treatment between BI 1839100 dose groups and the placebo group

For both Phase IIa and IIb, the primary treatment comparisons will be made for randomised participants and based on the planned treatment assignments.

The same MMRM analysis as used for the primary endpoint will be applied for FVC decline from baseline and other continuous secondary endpoints. The binary secondary endpoint, i.e. cough responder status, defined as a $\geq 30\%$ 24-h cough frequency reduction (CC/h) from baseline at Week 12, will be summarized descriptively via frequency tables or logistic regression model with AF group, randomised treatment, and baseline CC/h (log transformed) as independent variables. The analysis will be conducted separately for trial participants with IPF and PPF.

Additional details regarding the analysis of secondary objectives and endpoints will be included in the TSAP.

7.2.5 Further objective analyses

In general, further objective analyses will be descriptive in nature based on observed data without imputation however in cases where statistical modelling will be performed, the same modelling approaches described in the analysis of the secondary objectives will be utilized.

Complete details of further objective analyses will be described in the TSAP.

7.2.6 Safety analyses

AEs will be coded using the MedDRA. Standard Boehringer Ingelheim summary tables and listings will be produced. All AEs with an onset between start of treatment and [REDACTED] (see Section [1.2](#)), will be assigned to the on-treatment period for evaluation.

All treated trial participants will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on Boehringer Ingelheim standards. No hypothesis testing is planned. The TS will be used all safety analyses.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between the start of treatment and the end of the REP. AEs that start before first IMP intake and deteriorate under treatment will also be considered ‘treatment-emergent’.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA at database lock.

Laboratory data will be analysed 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 trial participants 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 with findings before the start of treatment.

7.2.7 Other analyses

Population PK modelling will be conducted to estimate PK parameters of interest.

In addition, the relationship between BI 1839100 plasma exposure and response (e.g. clinical outcome, biomarkers, AEs, and/or other clinical safety parameters) may be explored.

PopPK and potential PK/PD analyses will be described and reported separately outside the CTR.

7.2.8 Interim analyses

The primary analysis for Phase IIa will be conducted after approximately 25 IPF participants each in the placebo and BI 1839100 [REDACTED] groups complete 4 weeks of treatment. To ensure the integrity in the collection, handling, and evaluation of the interim data, the trial team, trial participants, and investigators will remain blinded. The analysis will be performed by an unblinded team independent of the trial team, and an independent internal DDC will review the results and provide a recommendation regarding trial continuation (see Section [8.7.4](#)). No multiplicity adjustment is considered for this IA given the [REDACTED]

In the case that the IPF cohort completes the trial before the PPF cohort, the primary analysis for Phase IIb in the IPF cohort will be conducted once all participants in the IPF cohort have either completed 12 weeks of treatment or discontinued. At this timepoint, only the participants in the IPF cohort will be unblinded in the trial database and the analysis will be performed by trial and project team; the data for PPF cohort will remain blinded.

To ensure participant’s safety during the trial, a fully external DMC, independent of the trial and project teams, will review periodically all available safety data. A DMC SAP which describes

the analyses required for assessment by the DMC will be produced. Further details will be provided in a DMC charter.

Additionally, preliminary PK analysis may be performed prior to the database lock to allow early assessment of pharmacokinetics. The results would be reviewed to facilitate future project planning. See Section [4.1.5.1](#) for details.

In addition to the planned IA described above, an administrative IA may be performed for unforeseen blinded trial results or external results that put into question critical trial design assumptions. Examples may include unresolvable recruitment problems, unexpected patterns of blinded efficacy or safety data, upcoming urgent drug development decision needs, or results from other trials leading to concerns about the benefit-risk of treatment groups or the trial.

The decision to conduct such an administrative IA will be documented in the decision log and accompanied by a Data Logistics Plan and Results Access Plan according to sponsor SOPs, together with details about how to protect the scientific credibility of the trial. Whether and how results of such an administrative IA will be used for a subsequent trial adaptation will be stated, which is to be planned in a protocol amendment.

7.3 HANDLING OF MISSING DATA

In the primary analysis of primary and continuous secondary 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’. This means participants with missing data would have behaved similarly to participants with observed data. Sensitivity analyses for handling of missing primary and continuous secondary endpoints data will be specified in the TSAP.

In the primary analysis of binary secondary endpoints, a non-response imputation (NRI) approach will be applied, i.e. imputing as failures.

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

Other methods for handling of missing data for further endpoints as well as for sensitivity analysis will be described in the TSAP.

Handling of missing PK data will be performed according to the relevant Corporate Procedure.

7.4 RANDOMISATION

Boehringer Ingelheim will arrange for the randomisation and the packaging and labelling of trial IMP. The randomisation 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. Specific parameters used for the creation of the randomisation schedule (e.g.

block size or biasing coin probabilities) will be documented in the CTR. Access to the codes will be controlled and documented.

Randomisation will be stratified based on the use of AF medication at baseline, Yes/No as described in Section [3.1](#). Within each stratum, the participants will be randomised in a 2:1:1:2 ratio to receive either placebo, BI 1839100 [REDACTED] respectively. The randomisation will be done in blocks to achieve balanced allocation. The process of randomisation is done via an IRT.

The [REDACTED] PPF cohort will be randomised in a 1:1 ratio to either BI 1839100 [REDACTED] or placebo. Randomisation of participants in this cohort will also be stratified by the use of AF medication at baseline.

Further details of the treatment allocation process are detailed in Section [4.1.3](#).

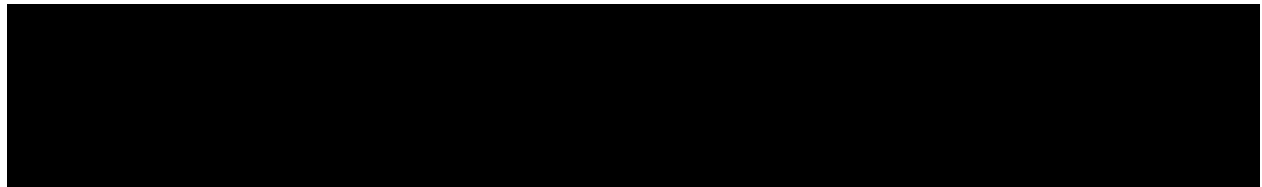
7.5 DETERMINATION OF SAMPLE SIZE

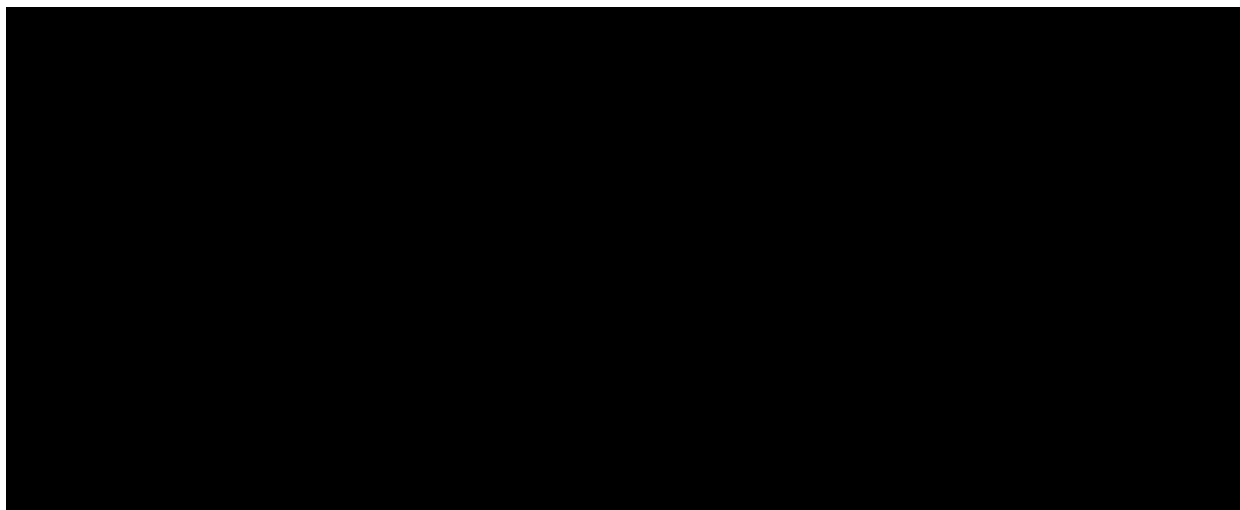
IPF cohort

Phase IIa

The PoCP success criteria will be assessed in the end of Phase IIa, based on the reduction from baseline of 24-h cough frequency (CC/h) at Week 4 comparing participants in BI 1839100 [REDACTED] group with participants in placebo group.

