Clinical Trial Protocol

	Document Number:	**c34975667-06**
EudraCT No. **EU Trial No.**	Not applicable	
BI Trial No.	1199-0434	
BI Investigational Medicinal Product(s)	Ofev®, Nintedanib	
Title	A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype	
Lay Title	A study in China to find out if a medicine called nintedanib helps people with progressive lung fibrosis	
Clinical Phase	IIIb	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Email: [redacted] Phone : [redacted]	
Version and Date	**Version: 5.0**	**Date: 18 Sep 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	10 Feb 2021
Revision date	18 Sep 2023
BI trial number	1199-0434
Title of trial	A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial conducted in China
Clinical phase	Phase IIIb
Trial rationale	The rationale of performing this trial is, upon completion of the international multicentre randomized placebo-controlled Phase III trial (INBUILD, 1199-0247), to generate additional data in Chinese patients with progressive fibrosing ILDs.
Trial objective(s)	The objective of the trial is to generate additional data on the efficacy of 150 mg bid nintedanib in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype compared to placebo over 52 weeks.
Trial endpoints	The primary efficacy endpoint is the annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks), defined as in the INBUILD study. There are no secondary efficacy endpoints. Safety of nintedanib will also be assessed via laboratory tests and (S)AEs.
Trial design	Double blind, randomized, placebo-controlled design of 2 groups over 52 weeks Stratification by HRCT pattern: approximately two thirds of patients with UIP-like HRCT fibrotic patterns, one third of patients with other fibrotic patterns.
Total number of patients randomized	Approx. 90
Number of patients on each treatment	Approx. 60 in nintedanib 150 mg b.i.d. group Approx. 30 in placebo group
Diagnosis	Chronic Fibrosing ILDs with Progressive Phenotype
Main in- and exclusion criteria	Inclusion criteria : • Male or female patients aged ≥ 18 years at Visit 1. • Patients with physician diagnosed ILD who fulfil at least one of the following criteria for Progressive Phenotype within 24 months of Visit 1 despite treatment with unapproved medications used in clinical practice to treat ILD, as assessed by the investigator:

	a. Clinically significant decline in FVC % predicted based on a relative decline of ≥10% b. Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with worsening of respiratory symptoms c. Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with increasing extent of fibrotic changes on chest imaging d. Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging. • Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 12 months of Visit 1 as confirmed by central readers. • FVC ≥ 45% predicted at Visit 2. Exclusion criteria : • Previous treatment with nintedanib or pirfenidone. • Use of any of the following medications for the treatment of ILD: azathioprine (AZA), cyclosporine, MMF, tacrolimus, oral corticosteroids (OCS) >20mg/day and the combination of OCS+AZA+NAC within 4 weeks of Visit 2, cyclophosphamide within 8 weeks of Visit 2, rituximab within 6 months of Visit 2. • Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2018 Guideline. • Diagnosis of Systemic Sclerosis (SSc) based on 2013 ACR/EULAR classification. • Primary obstructive airway physiology (pre-bronchodilator FEV1/FVC < 0.7 at Visit 1. • The patient has a confirmed infection with SARS-CoV-2 within the 4 weeks prior to Visit 1 and/or during the screening period.
Test product(s)	Ofev®, Nintedanib
dose	150 mg b.i.d (300 mg daily) with optional dose reduction to 100 mg bid (200 mg daily) to manage adverse events
mode of administration	Oral
Comparator product(s)	Placebo
dose	Matching
mode of administration	Oral
Duration of treatment	52 weeks
Statistical methods	The primary analysis will use a restricted maximum likelihood (REML)-based approach with a random slope and intercept model.

	The analysis includes fixed effects for treatment, HRCT pattern, and baseline FVC [mL], as well as the treatment-by-time and baseline-by-time interactions. Random effects will be included for the patient response for both time and intercept. The point estimate of treatment difference between the nintedanib and placebo group will be provided as well as 95%CI. No statistical testing will be performed.

FLOW CHART

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**6a[11]**	**7**	**7a[11]**	**8**	**8a[11]**	**9**	**EOT[12]**	**FU[12]**
	Screening*		**Treatment#**												**FU**
Weeks			**D1**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**		**+1**
Day **Time window**	Before or at the latest at visit 1	≥ 4d before V 2	**1**	**15** **±3**	**29** **±3**	**43** **±3**	**85** **±3**	**127** **±7**	**169** **±7**	**211** **±7**	**253** **±7**	**309** **±7**	**365** **±7**		**+7** **+3**
Informed consent	X*														
HRCT sent to central review[1]	X														
Demographics		X													
Medical history		X	X												
Adverse events, concomitant medication		X	X	X	X	X	X		X		X		X	X	X
In-/exclusion criteria		X	X												
Physical examination, vital signs		X	X	X	X	X	X		X		X		X	X	X
Safety laboratory (blood and urine)		X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
Resting 12-lead ECG[6]		X	X						X				X	X	
[redacted]															
Randomization			X												
IRT notification	X[8]		X		X		X		X		X		X	(X)	
Release patient diary			X	X	X	X	X		X		X				
Review and collect patient diary				X	X	X	X		X		X		X		
Administer 1st trial medication at the clinic			X												
Dispense trial medication			X		X		X		X		X				

Visit		**1**	**2**	**3**	**4**	**5**	**6**	**6a[11]**	**7**	**7a[11]**	**8**	**8a[11]**	**9**	**EOT[12]**	**FU[12]**
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Weeks			**D1**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**		**+1**
Day	Before or at the latest at visit 1	≥ 4d before V 2	**1**	**15**	**29**	**43**	**85**	**127**	**169**	**211**	**253**	**309**	**365**		**+7**
Time window				**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		**+3**
Collect trial drug					X		X		X		X		X	X	
Compliance / drug accountability				X	X	X	X		X		X		X	X	
Trial medication termination														X	
Vital status assessment[9]													X		
Conclude subject participation															X[10]

* Informed consent needs to be signed before any procedure related to the study. When it is signed before visit 1, e.g. to allow shipment of images for central review, all AEs and Concomitant Treatments occurring after the informed consent have to be recorded. The Screening period (informed consent to Visit 2) must not be longer than 8 weeks. Upon obtaining informed consent, the patient will be instructed on the medication wash-out and other restrictions needed. Patients will be asked to give informed consent about COVID-19 if necessary.

In case of dose change (reduction or re-escalation) additional visits have to be included (refer to Section 6.2.4). In case of premature discontinuation of trial medication, the patient will be expected to attend all visits as originally planned until the end of the trial (except for the laboratory visits 6a, 7a, 8a) (see Section 6.2.3).

[1] Review of high resolution computed tomography (HRCT) for meeting the HRCT criteria for fibrosing lung disease, for extent of ILD in the lung (10% or more), and for HRCT pattern. Central review HRCT not older than 12 months should be sent. If the patient does not have a HRCT within 12 months of Visit 1 or the available HRCT scan fails to meet the required image acquisition specification, a new HRCT can be performed for the purposes of participation in the trial, provided the patient meets all other inclusion and no exclusion criteria.

[2]The safety laboratory of Visit 1 must be repeated if screening is longer than 6 weeks.

[3] ß-HCG will be performed at Visit 2 only, at central laboratory. Urine dipstick pregnancy tests will be provided by central laboratory and should be performed in all women of childbearing potential every 4-6 weeks, i.e. at least at every visit and if necessary, additionally at home or at a local laboratory / local doctor. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory. Documentation will be done in patient's notes.

[4] High resolution CT scan will be done at baseline, 24 and 52 weeks in patients who agree as part of the informed consent. Participation is voluntary and is not a prerequisite for participating in the trial. Baseline scan will not be performed in patients where eligibility scan was performed during screening.

[5] If EOT takes place before Visit 7, HRCT should not be performed at EOT.

[6] Resting ECG will be performed (if possible prior to blood draw) at Visit 2 prior to randomization (only if abnormal at Visit 1).

[redacted]

IRT needs to be notified at the latest at Visit 1 but can be notified upon informed consent's signature.

[9] Vital status at 52 weeks (Visit 9) should be available for all randomized patients. Consent for a vital status call at 52 weeks in case of premature discontinuation of trial participation will be requested for all patients as part of the informed consent.

[10] Conclusion of trial participation is for all subjects who complete all treatment visits.

[11]a-Visits (6a, 7a and 8a) are optional based on the investigator's assessment.