With $n = 25$ /arm at randomisation, assuming a 20% drop-out rate, effective sample size for analysis is $n = 20$ /treatment group. The standard deviation for CC is assumed to be 0.8 on the natural log scale.





Phase IIb

The MCP-Mod method combining multiple comparison procedures principles with modelling techniques will be used for the primary analysis of the primary efficacy endpoint.

The model shapes that have been selected as the candidate set of possible dose-response patterns based on current expectation are described in Section [7.2.3.1](#). The assumed contrast coefficients for each model and dose are within [Table 8](#).

Table 8 Contrast coefficients for the candidate dose-response curves used for sample size evaluation

	Contrast coefficients for different dose groups			
	0			
Model				
Linear	-0.577	-0.367	0.262	0.681
E _{max} 1	-0.655	-0.296	0.350	0.601
E _{max} 2	-0.794	-0.058	0.384	0.468
Logistic	-0.516	-0.472	0.387	0.601
Exponential model	-0.366	-0.354	-0.130	0.851

The sample size evaluation for the trial is based on the following criteria for success of the trial:

- Statistically significant result in multiple comparison test (MCT-step of MCP-Mod) indicating a non-flat dose response curve
- AND
- At least 1 dose regimen showing a treatment benefit of at least 'delta' compared with placebo in CC reduction from baseline and FVC decline from baseline at Week 12

For the second criteria, the joint distribution of reductions at Week 12 for CC/h with a standard deviation of 0.8 (natural log scale) and FVC decline from baseline with a standard deviation of 200 mL and a correlation coefficient of 0.5 between the 2 variables was assumed. Based on the

assumptions described above for candidate dose-response curves and the joint distribution of the reductions in CC/h and FVC (mL), operating characteristics and probabilities of success were calculated for the total sample size of 180 participants with allocation of 60:30:30:60 to placebo, [REDACTED] respectively, and assuming a drop-out rate of 20% resulting in an effective sample size is 48:24:24:48. These are summarized below in [Table 9](#).

Table 9 Operating characteristics given a total sample size of 180 participants based on MCP-Mod nominal alpha-level of 5% (1-sided) and assessment of quantitative treatment effect size

Scenario	Assumed maximum treatment difference	Assumed effect sizes adjusted for placebo effect for 4-arm [REDACTED]	Power ¹	Success criteria	Probability of success ²
Positive scenario	50% in CC and 50 mL in FVC	CC: (0, 0.064, 0.554, 0.693) FVC: (0, 10, 35, 50)	90.71%	CC reduction $\geq 30\%$ and FVC decline ≥ 20 mL CC reduction $\geq 20\%$ and FVC decline ≥ 30 mL	[REDACTED]
Intermediate	40% in CC and 30 mL in FVC	CC: (0, 0.051, 0.409, 0.511) FVC: (0, 8, 21, 30)	71.68%	CC reduction $\geq 30\%$ and FVC decline ≥ 20 mL CC reduction $\geq 20\%$ and FVC decline ≥ 30 mL	
Non-viable	10% in CC and 10 mL in FVC	CC: (0, 0.011, 0.08, 0.105) FVC: (0, 1, 7, 10)	5.60%	CC reduction $\geq 30\%$ and FVC decline ≥ 20 mL CC reduction $\geq 20\%$ and FVC decline ≥ 30 mL	
Negative (No effect)	0 in CC and 0 in FVC	Cough count: (0, 0, 0, 0) FVC: (0, 0, 0, 0)	1.24%	CC reduction $\geq 30\%$ and FVC decline ≥ 20 mL CC reduction $\geq 20\%$ and FVC decline ≥ 30 mL	

¹ Power: probability that PoCP is achieved and the best dosing-response contrast is significant at 1-sided alpha of 0.05.

² Success probability: Probability for the defined success criteria of (1) Significant non-flat dosing-response achieved based on at least 1 of the candidate set models AND (2) the observed treatment benefit of at least 'delta' compared with placebo for at least 1 dosing group within the considered dosing range. Power and success probabilities were calculated based on simulated data assuming dose-response relationships according to the 3 candidate models; the results were then averaged across models. All calculations were done using R Version 4.1.2 based on simulations (10000 simulations per scenario). The calculations for the MCP-Mod step were performed using Dose Finding R-package 1.0.2 [[R15-2001](#)].

Under the positive scenario of a maximum effect of both placebo-corrected 50% CC reduction (i.e. corresponding to a difference of -0.693 on the log scale) and 50 mL placebo-corrected FVC decline from baseline, a total sample size of 180 (with randomisation ratio of 2:1:1:2, and taking

into account a potential drop-out rate of 20%) provides a 81.4% probability of success (CC reduction $\geq 30\%$ and FVC decline ≥ 20 mL).

In contrast, in the negative scenario of 0% CC reduction over placebo (i.e. 0 of the ratio on the log scale) and 0 mL FVC decline from baseline over placebo, a total sample size of 180 (with randomisation ratio of 2:1:1:2 [60:30:30:60]), and also already taking into account a potential drop-out rate of 20%) controls the probability of making an incorrect decision to proceed (false Go) $\leq 1.1\%$.

PPF cohort

The sample size of 50 participants for PPF cohort is determined from a feasibility perspective.

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 GCP, relevant Boehringer Ingelheim SOPs, 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 will be treated as ‘protocol deviation’.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the treating physician of the trial participant.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial participants 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 finalisation of the clinical trial report.

The certificate of insurance cover is made available to the investigator and the trial participants 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 IRB/IEC and competent authority according to national and international regulations. The same applies for the implementation of changes introduced by substantial amendments.

Prior to participation in the trial, written informed consent must be obtained from each participant according to ICH GCP and the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent form and any additional participant-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional participant information must be given to each participant.

The investigator or delegate must give a full explanation to trial participants based on the participant information form. A language understandable to the trial participant should be chosen, technical terms and expressions avoided, if possible.

The trial participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the trial participant's own free will with the informed consent form after confirming that the trial participant understands the contents. The investigator or 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 be 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 participant 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, 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 designee, IRB/IEC, or 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 trial participants 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

A detailed description of the transmission of electronic data (i.e. data flow) is provided in the Data Management Plan.

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 participant. Source data as well as reported data

should follow the ‘ALCOA principles’ and be attributable, legible, contemporaneous, original, and accurate. 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 participant 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 3 documented attempts to retrieve previous medical records. If this fails, a verbal history from the participant, documented in their medical records, would be acceptable.

Copies of source documents necessary for AEs may need to be submitted to the pharmacovigilance department. Participant’s HRCT scan will be submitted to the vendor for the eligibility confirmation. Before sending or uploading those copies, the investigator must ensure that all participant identifiers (e.g. participant’s name, initials, address, phone number, identification number) have been properly removed or redacted from all copies of the participant’s source documents.

Electronic records of PROs will be regarded as source data.

Electronic recording from the cough monitor and activity monitor will be regarded as source data. Source data must include documentation of the participants training and documentation when recording was started if the recording is initiated at the visit.

If the trial participant is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the participant file.

For the CRF, data must be derived from source documents, for example:

- Participant identification: sex, year of birth (in accordance with local laws and regulations)
- Participant participation in the trial (substance, trial number, participant number, date participant was informed)
- Dates of participant’s visits, including dispensing of trial IMP
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory] and end date [if available])
- SAEs (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, with proper documented medical evaluation (in validated electronic format, if available). These include results from spirometry, DLCO, pulse oximetry, etc

- Completion of participant's participation in the trial (end date; in case of premature discontinuation, document the reason)
- Prior to allocation of a trial participant to a treatment in 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 participant, or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the participant eligible for the clinical trial
- Documentation of physical exam findings
- Vital signs, height and weight measurements
- Confirmation of eligibility from the central HRCT review

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 and 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 consent forms. 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 site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to the contract or local requirements valid at the time of the end of the trial (whichever is longer).

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible for fulfilling their legal and regulatory reporting obligation in accordance with regulatory requirements.

SAE/AESI are processed in the global safety database and assessed for the sponsor causal relationship, as well as the expectedness of the event according to the reference safety information. Individual case safety reports are subsequently reported according to local regulations. SUSARs will be reported to the EMA via E2B transmission of individual case safety reports to the Eudravigilance CT Module.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

- Participants will be assigned a unique identifier by the sponsor, i.e. pseudoanonymised. Any participant data or records that are transferred to the sponsor or to vendors will be identified only by this unique identifier. Participant names or any information which would make the participant identifiable will remain at the site and will not be transferred
- Data is entered at sites in a validated eDC system via eCRFs by the investigator and/or site staff. This study uses the eDC system Vault CDMS (supplier: Veeva)
- In addition, clinical study data are collected via external supplier systems and are transferred to the sponsor. These study data are referred to as non-eDC 'external data'. Reporting of data and results from vendors to sites will be through the vendor's portals. IRT data are transferred to sponsor via API. Data or recordings collected by the study devices (spirometry, cough recording, activity recording, PROs, ECG) will be first transferred from the devices to the vendor. Those data or analysis of the data will then be electronically transferred to the sponsor. Results from the sample analysis at the designated laboratories will be electronically transferred to the sponsor. Sites will upload HRCT images to through the vendor portal for central overhead. Results of the overread will be electronically transferred to the sponsor. Transfer of data from vendors to the sponsor is through the secure electronic data transfer protocols (Veeva FTPs upload or EDT). Data Transmission Specification document will be prepared for each supplier and/or data type prior to the delivery of any external data to describe the clinical study data to be delivered and administrative aspects for the transfer by a third party. Study data will be exported internally to Boehringer Ingelheim PSPV Department for pharmacovigilance purposes and to Boehringer Ingelheim independent statistical analysis team for preparation of reports for DMC and DDC. Access to the data and vendor systems is given only to the authorised users from the sponsor or sites. Access is protected by the log-in credentials. All eDC and non-eDC data for the study are stored on the validated, secured, standardised, and harmonised CRE
- The participant must be informed that their personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities
- The sponsor has implemented privacy and security controls designed to help protect participants' personal data, including information security controls, firewalls, incident detection, and secure transfer measures
- The sponsor has implemented appropriate measures to ensure confidentiality of records and personal data of participants as required by applicable data protection laws, including replacement of participant identifiable information with unique identifiers, access

restrictions to data and vendor systems, and the use of validated, secured, standardised, and harmonised CRE for eDC and non-eDC data

- In the event of an accidental or unlawful destruction, loss, alteration, unauthorized disclosure, or access to personal data ('breach'), the sponsor has implemented procedures and measures to promptly address and mitigate any risk to the participant in accordance with applicable data protection laws. This includes an initial assessment as to whether the breach constitutes a 'personal data breach' as defined by the EU General Data Protection Regulation and responsive measures to mitigate adverse effects, the specifics of which depend on the nature and severity of the individual breach. In the event of a breach, the sponsor will notify the appropriate regulatory authorities and/or the participant(s) in accordance with applicable data protection law
- The contract between sponsor and trial sites specifies the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access
- A Data Protection Impact Assessment established that data protection and mitigation measures in place by the sponsor are suitable to limit residual risk to the levels 'negligible' or 'limited'

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 must be in accordance with the separate biobanking informed consent
- The Boehringer Ingelheim 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, including 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 **first act of recruitment** represents the **start of the trial** and is defined as the date when the first trial participant in the whole trial signs informed consent.

The **end of the trial** is defined as the date of the last visit of the last trial participant in the whole trial (“last participant completed”)

The **“last participant last treatment”** (LPLT) date is defined as the date on which the last trial participant in the whole trial is administered the last dose of trial IMP (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial IMP 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 HA request.

The sponsor will prepare a clinical trial report within 1 year from the end of trial.

The sponsor will notify the IEC/competent authority in each participating EU member state about all required trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all trial participants 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 1 year from the end of a clinical trial as a whole, regardless of the country of the last trial participant (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

8.7.1 Sponsor

The trial is sponsored by Boehringer Ingelheim.

8.7.2 Coordinating Investigator

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

8.7.3 Data Monitoring Committee

An external DMC will be established with members independent from the sponsor. DMC members will include physicians experienced in the treatment of the disease under investigation and a statistician. The main focus of the DMC will be the evaluation of safety data. Efficacy data may be reviewed if requested by the DMC to support risk/benefit assessment. The DMC will receive urgent, significant, safety concerns and DILI, for immediate evaluation. 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 RAs/HAs, IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter. All relevant documents will be stored in sponsor's TMF. Minutes of the DMC blinded sessions will be stored at the vendor and transferred to BI at the end of the trial to avoid potential for unblinding.

8.7.4 Development Decision Committee

The IA will be conducted once 25 participants in both the [REDACTED] and placebo groups in the IPF cohort complete 4 weeks of treatment. The IA will be performed by an unblinded team independent of the trial team. The internal DDC will review the results of the IA and provide decision regarding trial continuation. The project team will remain blinded throughout the decision-making process. Further details regarding DDC composition and function will be defined in the DDC charter. All relevant documents will be stored in sponsor's TMF.

8.7.5 Investigators

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 Boehringer Ingelheim web portal, Clinergize, to access documents provided by the sponsor.

8.7.6 Trial management and performance

Boehringer Ingelheim 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, CRAs, and investigators of participating countries

In the participating countries, the trial will be performed by the respective local or regional Boehringer Ingelheim organisation (OPU) in accordance with applicable regulations and

Boehringer Ingelheim SOPs or by a CRO based on a contract. The CRO may perform project management, clinical field monitoring, medical monitoring, or reporting.

Data management and statistical evaluation will be done by Boehringer Ingelheim according to Boehringer Ingelheim SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to Boehringer Ingelheim SOPs. A list of responsible persons and relevant local information can be found in the ISF.

Vendors will be used in this trial for central laboratory services, randomisation and drug orders, drug shipment, spirometry, cough count and activity monitoring, eCOA administration management, central ECG services, HRCT central evaluation, and PK analytical determinations. Details are specified in the contract with each vendor. Respective manuals are available in the ISF.