[12] EOT should be done in cases of premature trial medication discontinuation during the study period with a follow-up Visit (FU) 1 week later.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALK	Alkaline phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AZA	Azathioprine
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CK	Creatine kinase
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Connective Tissue Disease
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CHP	Chronic Fibrosing Hypersensitivity Pneumonitis
DBL	Database Lock
DILI	Drug Induced Liver Injury
DMARD	Disease-Modifying Anti-Rheumatic Drug
EC	Ethics Committee
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcome Assessment

eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment
EoTrial	End of Trial
EudraCT	European Clinical Trials Database
FC	Flow Chart
FGFR	Fibroblast Growth Factor Receptor
FUP	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GI	Gastro-Intestinal
GGT	Gamma-glutamyl transferase
GLI	Global Lung Initiative
GMP	Good Manufacturing Practice
HA	Health Authority
Hb	Haemoglobin
Hct	Haematocrit
HP	Hypersensitivity Pneumonitis
HR	Hazard Ratio
HRCT	High-Resolution Computed Tomography
iNSIP	Idiopathic Non-specific Interstitial Pneumonia
i.v.	intravenous
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IIPs	Idiopathic Interstitial Pneumonias
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File

IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IPF	Idiopathic Pulmonary Fibrosis
LDH	Lactate dehydrogenase
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMF	Mycophenolate Mofetil
NAC	n-Acetylcysteine
NSCLC	Non-Small Cell Lung Cancer
OCS	Oral Corticosteroids
OPU	Operative Unit
PAH	Pulmonary Arterial Hypertension
PDGFR	Platelet-Derived Growth Factor Receptor
PT	Prothrombin Time
QoL	Quality of Life
RBC	Red Blood Cell Count
RA	Regulatory Authority
RA-ILD	Rheumatoid Arthritis-associated ILD
REP	Residual Effect Period
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RS	Randomized set
SAE	Serious Adverse Event
SCS	Screened Set
SOP	Standard Operating Procedure
SSc-ILD	Systemic Sclerosis-associated ILD
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TOEP	Toeplitz
TOEPH	Heterogeneous Toeplitz

TS	Treated Set
TMF	Trial Master File
UIP	Usual Interstitial Pneumonia
ULN	Upper Level of Normal
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

1.1.1 Chronic fibrosing interstitial lung diseases with a progressive phenotype

The term interstitial lung disease (ILD) encompasses a large group of over 200 pulmonary disorders including idiopathic interstitial pneumonias (IIPs) and autoimmune or environmental ILDs. Idiopathic pulmonary fibrosis (IPF) is the most common disease entity within the group of IIPs and has a dismal prognosis, with a median survival of 2-3 years after diagnosis.

The major abnormality in ILDs is the disruption of the distal lung parenchyma. It is generally agreed that some form of injury of the alveolar epithelial cells initiates an inflammatory response coupled with repair mechanisms. The initiating injury can be introduced via the airways (e.g. inhalation of mineral fibres or dust as in occupational diseases or sensitisation to inhaled allergens as in hypersensitivity pneumonitis [HP]) or via the circulation (e.g. Connective Tissue Disease [CTD] and drug-induced ILDs). The injury-repair process is reflected pathologically as inflammation, fibrosis or a combination of both. Irrespective of the underlying pathophysiology, the resulting alteration of the interstitial space leads to clinical symptoms such as dyspnoea and cough, and results in restrictive ventilatory and gas exchange deficits on pulmonary function testing [R16-0722].

There is no universally accepted single classification of ILDs. They can generally be categorised based on:
- Aetiology: idiopathic or ILDs with known association or cause
- Clinical course: acute, subacute or chronic ILDs
- Main pathological features: inflammatory or fibrotic ILDs

Fibrotic ILDs can be subdivided into 3 groups based on their longitudinal disease behaviour [P18-05024]:
- Intrinsically non-progressive, e.g. drug-induced lung disease after removal of the drug or some cases of HP after removal of a trigger
- Progressive but stabilised by immunomodulation, e.g. some cases of CTD-ILDs [R14-5407, R14-1149, R18-0122, R18-1815]
- Progressive despite treatment considered appropriate in individual ILDs

To describe the group of patients with differing clinical ILD diagnoses who develop a progressive fibrosing phenotype during the course of their disease, BI has been using the terminology ‘patients with progressive fibrosing interstitial lung disease’ (Chronic Fibrosing ILDs with a Progressive Phenotype). These patients demonstrate a number of similarities to patients with IPF, with their disease being defined by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function despite immunomodulatory therapies and, ultimately, early mortality. The working hypothesis is that the response to lung injury in these patients includes the development of fibrosis, which becomes progressive, self-sustaining, and independent of the original clinical association or trigger [P17-10582].

Based on expert consensus, the main chronic fibrosing ILDs that may show a progressive phenotype similar to IPF include:

- Idiopathic non-specific interstitial pneumonia (iNSIP)
- Unclassifiable IIP
- Autoimmune ILDs that include CTD-ILDs (mainly Rheumatoid Arthritis-associated ILD [RA-ILD] and Systemic Sclerosis-associated ILD [SSc-ILD])
- Chronic fibrosing hypersensitivity pneumonitis (CHP)
- Environmental or occupational fibrosing lung diseases

Nintedanib and pirfenidone are available for patients with IPF. Based on clinical and mechanistic parallels between IPF and other chronic fibrosing ILDs with a progressive phenotype, it was anticipated that nintedanib will elicit similar effects in patients with Chronic Fibrosing ILDs with a Progressive Phenotype as it does in patients with IPF, that is, slowing the progression of the disease [c02153150-02]. This assumption was supported by preclinical data indicating that nintedanib impacts fundamental processes of lung fibrosis and that the anti-fibrotic activity of nintedanib is independent of the cause of the fibrosing lung disease [P14-02860, P14-17410, P15-02392, P15-06100]. The results of the INBUILD trial (1199-0247) showed that in patients with progressive fibrosing interstitial lung diseases, the annual rate of decline in the Forced Vital Capacity (FVC) was significantly lower among patients who received nintedanib than among those who received placebo. The absolute treatment effects in these patient populations were similar in magnitude to those observed in pooled data from the INPULSIS trials in patients with IPF. [P19-08802]

Apart from IPF and SSc-ILD, no prospective, controlled clinical trials have been performed in other ILDs previous to the Chronic Fibrosing ILDs with a Progressive Phenotype programme. This is likely due to the relatively low number of patients within each different ILD; the number of patients with a progressive phenotype within each group, is even lower [R19-1104]. In order to address the unmet medical need, patients with differing clinical diagnoses of chronic fibrosing ILDs with a progressive phenotype were grouped together in trial 1199-0247. This ‘basket approach’ was considered the only feasible way to conduct an adequately powered clinical trial to evaluate the long-term efficacy and safety of nintedanib in patients with Chronic Fibrosing ILDs with a Progressive Phenotype.

1.1.2 Interstitial Lung Diseases in China

Although there is no large-scale epidemiological study of IPF or ILD released in China, a gradual increase of ILD incidence and hospitalisation has been observed by clinical experts [R19-1170, R16-4086, R19-2980]. Some medical centres focus on the diagnosis and treatment of ILD as a respiratory disease specialty and follow international standards regarding the diagnostic procedures and treatment of IPF patients [P19-03962].

The highest official guidance institution for ILD in China is the ILD Study Group of the Chinese Thoracic Society, which is responsible for the introduction of the latest international consensus and research progress on ILD to clinicians specialised in respiratory medicine throughout the country via lectures and articles, as well as for nationwide clinical research related to ILD [P16-03854].

IPF was listed on Rare Disease List which was released in year 2018. IPF accounts for 1/4 of hospitalised ILD cases [R19-1170]. Both nintedanib and pirfenidone are recommended for IPF maintenance treatment. Nintedanib was approved for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) in 2020. Nintedanib is the only medication approved to treat patients with "chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype".

1.2 DRUG PROFILE

Nintedanib (Ofev®), 100 mg and 150 mg soft capsules, is an approved treatment for patients with IPF. It was first authorised in the USA on 15 Oct 2014 and in the EU/EEA on 15 Jan 2015. In China, the indication of IPF was approved on 20 Sep 2017. To date, Ofev® has been approved for the treatment of IPF in more than 70 countries worldwide [c01783972]. The indication of chronic fibrosing ILDs with a progressive phenotype was approved in China on 15 Dec 2020.

Mode of action

Nintedanib is a small molecule tyrosine kinase inhibitor that potently inhibits platelet-derived growth factor receptor (PDGFR) α/β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3 [U02-1109, U02-1310, P08-08684]. Nintedanib binds competitively to the adenosine triphosphate binding pocket of these receptors and blocks the intracellular signalling. These growth factor pathways and their down-stream signalling cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling. In addition, nintedanib inhibits Flt-3 (Fms-like tyrosine protein kinase), Src family kinases (Src, Lck, Lyn) [P08-08684], and colonystimulating factor 1 receptor (CSF1R) [P18-00197].

Nintedanib inhibited the proliferation and migration of human lung fibroblasts from patients with IPF. It demonstrated anti-fibrotic and anti-inflammatory activity in 3 animal models of lung fibrosis and in more specific models of SSc-ILD and RA-ILD. Although different in origin, these model systems share a final common pathway: progressive fibrotic lung pathology with proliferation, migration, and transformation of fibroblasts into pathogenic myofibroblasts [U06-1451, U06-1479, U12-2437-01, U12-2066-01, n00239669, n00247887].

Key pharmacokinetic characteristics

A soft gelatin capsule formulation of nintedanib is used in humans. Maximum Plasma Concentration (Cmax) occur between 2 to 4 hours after oral administration. Steady state is reached at the latest within 1 week of dosing. After food intake, a trend towards an increased systemic exposure (around 20%) and a delayed absorption is observed compared to administration under fasted conditions. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87. The terminal half-life is in the range of 7 to 19 hours. The absolute bioavailability of nintedanib is slightly below 5%. Nintedanib is recommended to be taken with food and is mainly eliminated via faeces.

For further details on the pharmacokinetics of nintedanib including drug-drug interaction studies, refer to the Investigator's Brochure [c01783972].

Residual Effect Period

The Residual Effect Period (REP) of nintedanib is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from clinical studies

The clinical efficacy of nintedanib has been studied in over 1400 patients with IPF in 1 Phase II dose finding trial (TOMORROW [P11-11216]) and 2 replicate Phase III trials (INPULSIS® 1 and 2 [P14-07514]). These were randomised, double-blind, placebo-controlled trials comparing treatment with nintedanib twice daily to placebo for 52 weeks. A statistically significant reduction in the annual rate of decline in FVC was demonstrated in patients receiving nintedanib 150 mg bid compared with patients receiving placebo. The magnitude of the effect on FVC was similar in all 3 studies, i.e. a relative reduction of decline of approximately 50%. Supporting the effect of nintedanib on slowing disease progression, nintedanib 150 mg bid significantly reduced the risk of first acute exacerbation compared with placebo in INPULSIS® -2 and in the TOMORROW trial and reduced the risk of acute exacerbations (adjudicated) by 68% in a pre-specified sensitivity analysis of pooled data from the INPULSIS ® trials.

Nintedanib was investigated in a Phase III trial in patients with SSc-ILD (287 patients treated with nintedanib 150 mg bid and 288 patients treated with placebo). The trial met its primary endpoint: nintedanib significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo. The decline in the nintedanib group was about 44% lower than in the placebo group [c22686034-01].

Nintedanib was also investigated in a Phase III trial in patients with Chronic Fibrosing ILDs with a Progressive Phenotype (332 patients treated with nintedanib 150 mg bid and 331 patients treated with placebo). Nintedanib significantly reduced the annual rate of decline in FVC [mL/year] over 52 weeks compared with placebo in both co-primary populations ($p<0.0001$), namely the overall population and patients with HRCT with Usual Interstitial Pneumonia (UIP)-like fibrotic pattern. The results in the complementary population were consistent. The treatment effect was independent of HRCT pattern (interaction p-value 0.2268). The adjusted differences for the annual rate of decline represent relative reductions of 57% in the overall population, 61% in patients with HRCT with UIP-like fibrotic pattern, and 49% for patients with other HRCT fibrotic patterns. Analyses of time-to-event endpoints indicated reductions in clinically meaningful outcome events and provided supportive evidence for a slowing of disease progression by nintedanib [c26471552-02].

The observed safety profile of nintedanib in patients with progressive fibrosing ILD comprised risks that were manageable or occurred at a low frequency. The most frequently reported AEs were gastrointestinal disorders, in particular diarrhoea, nausea, and vomiting. Common AEs were mostly mild or moderate in intensity. In addition, treatment with nintedanib was associated with elevations in liver enzymes. The large majority of liver

enzyme elevations normalised upon treatment interruption, dose reduction, treatment discontinuation, or spontaneously with continued treatment.

More details on nintedanib can be found in the Investigator's Brochure [c01783972].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The efficacy and safety of nintedanib were confirmed in the multinational pivotal trial (1199-0247), but a very limited number of Chinese patients (15 patients accounting for 2.3% of the entire study population) were randomized in this study. The new indication of "chronic fibrosing Interstitial Lung Diseases with a progressive phenotype" was conditionally approved in China on 15 Dec 2020, it was also requested by the Center for Drug Evaluation (CDE) to complete a post marketing study and submit the CSR of this post-approval commitment study(1199-0434) within 5 years since Chronic Fibrosing ILDs with a Progressive Phenotype approval date (before Dec 14th 2025).

The rationale of performing this trial is, upon completion of the international multicentre randomized placebo-controlled Phase III trial (INBUILD, 1199-0247), to generate additional data in Chinese patients with progressive fibrosing ILDs.

The aim of the current study is to generate additional data on the efficacy of 150 mg bid nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype. The definition of the patient population is the same as in the INBUILD trial i.e. is defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT) and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD.

Patients were selected for participation in trial 1199-0247 based on the common progressive disease behaviour – or phenotype – of their ILD. Baseline characteristics of the patients and data describing the clinical course of the placebo group in trial 1199-0247 provide supportive evidence that chronic fibrosing ILDs with a progressive phenotype represent a serious or life-threatening condition similar to idiopathic pulmonary fibrosis (IPF).

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

In the group of patients with Chronic Fibrosing ILDs with a Progressive Phenotype, the natural history of the disease appears to follow a course similar to IPF with worsening of respiratory symptoms, lung function, quality of life (QoL) and functional status, as well as early mortality. The trial population of INBUILD trial (1199-0247) was characterised by moderate lung function impairment and an overall progressive phenotype similar to IPF, while representing different major categories of underlying fibrosing ILDs.

In the entire patient population, the primary endpoint of the trial was met in both co-primary populations. Treatment with nintedanib significantly reduced the annual rate of decline in FVC [mL/year] over 52 weeks compared with placebo in the overall population and in patients with HRCT with UIP-like fibrotic pattern. Analyses of time-to-event endpoints indicated reductions in clinically meaningful outcome events and provided supportive evidence for a slowing of disease progression by nintedanib.

In INBUILD trial (1199-0247), efficacy on FVC decline rate in East Asian patients which included Chinese patients was consistent with the entire study population. And it is not recommended to perform any subgroup analysis with a small sample size (15 randomized patients accounting for 2.3% of the entire study population) since the findings may be due to chance and lack clinical representativeness or statistical robustness. On the other hand, in INPULSIS trials (1199-0032 and 1199-0034), efficacy on FVC decline rate in Chinese patients was consistent with the entire study population. It is expect that Chinese patients with chronic fibrosising ILDs with a progressive phenotype can benefit from nintedanib treatment. In this study, two thirds of Chinese patients will be randomized to receive nintedanib and are expected to benefit from nintedanib treatment.

1.4.2 Risks

The observed safety profile of nintedanib for chronic fibrosing ILDs with a progressive phenotype was largely consistent with the known safety profile of nintedanib in patients with IPF and SSc-ILD. Common AEs were mostly mild or moderate in intensity. The most frequently reported AEs were gastrointestinal disorders, especially diarrhoea, nausea, and vomiting. To a lesser extent, treatment with nintedanib was associated with elevations in liver enzymes, which mostly resolved upon treatment interruption, dose reduction, or treatment discontinuation. Close monitoring is recommended in patients with risk factors for liver enzyme elevations (Asian race, females, low body weight, and advanced age). There were no new or unexpected safety concerns observed in patients with chronic fibrosing ILDs with a progressive phenotype.

Risks of nintedanib treatment also include gastrointestinal perforations, thromboembolism and bleeding. Therefore, patients who have planned major elective surgery or suffer from severe vascular disease will be excluded from this trial. Patients requiring full dose therapeutic anticoagulation, fibrinolysis or high-dose antiplatelet therapy may be considered for inclusion and/or continuation in the trial (if the requirement arises after commencement of trial participation) if the anticipated benefit of nintedanib outweighs the potential risk of bleeding. Patients with severe pulmonary hypertension will be excluded. Echocardiography is used to monitor patients with mild to moderate pulmonary hypertension.

Nintedanib may cause foetal harm. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with nintedanib and to use highly effective contraceptive methods during the clinical trial and at least 3 months after the last dose of nintedanib.

Based on the pharmacological mechanism, existing non-clinical, clinical and post-marketing data there is no indication that treatment with nintedanib may increase the risk for infection with SARS-CoV-2 or for worsening the disease course of COVID-19.

It is currently unknown if chronic fibrosing ILDs with a progressive phenotype conveys a higher risk for adverse outcomes in case of COVID-19.

Table 1.4.2:1 Overview over 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 and concomitant treatments		
Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting)	Most frequent, mostly non-serious and reversible with dose reductions, temporary drug interruption or drug discontinuation.	Increased awareness of symptoms and early management, guideline to manage gastrointestinal disorders
Hepatic enzyme increased	Frequent, mostly non-serious and reversible with dose reductions, temporary drug interruption or drug discontinuation.	Increased awareness of symptoms and early management, guideline to liver enzyme elevations.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Increased awareness and expedite reporting (AESI). Careful monitoring of liver function and early management, guideline to liver enzyme elevations. Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Teratogenic potential	Nintedanib is teratogenic.	Women of childbearing potential not willing or able to comply with contraception requirements are excluded from trial participation. Pregnancy testing in all female patients, even pre-menarche, every 4-6 weeks.

Table 1.4.2:1 Overview over trial related risks (cont.)

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 (paresthesia), 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;
Lung function measurements	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;
Other risks		
Placebo	If the patient is randomized to receive a placebo, the patient´s condition could get worse during the course of the trial.	Patients will be randomized in 2:1 ratio to either nintedanib or placebo in this trial, and more patients will benefit from the treatment of Nintedanib. Patients are allowed to be treated with the selected medication if judged necessary by the investigator
Infection with SARS-CoV-2	Based on the pharmacological mechanism, existing non-clinical, clinical and post-marketing data there is no indication that treatment with nintedanib may increase the risk for infection with SARS-CoV-2 or for worsening the disease course of COVID-19. It is currently unknown if chronic fibrosing ILDs with a progressive phenotype conveys a higher risk for adverse outcomes in case of COVID-19.	Even though an increased risk of SARS-CoV-2 infection – or of a more severe COVID-19 disease in case of such an infection appears unlikely, patients with active or recent SARS CoV-2 infection will not be included in the trial. In addition, during the course of the trial, whether or not treatment with nintedanib will be continued for a confirmed SARS-CoV-2 infection, which will be based on investigator judgement.

Table 1.4.2:1 Overview over trial related risks (cont.)

Risk related to Pandemic situations COVID-19	Travelling to site, being at site for assessments, increased infection risk for lung function testing. Patients may receive COVID-19 vaccination in line with local recommendations/guidance and approved laboratoryels.	Site visits could be reduced by using telephone visit or shipping medication to patient's home. Local laboratory could also be considered. Every subject or patient will be assessed thoroughly, and individual benefit-risk assessments are made prior to study entrance and during the study by the investigator.