9. REFERENCES

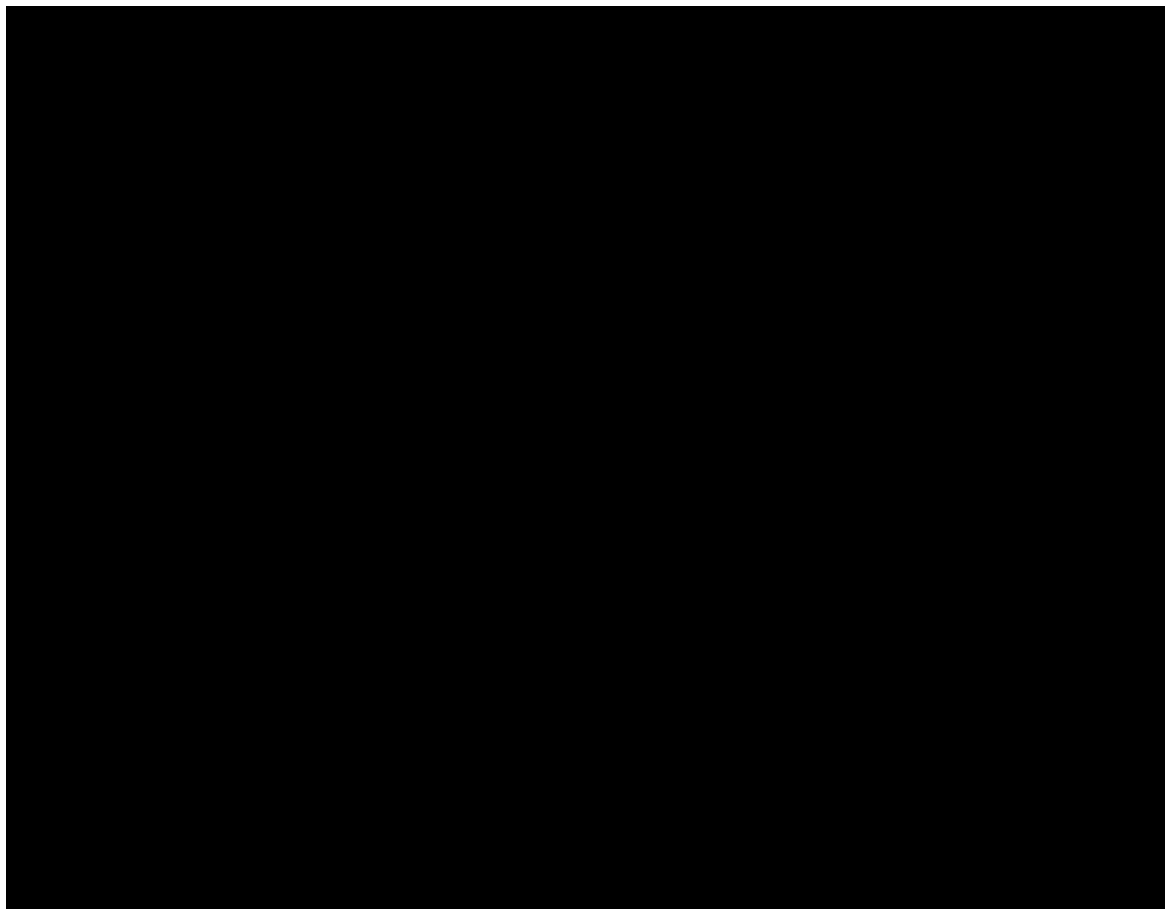
9.1 PUBLISHED REFERENCES

- P15-01629 Prasad R, Gupta P, Singh A, et al. Drug induced pulmonary parenchymal disease. *Drug Discov Ther.* 2014;8(6):232-237.
- P15-05871 Chambers RC, Mercer PF. Mechanisms of alveolar epithelial injury, repair, and fibrosis. *Ann Am Thorac Soc.* 2015;12(Suppl 1):S16-S20.
- P16-06899 Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. *Am J Respir Crit Care Med.* 2016;194(3):265-275.
- P17-02366 Jo HE, Glaspole I, Grainge C, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J.* 2017;49:1601592.
- P19-08802 Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med.* 2019;381(18):1718-1727.
- P22-00512 Khan FA, Stewart I, Moss S, et al. Three-month FVC change: a trial endpoint for idiopathic pulmonary fibrosis based on individual participant data meta-analysis. *Am J Respir Crit Care Med.* 2022;205(8):936-948.
- P22-03204 Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med.* 2022;205(9):e18-e47.
- P22-03537 Richeldi L, Azuma A, Cottin V, et al. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. *N Engl J Med.* 2022;386(23):2178-2187.
- P22-05773 Lee J, White E, Freiheit E, et al. Cough-specific quality of life predicts disease progression among patients with interstitial lung disease: data from the Pulmonary Fibrosis Foundation Patient Registry. *Chest.* 2022;162(3):603-613.

- P23-01135 Bryan CS, Williams MS, Kolb M, et al. An open label study of the efficacy, safety and tolerability of NP-120 on idiopathic pulmonary fibrosis and its associated cough. Poster presentation at: 21st Int Colloquium on Lung and Airway Fibrosis; 2022 Oct 1-5; Reykjavik, Iceland.
- R06-2002 Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720-735.
- R10-1424 Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. *J Biopharm Stat*. 2006;16(5):639-656.
- R12-1608 Ryerson CJ, Abbritti M, Ley B, et al. Cough predicts prognosis in idiopathic pulmonary fibrosis. *Respirology*. 2011;16:969-975.
- R15-2001 Bornkamp B, Pinheiro J, Bretz F. Package ‘DoseFinding’ (February 19, 2015). Website: cran.r-project.org/web/packages/DoseFinding/DoseFinding.pdf (access date: 28 April 2015); Comprehensive R Archive Network; 2015.
- R15-4125 Greene KE, King TE, Kuroki Y, et al. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. *Eur Respir J*. 2002;19(3):439-446.
- R15-4293 Pinheiro J, Bornkamp B, Glimm E, et al. Model-based dose finding under model uncertainty using general parametric models. *Stat Med*. 2014;33(10):1646-1661.
- R17-2148 Cheng JZ, Wilcox PG, Glaspole I, et al. Cough is less common and less severe in systemic sclerosis-associated interstitial lung disease compared with other fibrotic interstitial lung diseases. *Respirology*. 2017;22(8):1592-1597.
- R18-0482 Ryerson CJ, Tan B, Fell CD, et al. The Canadian Registry for Pulmonary Fibrosis: design and rationale of a national pulmonary fibrosis registry. *Can Respir J*. 2016;2016:3562923.
- R20-2419 Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update: an official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med*. 2019;200(8):e70-e88.

- R20-3564 Barlo NP, Moorsel CHM van, Ruven HJT, et al. Surfactant protein-D predicts survival in patients with idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2009;26:155-161.
- R21-1708 Manen M van, Birring S, Vancheri C, et al. Cough measurements in patients with idiopathic pulmonary fibrosis (ipf). Poster presented at 111th Int Conf of the American Thoracic Society (ATS); 2015 May 15-20; Denver, CO.
- R21-1709 Key AL, Holt K, Hamilton A, et al. Objective cough frequency in idiopathic pulmonary fibrosis. *Cough.* 2010;6:4.
- R21-1710 Harrison NK. Cough, sarcoidosis and idiopathic pulmonary fibrosis: raw nerves and bad vibrations. *Cough.* 2013;9:9.

9.2 UNPUBLISHED REFERENCES



10. APPENDICES

10.1 ELIGIBILITY CONFIRMATION OF IDIOPATHIC PULMONARY FIBROSIS DIAGNOSIS

Participants are eligible with a clinical diagnosis of IPF based on the 2022 guideline *Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline* as confirmed by the investigator based on chest HRCT scan taken within 12 month of Visit 1 and, if available, surgical lung biopsy or TBLC, as well as a ‘UIP’ or ‘Probable UIP’ HRCT pattern consistent with the clinical diagnosis of IPF, as confirmed by central review prior to Visit 2B. If the HRCT finding is ‘Indeterminate’, the clinical diagnosis of IPF may be confirmed locally by (historical) surgical lung biopsy or TBLC demonstrating a ‘UIP’ or ‘Probable UIP’ histopathology pattern. If the HRCT findings are ‘suggestive of an alternative diagnosis’, the clinical diagnosis of IPF may be confirmed locally by (historical) surgical lung biopsy or TBLC demonstrating a ‘UIP’ histopathology pattern.

All chest HRCTs will be sent for central review by an experienced expert based on the recent ATS/ERS/JRS/ALAT guideline on the diagnosis of IPF [[P22-03204](#)].

Participants with a centrally reviewed HRCT pattern qualifying as ‘UIP’ or ‘Probable UIP’ are eligible for participation and are not required to have a surgical lung biopsy in the appropriate clinical context for the diagnosis of IPF.