1.4.3 Discussion

The benefit-risk profile of nintedanib for the treatment of chronic fibrosing ILDs with a progressive phenotype is well established and considered positive based on the evidence collected in the multiregional pivotal trial (1199-0247). A positive benefit-risk profile for nintedanib in East-Asian patients with Chronic Fibrosing ILDs with a Progressive Phenotype was shown in a subgroup analysis report of the same pivotal trial.

The aim of the current study is to generate additional data on the efficacy of 150 mg bid nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype. A placebo group is needed to allow for a true assessment of the effects of nintedanib on the rate of decline in FVC in Chinese patients. However, two thirds of Chinese patients will be randomized to receive nintedanib so that more patients can benefit from the active treatment.

2. TRIAL OBJECTIVES AND ENDPOINTS

While the efficacy and safety of nintedanib were confirmed in the multinational pivotal trial (1199-0247), in which a very limited number of Chinese patients were randomized. The aim of the post approval commitment study is to generate additional data on the efficacy and safety of 150 mg bid nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The objectives of the current trial are based on those of the INBUILD trial (1199-0247). The objective of the current trial is to generate additional data on the efficacy of 150 mg bid nintedanib in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype compared to placebo over 52 weeks. The primary endpoint is defined the same way as in the INBUILD trial (1199-0247). The efficacy of reduction in lung function decline will be measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52 weeks.

2.1.2 Primary endpoint(s)

The primary efficacy endpoint is the same as in the INBUILD trial (1199-0247), the annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks).

2.1.3 Secondary endpoint(s)

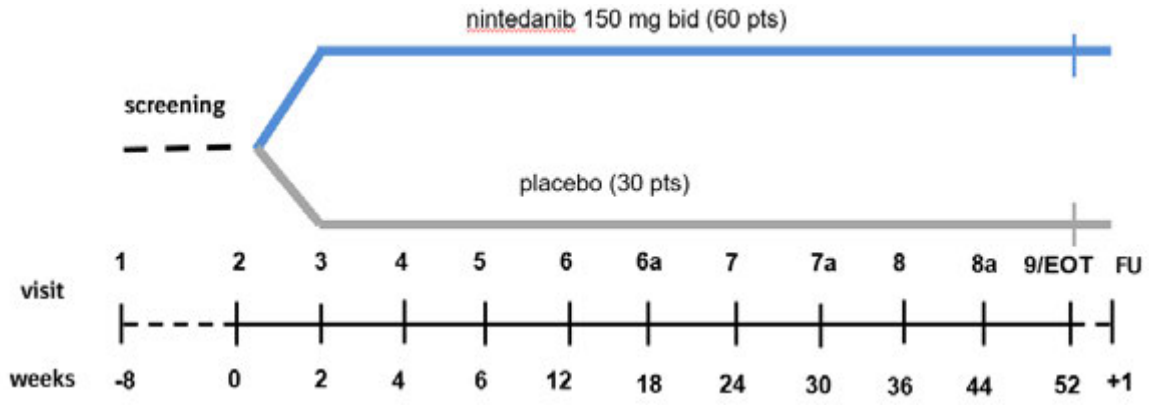
Not applicable since there is no secondary endpoint.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multi-centre, national, prospective, randomized, placebo-controlled, double blind clinical trial to generate additional data on the efficacy and safety of nintedanib at a dose of 150 mg bid, in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype over 52 weeks.

Figure 3.1:1 Trial design



A total of approximately 90 patients will be randomized, 60 in the active treatment group and 30 in the placebo group. It is planned to randomize two thirds of patients (60 patients) with UIP-like HRCT fibrotic pattern.

After signing informed consent (IC), the initial screening visit (Visit 1) will be performed to determine eligibility. Following completion of Visit 1, patients with established Chronic Fibrosing ILDs with a Progressive Phenotype, as assessed by the Investigator, will enter a screening period of maximum 8 weeks to confirm HRCT eligibility and determine HRCT pattern for randomization, and to allow for wash-out of restricted medications, if applicable.

Written confirmation by the central readers that the protocol criteria for qualifying HRCT are met will be mandatory for randomization.

Once HRCT eligibility is confirmed, Visit 2 will be scheduled to collect all clinical and safety information, and review all inclusion and exclusion criteria. Patients will be randomized in 2:1 ratio to either nintedanib or placebo and then enter the treatment phase for 52 weeks treatment. Randomization (stratified by HRCT pattern: “UIP-like fibrotic pattern”, or “Other fibrotic patterns”) will be performed by phone or Internet, using an Interactive web Response System (IRT).

The treatment duration of the study will consist of Visits 2 through 9, which will occur within one year of randomization. A follow-up visit will be performed 7 days after treatment completion.

For each patient, the study period is from the signature of the Informed Consent until their last visit. Adverse events are collected during the entire study period and are considered treatment-emergent from first study drug intake until 7 days after drug discontinuation.

All patients who prematurely discontinue trial medication will need to complete an End of Treatment (EOT) visit and a Follow-up (FU) visit 1 week later. Patients who prematurely discontinue trial medication will be asked to remain in the study and to return to all regularly scheduled visits until the end of the trial. This request will be outlined in the patient information / informed consent procedure prior to randomization.

For those patients who are unable to complete the scheduled visits, every attempt will be made to get information on vital status at 52 weeks after randomization, as well as at the end of the trial. The need for vital status information will be explained to patients prior to their participation in the trial and will be part of the patient information / informed consent procedure prior to randomization.

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

Placebo control

Chronic Fibrosing ILDs with a Progressive Phenotype is an important phenotype of ILDs introduced into academia in recent years. Due to the lack of historical data on the corresponding Chinese population there is currently no consensus on domestic and foreign guidelines for the treatment of patients with this phenotype. In the international multi-center phase III clinical trial (INBUILD trial), few Chinese subjects were included (15 cases in total, only account for 2.3% of the study population). The new indication of Nintedanib for the treatment of "Chronic Fibrosing ILDs with a Progressive Phenotype" was conditionaly approved by the CDE on 15 Dec 2020. 1199-0434 trial is asked to continue to collect data on effectiveness and safety of Nintedanib in Chinese population. Main design features from INBUILD also apply to this clinical trial, so that the results of patients in the placebo group of 1199-0434 trial will provide a control group for the effectiveness and safety of Nintedanib in Chinese patients.

In addition, patients who meet inclusion criteria of the study will be randomized into the Nintedanib group and the placebo group at a ratio of 2:1, so as a whole more patients may benefit from Nintedanib therapy.

Dose regimen

The dosing regimen to be investigated is the same as approved for IPF indication, i.e. 150 mg bid with the option of dose reduction to 100 mg and/or interruptions to manage adverse events (AEs).

The primary assessment of benefit-risk of nintedanib in patients with Chronic Fibrosing ILDs with a Progressive Phenotype will be based on efficacy and safety data over 52 weeks (12 months) of study treatment. As shown in INBUILD this is based on that Chronic Fibrosing

ILDs with a Progressive Phenotype is similar to IPF and the treatment effect of nintedanib demonstrated in IPF will be reproduced in Chronic Fibrosing ILDs with a Progressive Phenotype.

In IPF, the association between decline in FVC over one year and clinical outcome has been examined in the scientific literature (R10-6539, R06-4127, P12-10347, R14-1150, P14-06844, R14-1149). While these publications do not, by stringent statistical criteria, prove that reduction in the annual rate of FVC decline is a surrogate for improved survival, they do strongly suggest that an increased rate and extent of decline in FVC at 12 months is associated with an increased risk of death. Due to the shown similarity in disease progression, especially for FVC decline and mortality, between Chronic Fibrosing ILDs with a Progressive Phenotype patients and IPF patients, the proposed benefit-risk assessment over12 months is regarded as the most appropriate period to detect a difference in the reduction of FVC decline between nintedanib and placebo in Chronic Fibrosing ILDs with a Progressive Phenotype patients.

Primary endpoints

The primary endpoint of the study is the annual rate of decline in forced vital capacity (FVC). In clinical trials in IPF, FVC is an established efficacy parameter; mean changes in FVC over time are considered relevant to assess the effect of a pharmacologic intervention at population level (P11-13635, P12-10347, R06-4126, R06-4127). FVC as primary endpoint has served as basis for worldwide regulatory approvals for nintedanib and pirfenidone in IPF (P14-07514, P10-13367).

Similar to IPF, in other interstitial lung diseases (ILDs) the accelerated decline in lung function over time is considered consistent with disease progression and is thought to be associated with mortality (R10-6539, R06-4127, P12-10347, R14-1150, P14-06844, R14-1149). In Chronic Fibrosing ILDs with a Progressive Phenotype, and even more so for patients with Chronic Fibrosing ILDs with a Progressive Phenotype with histologic usual interstitial pneumonia (UIP) pattern, it is expected that the placebo decline in FVC is similar to the decline observed in patients with IPF and that nintedanib will slow the decline in FVC in a similar way as it does in IPF.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 90 patients with Chronic Fibrosing ILDs with a Progressive Phenotype will be randomized (60 in the active dose group and 30 in placebo) in China.
It is planned to randomize approximately two thirds of patients with UIP-like HRCT fibrotic pattern. This will allow for a certain enrichment of patients with more rapid progression, as has been shown in INBUILD. Patients with clinical diagnosis of IPF will be excluded from the current study.

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

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Outpatients aged ≥ 18 years with Chronic Fibrosing ILDs with a Progressive Phenotype, defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on HRCT and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD, are eligible for inclusion if they fulfil all the inclusion criteria (Section 3.3.2) and do not present any of the exclusion criteria (Section 3.3.3).

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

3.3.2 Inclusion criteria

1. Written Informed Consent consistent with ICH-GCP and local laws signed prior to entry into the study (and prior to any study procedure including shipment of HRCT to reviewer).
2. Male or female patients aged ≥ 18 years at Visit 1.
3. Patients with physician diagnosed ILD who fulfil at least one of the following criteria for Progressive Phenotype within 24 months of screening visit (Visit 1) despite treatment with unapproved medications used in clinical practice to treat ILD, as assessed by the investigator (refer to Section 3.3.3):
    a. Clinically significant decline in FVC % predicted based on a relative decline of ≥10%
    b. Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with worsening of respiratory symptoms
    c. Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with increasing extent of fibrotic changes on chest imaging
    d. Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging

    [Note: Changes attributable to comorbidities e.g. infection, heart failure must be excluded. Unapproved medications used in the clinical practice to treat ILD include but are not limited to corticosteroid, azathioprine, mycophenolate mofetil (MMF), n-acetylcysteine (NAC), rituximab, cyclophosphamide, cyclosporine, tacrolimus].

4. Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 12 months of Visit 1 as confirmed by central readers.
5. For patients with underlying CTD: stable CTD as defined by no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1.
6. FVC ≥ 45% predicted at Visit 2.

3.3.3 Exclusion criteria

1. AST and / or ALT > 1.5 x ULN at Visit 1
2. Bilirubin > 1.5 x ULN at Visit 1
3. Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula at Visit 1.

   [Note: Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. Visit 2 laboratory results will be available only after randomization. In case at Visit 2 the results do no longer satisfy the entry criteria, the Investigator has to decide whether it is justified that the patient remains on study drug. The justification for decision needs to be documented. Laboratory parameters that are found to be abnormal at Visit 1 are allowed to be re-tested (once) if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign) or the result of a temporary and reversible medical condition, once that condition is resolved].
4. Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment).
5. Previous treatment with nintedanib or pirfenidone.
6. Other investigational therapy received within 1 month or 6 half-lives (whichever was greater) prior to screening visit (Visit 1).
7. Use of any of the following medications for the treatment of ILD: azathioprine (AZA), cyclosporine, MMF, tacrolimus, oral corticosteroids (OCS) >20mg/day and the combination of OCS+AZA+NAC within 4 weeks of Visit 2, cyclophosphamide within 8 weeks of Visit 2, rituximab within 6 months of Visit 2. Equivalent Doses of Corticosteroids refer to Appendix 10.3.

   Note: Patients whose RA/CTD is managed by these medications should not be considered for participation in the current study unless change in RA/CTD medication is medically indicated (refer to Inclusion Criterion #5)
8. Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2018 Guideline [R18-2794].
9. Diagnosis of Systemic Sclerosis (SSc) based on 2013 ACR/EULAR classification
10. Significant Pulmonary Arterial Hypertension (PAH) defined by any of the following:
    a. Previous clinical or echocardiographic evidence of significant right heart failure
    b. History of right heart catheterization showing a cardiac index ≤ 2 l/min/m²
    c. PAH requiring parenteral therapy with epoprostenol/treprostinil

11. Primary obstructive airway physiology (pre-bronchodilator FEV1/FVC < 0.7 at Visit 1).
12. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
13. Major extrapulmonary physiological restriction (e.g. chest wall abnormality, large pleural effusion)
14. Cardiovascular diseases, any of the following:
    a. Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 month of Visit 1
    b. Myocardial infarction within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1
15. Bleeding risk, any of the following:
    a. Known genetic predisposition to bleeding.
    b. Patients who require
        i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
        ii. High dose antiplatelet therapy.

    [Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited].

    c. History of haemorrhagic central nervous system (CNS) event within 12 months of Visit 1.
    d. Any of the following within 3 months of Visit 1:
        i. Haemoptysis or haematuria
        ii. Active gastro-intestinal (GI) bleeding or GI – ulcers
        iii. Major injury or surgery (Investigators judgment).
    e. Coagulation parameters: International normalized ratio (INR) >2, prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) by >1.5 x ULN at Visit 1.
16. History of thrombotic event (including stroke and transient ischemic attack) within 6 months of Visit 1.
17. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin)
18. Patients with peanut allergy.

19. Other disease that may interfere with testing procedures or in the judgment of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial.
20. Life expectancy for disease other than ILD < 2.5 years (Investigator assessment).
21. Planned major surgical procedures.
22. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
23. Women of childbearing potential* not willing or able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to and 3 months after nintedanib administration. A list of contraception methods meeting these criteria is provided in the patient information.
24. In the opinion of the Investigator, active alcohol or drug abuse.
25. Patients not able to understand or follow trial procedures including completion of self-administered questionnaires without help.
26. The patient has a confirmed infection with SARS-CoV-2** within the 4 weeks prior to Visit 1 and/or during the screening period.

*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.

**Testing for SARS-CoV-2 is not the part of this trial. If required this needs to be done per local requirements or investigator's assessment.

3.3.4 Imaging criteria

Patients with original physician diagnosis of different fibrosing ILDs, e.g. CTD-ILD, chronic fibrosing HP, iNSIP, unclassifiable IIP and environmental/ occupational fibrosing lung disease will be included if they meet the protocol criteria for PF-ILD. While the clinical ILD diagnosis will not be verified, central review of the screening HRCT images will ensure that relevant lung fibrosis is present and the HRCT pattern is not indicative of other causes of progression.

At screening the recent (not older than 12 months at screening) HRCT image of the patient will be evaluated; previous HRCT images will not be collected or reviewed. Hence inclusion based on increasing extent of fibrotic changes on chest imaging within 24 months will reflect the investigator's judgement.

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

The following co-existing features will be accepted:

- Ground glass opacity

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

The following co-existing features will not be allowed:
- Widespread consolidation
- Progressive massive fibrosis

In addition, determination of the HRCT pattern will also be done by central review and will be used for randomization stratification. The study will be enriched for patients meeting either criteria A, B and C, criteria A and C, or criteria B and C as described below. These patients will be referred to as "patients with HRCT with UIP-like fibrotic pattern only". Patients with PF-ILD who do not meet these criteria will be referred to as "patients with other HRCT fibrotic patterns".

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

Specifications for the HRCT acquisition will be provided in the ISF. Screening HRCT can be performed as part of the study in case the available HRCT does not meet the required image acquisition specifications.

3.3.5 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.5.1 and 3.3.5.2 below.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.

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

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

3.3.5.1 Discontinuation of trial treatment

Short term interruptions for adverse events (see also Section 4.2) are possible and should be used whenever possible to avoid permanent discontinuation of trial medication

The following will require a permanent discontinuation of trial treatment of an individual patient:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient can no longer receive trial treatment for medical reasons (such as chronic use of concomitant medication, adverse events, other diseases that puts a patient at risk, parenteral feeding requirement or pregnancy).
- The patient experiences signs of hepatic injury, defined in Section 5.2.6.1.4.
- No further dose reduction is possible for patients on the 100 mg bid regimen. In case of persistent adverse events observed at this dose, or severe effects at 150 mg bid, permanent treatment discontinuation should be considered.

Temporary interruption (see also Section 4.2.1) or permanent discontinuation of trial treatment is recommended (at the investigators discretion) for the following situations:

- Major surgery, including any abdominal or intestinal surgery.
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
- Increased risk of bleeding e.g. hemorrhagic CNS event, haemoptysis or haematuria, active gastro-intestinal bleeding or GI-ulcers.
- The patient experiences an infection with SARS-CoV-2.

The investigator, after assessment of available clinical data and taking into consideration the potential risks associated with administration of nintedanib, may decide not to permanently discontinue the trial medication. In such a case, continuation of treatment with trial medication should be discussed with the patient, and the decision and reasoning documented in the source data.

If a patient becomes pregnant during the trial, the investigational product must be stopped and the patient should be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report (CTR) until patient's last visit and any events thereafter will be reported in the BI drug safety database. Refer to Section 5.2.6.2.3 for detailed information on event reporting in case of pregnancy.

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

If a patient discontinues the trial medication prematurely, it is of utmost importance for the robustness and integrity of the trial results that his/her lung function parameters and safety data are further recorded until the end of the trial. Patients, who prematurely discontinue trial medication, will be asked to follow their original visit schedule (refer to Section 6.2.3).

3.3.5.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between permanent trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the importance for continued follow-up after trial treatment discontinuation.

Withdrawal of consent to trial participation is defined as the refusal to provide any further data, not even provide a vital status (either by contact or medical records) at the end of the planned observation period.