Participants clinically suspected to have IPF with an HRCT pattern of ‘Indeterminate for UIP’ require historical (i.e. not taken for the purpose of this trial) surgical lung biopsy or TBLC, which will be reviewed locally (by the investigator/local histopathologist). In these participants, specific combinations of HRCT patterns and histopathology patterns may still allow a diagnosis of IPF based on the 2022 ATS/ERS/JRS/ALAT Guideline, i.e. an HRCT pattern of ‘indeterminate for UIP’ in combination with a surgical lung biopsy or TBLC with a histopathologic pattern of ‘UIP or probable UIP’ could qualify for inclusion.

Participants clinically suspected to have IPF with an HRCT pattern ‘suggestive of an alternative diagnosis’ require historical (i.e. not taken for the purpose of this trial) surgical lung biopsy or TBLC which will be reviewed locally (by the investigator/local histopathologist). In these participants, specific combinations of HRCT patterns and histopathology patterns may still allow a diagnosis of IPF based on the 2022 ATS/ERS/JRS/ALAT Guideline, i.e. an HRCT pattern of ‘alternative diagnosis’ in combination with a surgical lung biopsy or TBLC with a histopathology pattern of ‘UIP’ could qualify for inclusion.

Appropriate documentation at site for these cases is required. Copies of the original, histopathological assessments and resulting diagnosis are required in participant files.

Table 10 Idiopathic pulmonary fibrosis diagnosis based upon chest HRCT and biopsy patterns

IPF suspected ¹		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely) ²	Non-IPF dx
	Indeterminate	IPF	IPF (Likely) ²	Indeterminate ³	Non-IPF dx
	Alternative diagnosis	IPF (Likely) ²	Indeterminate ³	Non-IPF dx	Non-IPF dx

dx–diagnosis; HRCT–high-resolution computed tomography; IPF–idiopathic pulmonary fibrosis; UIP–usual interstitial pneumonia.

(Adapted from Figure 9 in [P22-03204]).

¹ ‘Clinically suspected of having IPF’ = unexplained symptomatic or asymptomatic patterns of bilateral pulmonary fibrosis on a chest radiograph or chest computed tomography, bibasilar inspiratory crackles, and age greater than 60 years. (Middle-aged adults [40 yr and 60 yr], especially participants with risks for familial pulmonary fibrosis, can rarely present with the otherwise same clinical scenario as the typical patient older than 60 years.)

² IPF is the likely diagnosis when any of the following features are present:

- Moderate-to-severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in 4 or more lobes including the lingual as a lobe, or moderate to severe traction bronchiectasis in 2 or more lobes) in a man over age 50 years or in a woman over age 60 years
- Extensive (30%) reticulation on HRCT and an age >70 years
- Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- Multidisciplinary discussion reaches a confident diagnosis of IPF

³ Indeterminate for IPF

- Without an adequate biopsy remains indeterminate
- With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation

10.2 ELIGIBILITY CONFIRMATION FOR PROGRESSIVE PULMONARY FIBROSIS DIAGNOSIS

Participants must have fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis, with or without honeycombing, with a disease extent of >10%.

The following coexisting features were accepted:

- Ground glass opacity
- Upper lung or peribronchovascular predominance
- Mosaic attenuation
- Air trapping
- Centrilobular nodules

The following coexisting features were not allowed:

- Widespread consolidation
- Progressive massive fibrosis

HRCT patterns were used to classify participants as having a UIP-like fibrotic pattern or other fibrotic patterns (based on central review). Participants who met criteria A, B, and C; A and C; or B and C (see [Table 11](#)) were classified as having a UIP-like fibrotic pattern on HRCT.

Participants who did not meet these criteria were classified as having other fibrotic patterns on HRCT.

Table 11 HRCT criteria for classifying PPF patient fibrotic pattern

Criteria	Description
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

10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS

Table 12 Equivalent doses of corticosteroids

Drug	Equivalent dose (mg)	Conversion factor
Prednisone	15	x 1
Prednisolone	15	x 1
Triamcinolone	12	x 1.25
6-Methylprednisolone	12	x 1.25
Dexamethasone	3	x 5
Betamethasone	2.24	x 6.7
16-Methylprednisolone	18.75	x 0.8
Fluocortalon	15	x 1
Cloprednol	10-15	x 1.0-1.5
Deflazacort	18.75	x 0.8
Cortisol (hydrocortisone)	60	x 0.25
Cortisone	75	x 0.20

10.4 DEVICE PROFILE

The cough monitor will be used to objectively measure cough and other [REDACTED] parameters.

The cough monitor is a lung sound recording system that has achieved FDA 510K clearance and CE marking. The cough monitor has been validated to objectively measure cough count. It has been assessed in comparison with manual cough count in the inpatient and outpatient settings in persons with varying forms of cardiopulmonary disease (COPD, asthma, COVID infection, CHF). The cough monitor consists of the biosensor, which adheres to the chest wall via a consumable adhesive, replaced daily. Once the 24-h recording is complete, the biosensor will be placed on the charging station. The biosensor will connect via Bluetooth to the app on a study provided mobile phone, which should be placed next to the charging station. The biosensor will upload data to the app/smart sensor platform within a 24-h period. An acoustic signal output is made available via the platform. For quality control of the machine learning algorithm; all cough annotations are reviewed manually. Raw data outputs are also available for review and discussion.

10.5 SPIROMETRY: BRONCHODILATOR WASHOUT RECOMMENDATIONS

Based on ATS/ERS 2019 guidelines [[R20-2419](#)] for the conduct of spirometry, the following washout of bronchodilators is recommended before spirometry (see [Table 13](#)). According to the ongoing treatment, the investigator should advise the participant on the washout on/before the days of the onsite spirometry and document it in the source documents.

Table 13 Minimal washout timeframes for bronchodilators before spirometry

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

10.6 PATIENT REPORTED OUTCOMES

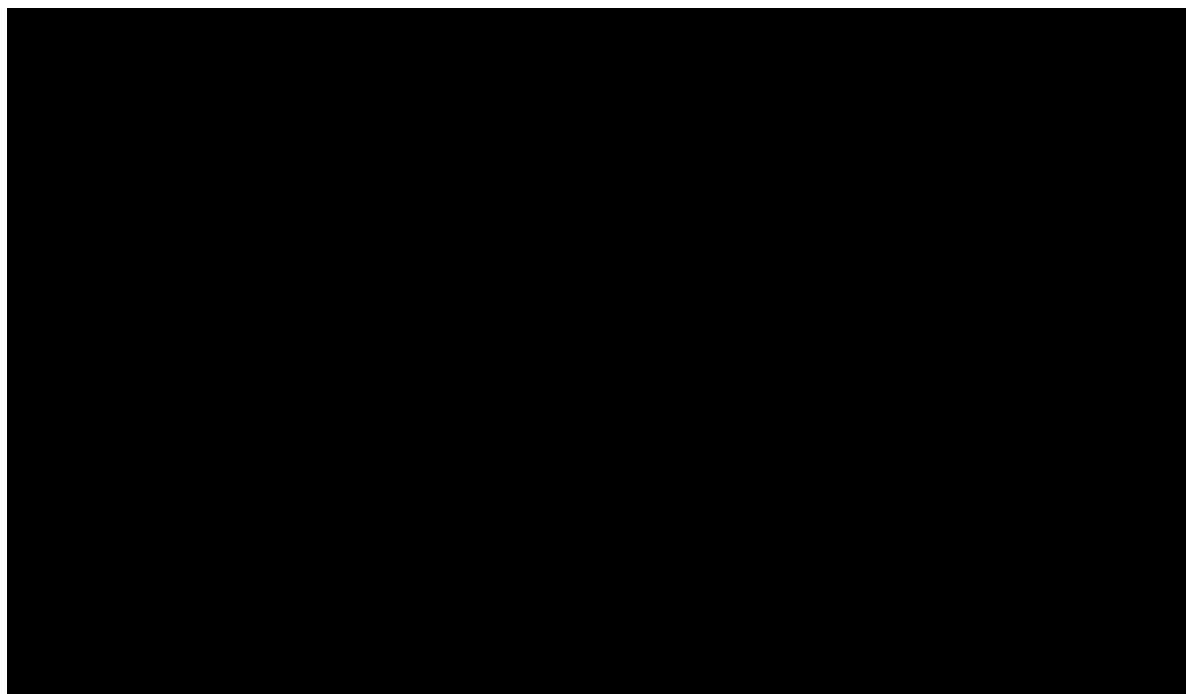
10.6.1 Cough Severity Numerical Rating Scale