3.3.5.3 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 3.3.5.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of patients affected will occur as described in Section 3.3.5.1. The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Identity of BI investigational product(s)

Substance:	Nintedanib
Pharmaceutical formulation:	Soft gelatin capsule
Source:	BI Pharma GmbH & Co. KG
Unit strength:	150 mg,100mg
Posology:	b.i.d
Mode of administration:	Oral (swallowed)

Substance:	Placebo matching in size, weight, colour and shape to 150 mg and 100mg soft gelatin capsule of Nintedanib
Pharmaceutical formulation:	Soft gelatin capsule
Source:	BI Pharma GmbH & Co. KG
Unit strength:	n.a
Posology:	b.i.d
Mode of administration:	Oral (swallowed)

4.1.2 Selection of doses in the trial and dose modifications

Based on the efficacy and safety from trials investigating nintedanib in IPF and the multiregional pivotal trial (1199−0247), a dose of 150 mg bid is selected for the Chronic Fibrosing ILDs with Progressive Phenotype program. With 150 mg bid, acceptable tolerability in Chronic Fibrosing ILDs with Progressive Phenotype patients is expected based on the risk profile seen in IPF patients. Similar to IPF and SSc-ILD, a prior dose reductions are not indicated and the proposed dosing regimen of 150 mg bid including the option to

reduce the dose to 100 mg bid or interrupt treatment to manage adverse event is considered to offer the best benefit-risk ratio, i.e. to optimize exposure-efficacy versus exposure-tolerability in the individual patient taking into account the moderate to high inter-patient variability in plasma exposure.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomized to treatment groups according to a randomization plan in a 2:1 ratio at visit 2 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

The randomization will be stratified according the background status of the patient (either UIP-like or non-UIP) via Interactive Response Technology (IRT). When we recruit 30 non-UIP patients (or 60 UIP patients), we will stop recruiting non-UIP patients (or UIP patients).

Each patient fulfilling all in- and exclusion criteria will be randomized via IRT at Visit 2 to one of the 2 following arms in a 2:1 ratio:

- Nintedanib 150 mg b.i.d
- Placebo b.i.d

4.1.4 Drug assignment and administration of doses for each patient

Table 4.1.4: 1 Dosage and treatment schedule

Treatment arm	Nintedanib 150 mg	Placebo matching 150 mg	Nintedanib 150 mg	Placebo matching 150 mg
	Morning		Evening	
Nintedanib 150 mg	1		1	
Placebo		1		1

Based on the treatment allocated at randomization, the IRT system will be used to dispense the appropriate medication kits at each visit. Patient will receive either active drug at a dosage of 150 mg bid or placebo bid.

The patients should take the trial medication with food, swallow whole with water, and should not be chewed or crushed because of a bitter taste, and should observe a dose interval of 12 hours as far as possible. Effort should be made to ensure that drug administration occurs at the same time every day +/- 30 min (between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening). A forgotten dose should be skipped if the time window to the next dose is less than 8 hours. The next dose should be taken as scheduled. The recommended maximum daily dose of 300 mg should not be exceeded.

The dose may be reduced to 100 mg bid due to AE after the investigator assessment. The investigator can dispense new medication kits with 100mg to the patient via IRT system.

A patient diary will be used to record the daily intake of the trial medication.

Trial medication will consist of 1 capsule twice daily (bid) administered orally throughout the study. Wallets covering 30 days + 5 days reserve treatment will be dispensed to the patient:

- 1 wallet at Day 1 (randomization = Visit 2) (30 days plus 5 days reserve)
- 2 wallets from Visit 4 (60 days plus 10 days reserve)
- 3 wallets from Visit 6 (90 days plus 15 days reserve)
- 3 Wallets from Visit 7 (90 days plus 15 days reserve)
- 4 wallets from Visit 8 (120 days plus 20 days reserve)

To ensure patients receive adequate supply of study medication, kits will be dispensed at clinical visits in quantities as outlined in Table 4.1.4: 2.

Table 4.1.4: 2 Number of IMP kits dispensed at each visit

Study visits	2	3	4	5	6	6a	7	7a	8	8a	9
Number of IMP kits dispensed	1	—	2	—	3	—	3	—	4	—	—

During the COVID-19 pandemic, physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment and trial medication may be shipped directly to the patients' home if acceptable according to local law and regulations. In agreement with the sponsor, a home visit service or telemedicine may assist the patient with medication administration.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock.
The access to the randomization code will be kept restricted until its release for analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page. However, treatment information is not to be further distributed.

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

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor 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 and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. 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 investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the

sponsor, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Rescue medication to reverse the action of nintedanib is not available.

Dose reduction from 150 mg bid to 100 mg bid or treatment interruption should be considered to manage adverse events. No further dose reduction is possible for patients on the 100 mg bid regimen. In case of persistent adverse events observed at this dose, or severe effects at 150 mg bid, permanent treatment discontinuation should be considered.

Treatment interruption, reduction and re-increase are allowed at multiple occasions.

Table 4.2.1: 1 Allowed treatment reduction / interruption periods:

	AEs considered related to study drug	**AEs not considered related to study drug**
Maximum interruption	4 weeks	8 weeks
Recommended restart	with reduced dose (100 mg bid)	with the same dose as before interruption (100 mg bid or 150 mg bid)
Re-escalation	within 4 weeks to 150 mg bid	N/A

4.2.1.1 Management of diarrhoea

Diarrhoea is a known side effect of nintedanib treatment (see Section 1.4.2). However, potential causes for diarrhoea other than study medication should always be considered and treated accordingly (e.g. viral infections, bacterial overgrowth, antibiotic treatment).

Diarrhoea should be managed as early as possible after onset of first symptoms with standard antidiarrheal symptomatic treatment, e.g. loperamide.

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and/or dose reduction of nintedanib to 100 mg bid should be considered according to the recommendations described in Table 4.2.1.1: 1.

Table 4.2.1.1: 1 Management of diarrhoea (considered related to trial medication)

Description	Symptomatic Treatment*	Action with trial medication
Diarrhoea with increase of <4 stools per day over baseline[1].	Initiate anti-diarrheal medicines at first signs of symptoms (e.g. 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day) until bowel movements cease for 12 hours.	Continue same trial medication dose.
Diarrhoea with increase of 4 to 6 stools per day over baseline[1].	Initiate/continue anti-diarrheal medicines; If diarrhoea of this severity persists for ≥48 to 72 hours assess for dehydration and electrolyte imbalance; In addition, consider IV fluids and electrolyte replacement as clinically indicated.	If diarrhoea persists for ≥48 to 72 hours despite optimal symptomatic care: 1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Re-escalate to 150 mg bid within 4 weeks if deemed clinically appropriate.
Diarrhoea with increase of ≥7 stools per day over baseline[1]; stool incontinence, or life threatening consequences.	Follow recommendations above. In addition, consider stool work-up to exclude infectious colitis; adequate IV fluid replacement ≥24 hours, hospitalization as clinically indicated; consider referral to a GI specialist to rule out potential differential diagnoses.	1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Consider re-escalation within 4 weeks to 150 mg bid if deemed clinically appropriate. In case of reoccurrence of diarrhoea of this severity despite optimal symptomatic treatment and dose reduction, treatment with trial medication should be permanently discontinued.

Footnotes:

* Other potential causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment)

[1] Baseline defined as usual stools/day prior randomization.

4.2.1.2 Management of liver enzyme elevation

Nintedanib can be associated with increased liver enzymes (see Section 1.4.2). Concomitant use of other drugs known to cause liver enzyme elevations should be evaluated. For a detailed guidance on how to manage liver enzyme elevations, please refer to Table 4.2.1.2: 1.

Table 4.2.1.2: 1 Recommendations for managing liver enzyme elevations

	AST and/or ALT increase to			Signs of hepatic injury* (Section 5.2.6)
	>1.5x to <3x ULN	≥3x to <5x ULN and no signs of hepatic injury (see Section 5.2.6)	≥5x to <8x ULN and no signs of hepatic injury (see Section 5.2.6)	
Visit 2 (randomization)	Withdraw trial medication or justify continuation[1]	Withdraw trial medication	Withdraw trial medication	Withdraw trial medication
Any other Visit	Continue as planned[2]	Reduce dose or interrupt trial medication [3]	Interrupt trial medication	Withdraw trial medication
		Close observation[4] After 2 weeks or any time later	Close observation[4] After 2 weeks or any time later	**CLINICAL EVALUATION OF HEPATIC INJURY** (Section 5.2.6.1.4)
	<3x ULN	≥3x ULN	< 3x ULN	≥3x ULN
	Reduced: return to initial dose. Interrupted: restart at reduced dose. Monitor bi-weekly for at least 8 weeks	Permanently discontinue trial medication Close observation[4]	Restart at reduced dose Monitor weekly for 4 weeks, then bi-weekly for at least 8 weeks	Permanently discontinue trial medication. Close observation[4]

Footnotes:

[*] Signs of hepatic injury are defined as

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold ULN and unexplained INR >1.5
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

[1] Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).

[2] According to visit schedule. Consider additional control visits as adequate.

[3] To be decided by Investigator, based on individual risk assessment.

[4] Close observation: Re-test ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks by using intermediate visit laboratory kit.

4.2.1.3 Management of acute ILD exacerbations

In case of acute ILD exacerbation (see Section 5.1.2), all treatment options considered adequate by the Investigator are allowed. The patient may interrupt study treatment for up to 8 weeks, if necessary (e.g. if short-term full anticoagulation is performed).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The aim of the study is to generate additional data on the efficacy and safety of nintedanib in patients whose progressive lung disease is the main contributor to morbidity.

Treatment of ILD

Immunomodulatory medications i.e. Azathioprine, cyclosporine, tacrolimus, Rituximab, Cyclophosphamide, mycophenolate mofetil, OCS have been utilized in the clinical practice for the treatment of ILD although their benefit-risk profiles in ILD have not been established and they are not approved for the treatment of ILD in China. In order to avoid the potential impact of these drugs on the assessment of the efficacy and safety of nintedanib in PF-ILD, their use will not be allowed at randomization and during the first six months of the treatment period.

Patients who receive any of these medications for the treatment of their ILD will have to discontinue these drugs prior to randomization. As the protocol requires that eligible patients progress despite treatment with these medications (i.e. do not or no longer benefit from these drugs), prohibition of these medications is considered justified. In case of acute worsening of PF-ILD during the treatment period, the use of any of these drugs after six months of study treatment will be allowed if judged necessary by the investigator.

Treatment of the underlying diseases associated with ILD

The largest group of patients with Chronic Fibrosing ILDs with a Progressive Phenotype that has an underlying disease associated with ILD is the group of patients with CTD. Eligible patients with underlying CTD should have *stable* CTD defined as no initiation or withdrawal of therapy for CTD within six weeks prior to screening. In addition, investigators are encouraged to maintain the baseline treatment of CTD during the entire study unless change is medically indicated.

The majority of the eligible patients with CTD is expected to have RA and to be receiving disease-modifying anti-rheumatic drug (DMARD) e.g. methotrexate or TNF inhibitors. All approved RA/CTD medications are allowed at stable doses at Baseline (Visit 2) and during the study with the exceptions of the following, less frequently used medications: Azathioprine, cyclosporine, tacrolimus, high dose steroids, and Rituximab. The use of these medications will not be allowed in this study. In addition, the following drugs used off-label

for the treatment of RA/CTD will not be allowed throughout the study: Cyclophosphamide and MMF.

The rationale for these limitations is that, as described above, these drugs have also been utilized in the clinical practice for the treatment of ILD. In order to avoid the potential impact of these drugs on the assessment of the efficacy and safety of nintedanib in Chronic Fibrosing ILDs with a Progressive Phenotype, their use will not be allowed.

Patients whose RA/CTD is well managed by these medications should not be considered for participation in the current study. In case a change in the RA/CTD treatment to another non-restricted medication is indicated, the patient's disease has to be stable (i.e. no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1) before entering in the current trial.

Table 4.2.2.1: 1 Medication restrictions

Restricted medications: Azathioprine, cyclosporine, tacrolimus, Rituximab, Cyclophosphamide, mycophenolate mofetil, OCS >20mg/day, investigational drugs		
	For ILD	**For CTD**
Baseline	Not allowed at V2*	Not allowed
Within first 6 months of study treatment	Not allowed	Not allowed
After 6 months of study treatment	Allowed in case of significant deterioration#	Allowed case of significant deterioration #
After EOT	Allowed	Allowed

* Wash-out periods to be observed as described in Table 4.2.2.1: 2 below

All can be used in case of clinically significant deterioration of Chronic Fibrosing ILDs with a Progressive Phenotype or worsening CTD at the discretion of the Investigator, except for investigational drugs. Introduction of new therapy for CTD should be minimized.

Table 4.2.2.1: 2 Wash-out schedule. Wash-out rules apply only for medications used for ILD treatment.

Medication	Wash-out period
Azathioprine Cyclosporine Tacrolimus Mycophenolate mofetil OCS >20mg/day	4 weeks prior to Visit 2
Rituximab	6 months prior to Visit 2
Cyclophosphamide	8 weeks prior to Visit 2
Investigational drug(s)	4 weeks or 6 half-lives (whichever is longer) prior to Visit 1

In case of clinically significant deterioration, initiation of additional therapy for ILD i.e. on top of the study medication is allowed after completion of the 6-month study visit (Visit 7) as described in Table 4.2.2.1:1, as determined by the Investigator. For example, introduction of additional therapy may be considered if the patient experiences ≥ 10% relative decline in FVC% pred from baseline that is not attributed to a reversible process (i.e. respiratory infection). Detailed (S)AE information following such events should be recorded in the eCRF. Please also refer to cautionary notes (Section 4.2.2.2).

Prohibited medications

As detailed in the exclusion criteria, patients receiving *pirfenidone, nintedanib, full dose therapeutic anticoagulation or high dose antiplatelet therapy* (e.g. acetyl salicylic acid >325 mg/day, or clopidogrel >75 mg/day, or equivalent doses of other antiplatelet therapy) are not eligible for participation in the study.

The use of pirfenidone and nintedanib are prohibited throughout the study, including the Follow-up period.

4.2.2.2 Cautionary notes

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Co-administration with oral doses of a potent P-gp and CYP3A4 inhibitors, e.g. ketoconazole, erythromycin, may increase exposure to nintedanib. In such cases, patients should be monitored closely. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with nintedanib.

Co-administration with oral doses of a potent P-gp and CYP3A4 inducers, e.g. rifampicin, carbamazepine, phenytoin, and St. John's wort may decrease exposure to nintedanib and should be avoided.

As the most common side effects known for nintedanib are GI effects i.e. diarrhoea, nausea and vomiting (see Section 4.2.1.1) the concomitant use of medication with an overlapping safety profile (e.g. mycophenolate mofetil) should be carefully considered.

Nintedanib is also associated with increases in liver enzymes and bilirubin. If in addition to the trial medication, a treatment is introduced that is known to induce AST/ALT elevations (e.g. methotrexate, bosentan), additional measurements of liver enzymes (ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils) every 2 weeks for approximately 6 weeks, by using intermediate (a-visit) trial laboratory kit are recommended.

4.2.2.3 Restrictions on diet and life style

There are no restrictions on diet and life style.

4.2.2.4 Contraception requirements

The anti-angiogenic properties of nintedanib indicate a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality.

WOCBP (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.) and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 3 months after last trial drug intake, and 28 days before treatment initiation, one barrier method, and one highly effective non-barrier method.

Men able to father a child must use two medically approved methods of birth controlthroughout the trial, and for a period of at least 3 months after last trial drug intake: one barrier method, and one highly effective non-barrier method.

Men (trial participant or partner of a trial participant) must be vasectomised with documented absence of sperm or use a condom if their sexual partner is a WOCBP.
WOCBP (trial participant or partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 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).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

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

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

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 FVC

Spirometry measurements will be performed according to ATS/ERS 2005 guideline (P05-12782). FVC will be assessed using standardised spirometry equipment which will be provided centrally with supplies of pre-calibrated disposable flow sensors. These sensors demonstrate variability within the required standards of +/-3% determined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [P05-12782]. 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 while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with preferably a maximum of five manoeuvres.

Efforts should be made, to schedule the spirometric measurements at approximately the same time of the day, with reference to baseline measurement (Visit 2). On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking should be discouraged throughout the visit days (clinic visit) and will not be permitted in the 30-minute period prior to spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes). If treated with bronchodilators, wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry. Spirometry results will be electronically transmitted. To ensure the quality of 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.

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

[redacted]

[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the Flow Chart.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

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

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the Flow Chart.
All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4 and the DILI Checklist provided in the ISF eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3:1 Safety laboratory tests

Category	Laboratory test
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK) Creatine kinase (CK) Lactate dehydrogenase (LDH) Total protein Total bilirubin Brain natriuretic peptide (BNP at V2, V7, V9 and EOT) Creatinine Glucose (non fasting) Uric acid

Table 5.2.3:1 Safety laboratory tests (cont.)

Biochemistry	Thyroid stimulating hormone (only at V2, V7, V9, and EOT)
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalized ratio (INR) Activated partial thromboplastin time (aPTT) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)
ß-HCG will be performed at Visit 2 only, at central laboratory. Urine dipstick pregnancy tests will be provided by central laboratory and should be performed in all women of childbearing potential every 4-6 weeks. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

The laboratory tests at intermediate ‘a’ visits will include:

Category	Laboratory test
Biochemistry	Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)
Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

At ‘a-Visits’, safety blood, pregnancy tests and urine samples will be collected and submitted to the central laboratory if needed for additional safety monitoring at the discretion of the investigator (see Section 4.2.2.2 for additional safety monitoring).

The samples and pregnancy tests may be collected at the office of a local doctor using trial specific lab kits that will be sent to a central laboratory for analyses. These kits will be provided to patients at study visits as applicable.

Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2).

If laboratory values indicate abnormality, adequate and more frequent blood sampling may be performed at the discretion of the Investigator.

In case of liver function value elevations, close monitoring must be ensured by the Investigator. Refer to Section 4.2.1.2 for monitoring elevations and Section 3.3.5 for withdrawal criteria.

Laboratory analysis will be done using central laboratory services. Venous whole blood will be collected through the assigned central laboratory. Details regarding centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the Sponsor. The Investigators will be informed and instructed by the central laboratory and detailed documentation will be included in the ISF.

5.2.4 Electrocardiogram

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

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

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

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.
The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

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 5.2.6.2, subsections “AE Collection” and “**AE reporting to sponsor and timelines”.**

5.2.6.1.4 Adverse events of special interest

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

Adverse events relating to gastrointestinal perforation and hepatic injury will be considered AESIs.

Hepatic injury
In this trial protocol, signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
- ALT and/or AST ≥3 fold ULN and unexplained INR > 1.5*
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without 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.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

In addition the intensity of diarrhoea adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for adverse events (CTCAE) (Version 4)

Table 5.2.6.1.5:1 CTCAE Categorization for diarrhoea

CTCAE Grade	**Diarrhoea**
1	Increase of <4 stools per day over baseline
2	Increase of 4 to 6 stools per day over baseline

Table 5.2.6.1.5:1 CTCAE Categorization for diarrhoea (cont.)