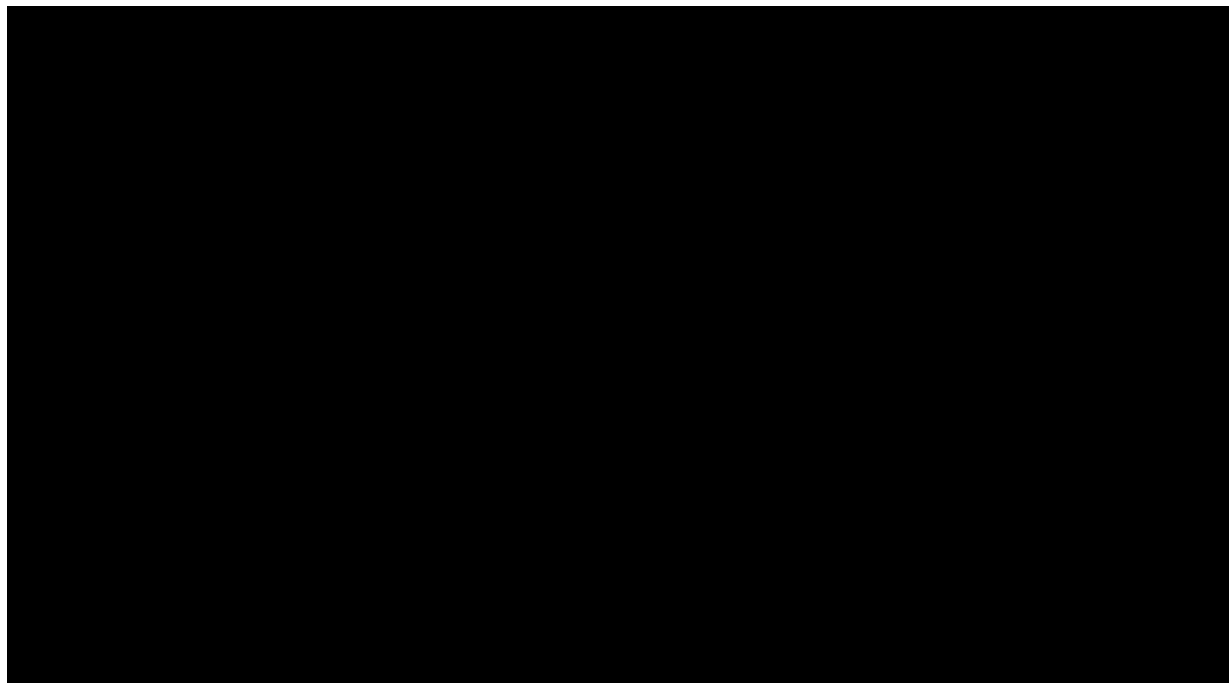
Cough Severity - Numerical Rating Scale

Please rate below the overall severity of your cough in the past 7 days.

(Select one response)

- ☐ 0 (no cough)
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10 (worst imaginable cough)





10.6.4 Cough Severity Visual Analog Scale

Patient's Global Impression of Cough Severity

Visual Analog Scale

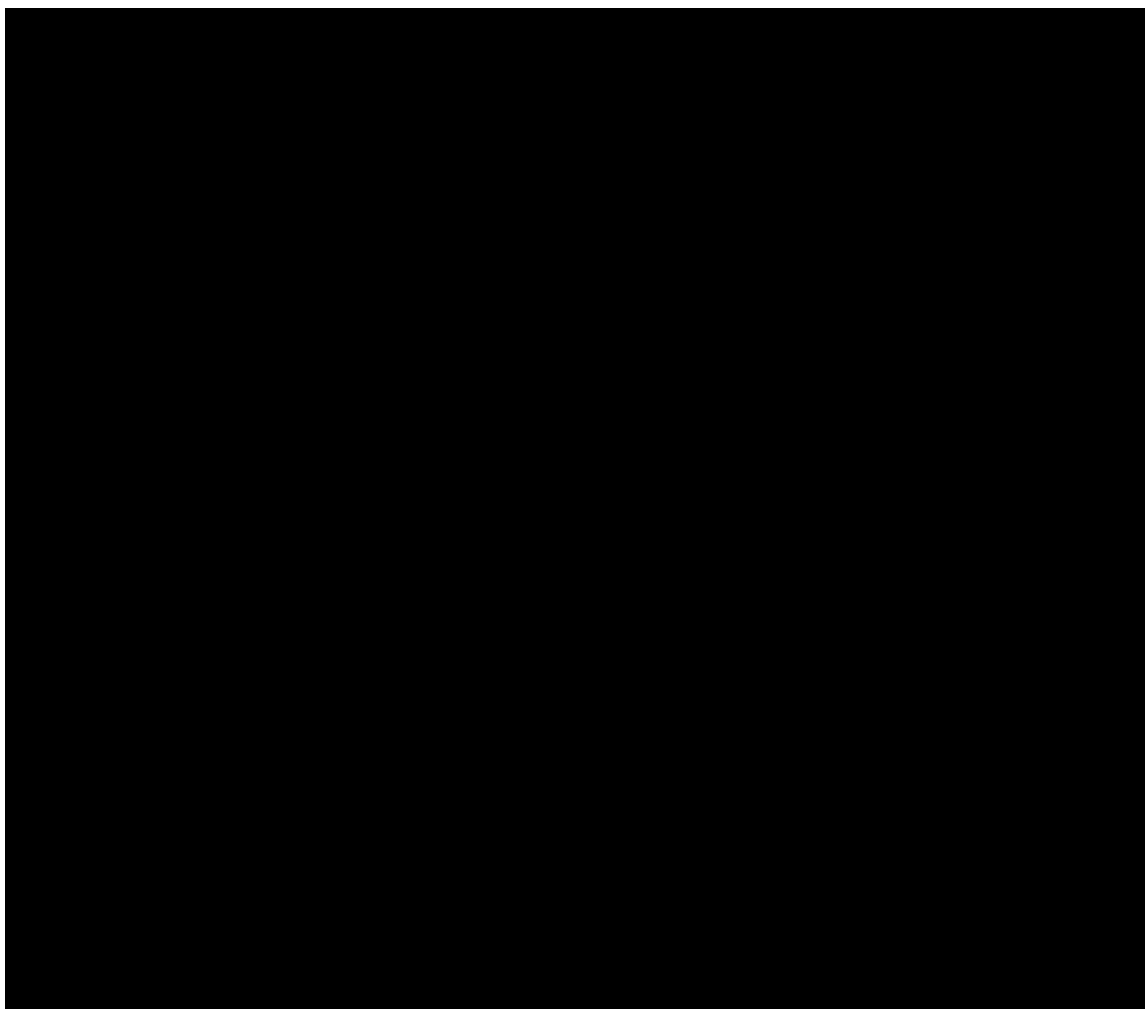
How was the overall severity of your cough in the past week?

*Please mark on the scale below with a vertical line anywhere between the two ends corresponding to the overall severity of your cough **in the past week**.*



No Cough

Worst possible Cough



10.6.6 Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire

Page 1 of 8

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

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 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 Constantly

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

Not at all Constantly

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

Not at all Constantly

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

Not at all Constantly

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

Not at all Constantly

Items 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 Excellent

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

Nothing Everything

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

No energy A lot

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

No effect at all 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 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 Extremely

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

Not at all Extremely

3. How was your stamina when you exerted physically?

Extremely poor Excellent

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

Not at all Extremely

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

Not at all Extremely

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

Not at all Extremely

7. How much did coughing embarrass you?

Not at all Extremely

8. How much did coughing frustrate you?

Not at all Extremely

On average, over the last 7 days...

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

Never All of the time

10. How frightening was your coughing to you?

Not at all Extremely

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

Not at all Extremely

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

None A lot

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

Not at all A lot

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

Not at all A lot

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

Very little time Extremely long time

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

Not at all 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 No negative effect

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

Made my quality of life extremely poor No negative effect

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

Made my quality of life extremely poor 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 Excellent

21. How has your quality of life been?

Extremely poor Excellent

The end.

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

10.6.7 Leicester Cough Questionnaire

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of your cough on various aspects of your life. Read each question carefully and answer by CIRCILING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
2. In the last 2 weeks, have you been bothered by phlegm production when you cough?
 1 Every time 2 Most times 3 Several times 4 Sometimes 5 Occasionally 6 Rarely 7 Never
3. In the last 2 weeks, have you been tired because of your cough?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
4. In the last 2 weeks, have you felt in control of your cough?
 1 None of the time 2 Hardly any of the time 3 A little of the time 4 Some of the time 5 A lot of the time 6 Most of the time 7 All of the time
5. How often during the last 2 weeks have you felt embarrassed by your coughing?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
6. In the last 2 weeks, my cough has made me feel anxious
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
9. In the last 2 weeks, exposure to paints or fumes has made me cough
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
10. In the last 2 weeks, has your cough disturbed your sleep?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
11. In the last 2 weeks, how many times a day have you had coughing fits?
 1 All of the time (continuously) 2 Most times during the day 3 Several times during the day 4 Sometimes during the day 5 Occasionally through the day 6 Rarely 7 None
12. In the last 2 weeks, my cough has made me feel frustrated
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
13. In the last 2 weeks, my cough has made me feel fed up
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
15. In the last 2 weeks, have you had a lot of energy?
 1 None of the time 2 Hardly any of the time 3 A little of the time 4 Some of the time 5 A lot of the time 6 Most of the time 7 All of the time
16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
17. In the last 2 weeks, have you been concerned that other people think something is wrong with you because of your cough?
 1 All of the time 2 Most of the time 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
18. In the last 2 weeks, my cough has interrupted conversations or telephone calls
 1 Every time 2 Most times 3 A lot of the time 4 Some of the time 5 A little of the time 6 Hardly any of the time 7 None of the time
19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends
 1 Every time I cough 2 Most times when I cough 3 Several times when I cough 4 Sometimes when I cough 5 Occasionally when I cough 6 Rarely 7 Never

Thank you for completing this questionnaire.

10.7 TIME SCHEDULE FOR PHARMACOKINETIC BLOOD SAMPLING

Table 14 Time schedule for PK blood sampling

Participant cohort	Visit	Day	Time point [hh:min]	Event	Sample No.
IPF	2	1	Just before drug administration	PK blood	1
			0:00	Drug admin.	---
			End of the visit (>1 h post dose)	PK blood	2
	3	29 ± 3	Just before drug administration	PK blood	3
			0:00	Drug admin.	---
			End of the visit (>1 h post dose)	PK blood	4
	4	57 ± 3	Just before drug administration	PK blood	5
PPF	5	85 + 3	At any time during the visit	PK blood	6
	2	1	Just before drug administration	PK blood	7
			0:00	Drug admin.	---
			End of the visit (>1 h post dose)	PK blood	8
	3	29 + 3	At any time during the visit	PK blood	9

10.8 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaires:

This trial will include an option for participants to complete questionnaire, ‘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.

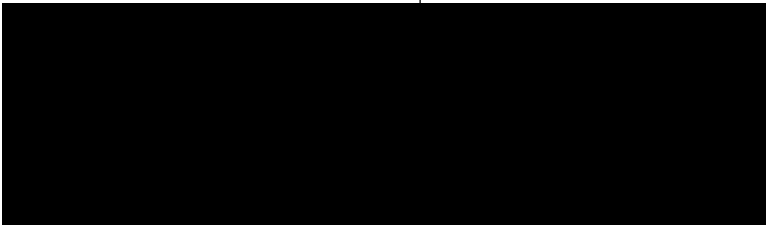
11. DESCRIPTION OF GLOBAL AMENDMENT

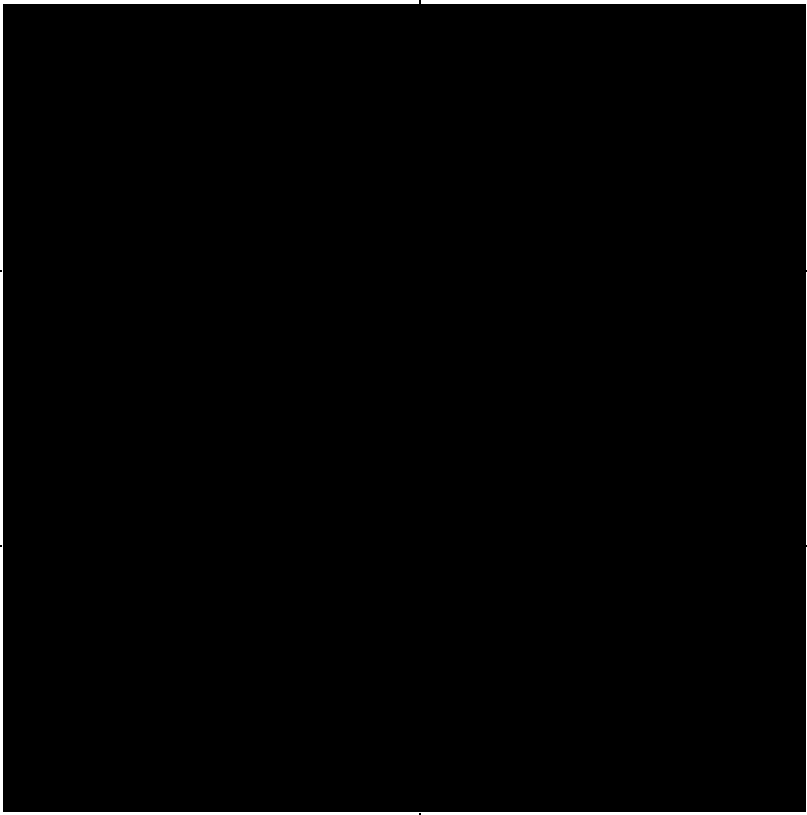
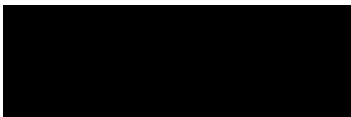
11.1 GLOBAL AMENDMENT 1

This amendment is considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

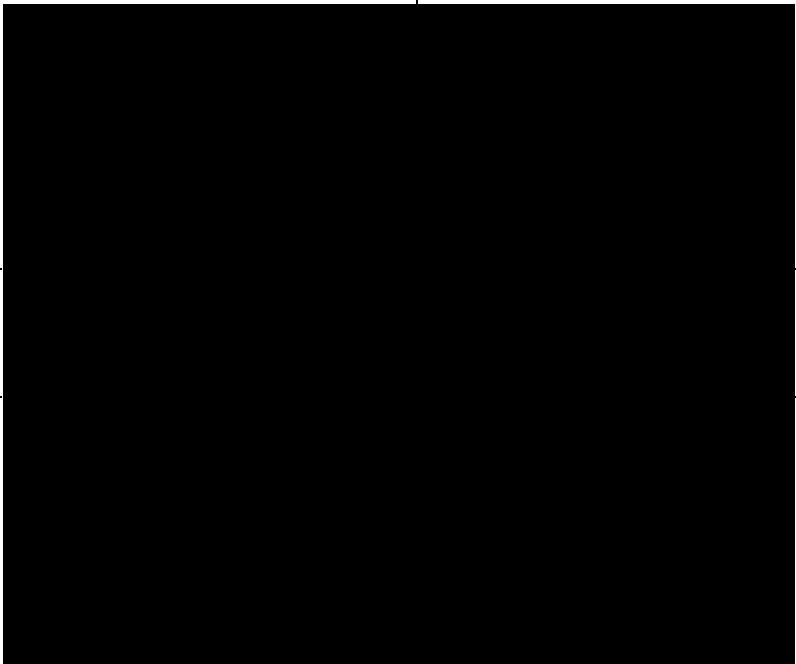
Overall rationale for the amendment:

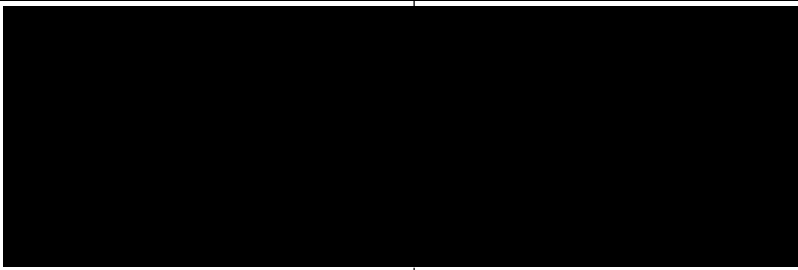
This protocol amendment addresses relevant updates from IB Version 5. It also includes changes due to health authority feedback received during the submission process, the results of completed non-clinical and clinical trials, and corrections for consistency within the protocol.

Amendment and date of amendment	Amendment 1, 22 Aug 2024	
Global Amendment	X	
Global Amendment due to urgent safety reasons	NA	
Section changed	Description of change	Rationale for change
Clinical trial protocol synopsis	Updated to match amendment changes in body of CTP. Added language to clarify that PPF cohort diagnosis criteria should be fulfilled in the 24 months prior to screening visit.	Capture amendment changes from body of CTP. Updated for consistency within CTP.
Schedule of Assessments	Added Cough Severity VAS assessment at Week 8 (Visit 4) for the IPF cohort.	Ensure consistency of the timing of assessments within the CTP.
1.2 – Drug Profile		
1.4.2 – Risks	Updated paragraphs proceeding Table 1, Overview of trial related risks	Clarified per health authority request.

1.4.2 – Risks		
1.4.2 – Risks		
1.4.2 – Risks		
2.2.2 – Further endpoints	Removed  from list of blood-based biomarkers being assessed as a further endpoint in the IPF and PPF cohorts.	 Therefore, biomarker assessment will no longer be performed.
3.1 – Overall trial design		
3.3.2 – Inclusion criteria	Clarified that nintedanib and/or pirfenidone therapy cannot be delayed in order to participate in the trial.	Clarified per health authority request.

3.3.2 – Inclusion criteria	Updated contraception requirements for IPF and PPF cohorts: • WOCBP are required to use 1 form of highly effective birth control • Contraception requirements for male participants and female partners of male participants were removed	Results of completed preclinical genotoxicity, embryo-faetal development, and fertility and early embryonic developmental toxicity studies indicated no genotoxicity or development toxicity.
3.3.2 – Inclusion criteria	Corrected numbering of ‘Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial’ inclusion criteria for PPF cohort.	Correction of misnumbering per Protocol Notification Letter #2.
3.3.3 – Exclusion criteria	Gefapixant was added to exclusion criteria #11.	Use of gefapixant may suppress cough, affecting clinical outcomes of participants.
3.3.3 – Exclusion criteria		
3.3.3 – Exclusion criteria	Revised exclusion criteria #21 to clarify that ‘Participants taking any of the restricted medications...’ are excluded from the trial.	Clarified per health authority request.
3.3.3 – Exclusion criteria	Addition of ‘or 5 half-lives (whichever is longer)’ to exclusion criteria #30	The 5 half-lives of some of these excluded medications is longer than 4 weeks. By using whichever time period is longer, the chance of these treatments affecting clinical outcomes is reduced.

3.3.4.1 – Discontinuation of trial treatment	Changed language describing discontinuation related to QTcF increase: ‘The trial participant experienced QTcF increase of >60 ms from baseline (Visit 2B) ~~together with~~ or absolute QT or QTcF >500 ms, as confirmed by a repeat ECG recording’	Changed as requested by health authority.
4.2.1.2 – Emergency procedures	Updated section to ‘In the case of acute IPF/PPF exacerbation, participants must be treated according to local SoC. If the participant requires a restricted medication to treat the exacerbation, the IMP must be discontinued according to Section 3.3.4.1.’	Clarified per health authority request.
4.2.2.1 – Restrictions regarding concomitant treatment	Added use of gefapixant to restricted medicine #2 d.	Use of gefapixant may suppress cough, affecting clinical outcomes of participants.
4.2.2.1 – Restrictions regarding concomitant treatment		
4.2.2.1 – Restrictions regarding concomitant treatment		
4.2.2.1 – Restrictions regarding concomitant treatment		

4.2.2.1 – Restrictions regarding concomitant treatment		
4.2.2.2 – Restrictions on diet and lifestyle	Removal of ‘nicotine’ from list of usual habits to keep throughout the trial.	Clarified per health authority request.
4.2.2.3 – Contraception requirements	Clarified that WOCBP must use 1 highly effective method of birth control. Clarified that using a highly effective method of birth control ‘until the end of the trial’ includes   Removal of requirement for WOCBP taking oral contraception also having to use 1 barrier method. Removal of contraception requirements for men and female partners of male participants.	Results of completed genotoxicity, embryo-faetal development, and fertility and early embryonic developmental toxicity studies indicated no genotoxicity or development toxicity.
5.1.4.6 – Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire	Updated item numbers included in symptom dyspnea domain.	Correction of error in listing of items included in the symptom dyspnea domain.
5.2.4 – Safety laboratory parameters		
5.2.4 – Safety laboratory parameters	Addition of safety labwork for thyroid function (TSH, free T3, and free T4) to Table 5.	Added as requested by health authority.

5.2.7.2.3 – Pregnancy	Removed requirement for reporting for IMP exposure during pregnancy for partners of male trial participants.	Results of completed genotoxicity, embryo-foetal development, and fertility and early embryonic developmental toxicity studies indicated no genotoxicity or development toxicity.
5.3.1 – Assessment of pharmacokinetics	Updated ‘The date and clock times of drug administration on the [REDACTED] before sample collection...’	Corrected for consistency within the CTP.
5.4.1 – Exploratory biomarkers	Removal of [REDACTED] from exploratory biomarkers.	[REDACTED] Therefore, biomarker assessment will no longer be performed.
5.4.1 – Exploratory biomarkers	Removed incorrect cross-reference to Appendix 10.7.	[REDACTED]
5.6.1 – Chest high-resolution computed tomography	Removal of ‘In Germany, no HRCT will be performed as trial procedure; only historical HRCT will be submitted.’	To align with Protocol Notification Letter #1.
7.2.3.4 – Supplementary analyses	Updated to ‘hypothetical approach’.	Corrected for consistency within CTP.
8.4 – Expedited reporting of adverse events	Added information on how SAE/AESIs are processed and reported.	Added per health authority request.
8.5 – Statement of confidentiality and trial participant privacy	Added information on data entry/upload, storage, transfer, and protection.	Updated per health authority request.
[REDACTED]		

10.7 – Time schedule for pharmacokinetic blood sampling	Removed sample taken with drug administration at Visit 3 and renumbered subsequent samples.	Corrected as no blood sample is taken with drug administration at Visit 3.
Throughout	Updated the protocol version number and date.	To align with the amendment.
Throughout	Minor editorial and document formatting revisions.	For clarity.

APPROVAL / SIGNATURE PAGE**Document Number:** c43433838**Technical Version Number:**3.0**Document Name:** clinical-trial-protocol-version-02

Title: A Phase IIa/IIb, randomised, double blind, placebo-controlled, parallel-group dose-finding study to examine the efficacy and safety of BI 1839100 administered orally over a 12 week treatment period in patients with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis with clinically meaningful cough

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		22 Aug 2024 18:23 CEST
Author-Clinical Trial Leader		22 Aug 2024 22:17 CEST
Approval-Clinical Program 		23 Aug 2024 13:23 CEST
Verification-Paper Signature Completion		23 Aug 2024 17:50 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
----------------------	-----------	-------------