3	Increase of ≥7 stools per day over baseline; stool incontinence
4	Life threatening consequences
5	Death

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account 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.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

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

Vital Status Data Collection

Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.5.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

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

5.2.6.2.3 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

Not applicable.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. Such alternative measures may be described in a specific Crisis Management Manual as part of the initial submission package, and will also be mentioned in the patient information leaflet. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

The study will consist of three sequential periods, a Screening period of up to 8 weeks, a treatment period of 52 weeks and a follow-up period of 1 week. The maximum duration is expected to be 437 days.

After giving his/her informed consent, the patient will be screened for inclusion (see Section 3.3.2) and exclusion criteria (see Section 3.3.3) for the trial at Visit 1 and Visit 2 (refer to Flow Chart).

Visit 2 can be performed once the results from central laboratory of Visit 1 and central HRCT review are obtained. If for any reason the screening phase for an individual patient lasts for more than 6 weeks, then the laboratory examination for Visit 1 has to be repeated before randomization. The screening phase must be no longer than 8 weeks. The patient will be randomized at Visit 2 if all inclusion and none of the exclusion criteria are fulfilled.

The results of laboratory parameters from Visit 2 will become available only after Visit 2. Therefore, laboratory results from Visit 2 cannot qualify as exclusion criteria; laboratory results from Visit 1 will be used instead. In case laboratory results of Visit 2 would retrospectively fulfil an exclusion criterion, the patient should not continue receiving trial medication unless continuation is justified in writing by the Investigator.

A window of ±3 days for Visits 3 to 6, ±7 days for Visits 6a to 9 is allowed to accommodate scheduling problems. If a delay is observed for a particular visit, the original calendar schedule should be kept for subsequent visits (delays should not accumulate).

If treatment is discontinued, an end of treatment visit (EOT) will be performed in all patients.

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

In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks, the investigator needs to further discuss with the sponsor and then makes a decision how to arrange the related visits.

All home/remote visits need to be discussed with and approved by the sponsor`s trial team. Local regulatory and legal requirements still apply.

For the details of the modifications refer to Section 6.2.

All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

Except for visit 1, visit 2 and EOT visit, in the event of force majeure or other disrupting circumstances the other visits may have to be performed at the patient's home after alignment with sponsor, remotely (by phone) or as a combination of home and remote visits. At these visits, the following assessments can be performed at the Patient's home or remotely:

- Concomitant therapy
- Pregnancy testing (urine) if need
- review results if some assessments can be done at local hospital except for FVC, please refer to Flow Chart for more details.
- all AEs / SAEs / AESIs
- IRT call after completing the above assessment, include the test results review from local laboratory
- Dispense trial medication
- compliance check

Trial medication will not be collected at visits performed remotely. Instead, the medication should be collected when the patient next visits the site, or when a visit is performed at the patient's home (see below).

The following assessments can be performed at the patient's home:

- vital signs
- physical examination if possible
- resting 12-lead ECG (using a portable ECG machine) if possible
- safety laboratory sampling and review of results if possible
- collect trial medication

If safety laboratory sampling via the central laboratory is not possible from the investigational site (and is instead performed at the patient's home or local hospital), analyses can be performed at a local laboratory. The results of the safety laboratory tests must be transferred to the Investigator who must ensure a medical review and document any clinically relevant safety issues as AEs. For a list of "minimum required safety laboratory parameters" refer to Section 5.2.3 and Table 5.2.3: 1.

When scheduling such visits every effort should be made to ensure a continuous supply of trial medication for the patient, whilst also taking into account that the next kit(s) of trial medication may need to be shipped from the site to the patient's home and, that medical pre-requisites should be performed and confirmed prior to shipment of new supplies.

The investigators should ensure as much as possible that FVC assessment can be finished on site for every visit.

All deviations from the original schedule of assessments as defined in the Flow Chart will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period(s)

Screening Period
All trial procedures at selected visits will be done according to Flowchart and footnotes and the CTP.

Informed consent (before or at the latest at Visit 1)

- Informed consent will be obtained prior to patient participation in the trial, which includes any medication wash-out procedures or restrictions as well as HRCT transfer to central review. Upon obtaining informed consent, the patient will be instructed on the medication washout and other restrictions needed.
- A preliminary check of in-/exclusion criteria is recommended at time of informed consent to avoid unnecessary wash-out procedures in non-eligible patients.
- An HRCT not older than 12 months will be sent for central review, after the investigator's evaluation,
  - to confirm that the extent of features of fibrosis is >10% is in accordance with the inclusion criteria (see Section 3.3.2),
  - to assess HRCT pattern for stratification.

Provided the patient meets all other eligibility criteria, the HRCT can be performed for the purposes of participation in the trial if the patient does not have a HRCT within 12 months at the time of the scheduled Visit 2 or the HRCT available does not meet the image acquisition specifications of the study.

- Site personnel will perform a screening registration in IRT to ensure in-time trial medication shipment.
- Upon obtaining informed consent the patient will receive a trial identification card.

Observations and procedures at Visit 1

- If a separate informed consent Visit was not done, obtaining informed consent and the above mentioned procedures will be done prior to any further procedure at this visit.

- Demographics will be recorded.
- Medical history including pre-existing conditions and smoking status will be recorded.
- Concomitant therapy including previous medications will be recorded.
- Any adverse events (since consent, if applicable) will be recorded.
- Local urine pregnancy test (dipstick) will be done, if applicable (see Section 5.2.3).
- Physical examination including vital signs will be performed.
- A resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated by the Investigator (if possible prior to blood draw).
- FVC measurement will be conducted with the spirometer.
- Blood and urine samples (safety laboratory) will be collected and submitted to the central laboratory (for details refer to Section 5.2.3). Prior to blood draw a pre-assessment of all inclusion and exclusion criteria is highly recommended.
- Site personnel will send/upload HRCT to central review (if not already done at time of informed consent).
- For patients qualified to enter the screening period, Visit 2 will be scheduled.

6.2.2 Treatment period(s)

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

The order of the different trial procedures should follow the protocol and should be planned for taking into account the specific structure of the investigational site and following the mandatory needs outlined in the clinical trial protocol.

Mandatory needs: the following has to be ensured during trial visits according to the study Flow Chart.

- Patient reported L-PF Symptoms and Impact questionnaires have to be filled out always prior to any other procedures by the patient in a quiet area and in the following order.
- Urine pregnancy test and any laboratory sample collection must be performed prior trial medication administration.
- FVC measurement at all visits should be performed approximately at the same time of the day to reference time point at Visit 2.

Baseline Visit 2 (randomization)

The following prerequisites must be available for randomization:

- Eligibility confirmation and HRCT pattern from central HRCT review.
- Safety laboratory results including haemoglobin and creatinine from Visit 1.

Procedures:

- All patients will be asked to fill out the patient reported L-PF Symptoms and Impact questionnaires prior to any other visit procedure.
- Site personnel will review questionnaires for completeness.
- Physical examination including vital signs will be performed.

- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- Medical history will be reviewed.
- Repeated resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated if resting ECG was abnormal at Visit 1 (if possible prior to blood draw).
- FVC measurement will be conducted with the spirometer.
- All in/exclusion criteria will be assessed based on Visit 1 laboratory and Visit 2 measures.
- HRCT will be performed in patients who agree to have follow-up HRCT done as part of the trial, unless a screening HRCT was done as part of the study to determine eligibility.
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- Local urine dipstick pregnancy test (if applicable).
- If a patient is eligible for the trial, randomization will be performed by using the IRT system.
- Treatment will be dispensed.
- Patient diary release.
- The next visit will be scheduled and prepared.

Visit 3, 4, 5, 6 and 8 ('medium visits') procedures

Please note that not all medium visits are drug dispensation visits (please always refer to Flow Chart). However, compliance of patients regarding drug intake should always be reviewed (see also treatment compliance in Section 4.3).

- Physical examination including vital signs will be performed.
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- L-PF Symptoms and Impact questionnaire will be scheduled prior to any other procedure and in the above described order and will be reviewed for completeness by site personal at Visits 6 and 8.
- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- Spirometry (FVC) in the allowed time window will be performed.
- Acute ILD exacerbations will be recorded.
- Treatment compliance will be reviewed by site personal at every visit (except at randomization visit).
- Trial medication will be collected and/or dispensed according to Flow Chart.
- Patient diary will be collected & reviewed and/or dispensed according to Flow Chart.

Visit 7, Visit 9 and EOT ('big visits') procedures

At Visit 7, Visit 9 and EOT (primary endpoint visit), the same procedures will be performed as done at baseline Visit 2. Exceptions are the typical randomization measures, e.g. eligibility review, medical history assessment and randomization which is only taken once. In addition, if EOT takes place before Visit 7, HRCT should not be repeated. For Visit 7, Visit 9 and EOT always refer to the Flow Chart.

General rules

- Treatment compliance will be reviewed by site personal.
- Trial medication will be collected and/or dispensed according to Flow Chart.

- Patient diary will be collected & reviewed and/or dispensed according to Flow Chart.
- Visit 9 and end of treatment visit (EOT) are identical visits. EOT is to be used in eCRF at any time a patient ends trial medication (scheduled or prematurely).
- Patient who prematurely discontinued trial medication will attend all originally planned visits until the end of the trial. In case on-site visit is not available, at least vital status needs to be collected via telephone call.
- IRT should always be notified on end of treatment (EOT).
- Vital status will be collected for patients who prematurely discontinued trial medication and failed to attend future visits as planned, as well as for those who did not attend scheduled visits as planned at week 52 (scheduled Visit 9/EOT).
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.

[redacted]

- Drug intake at Visit 7 should always be performed at site and after blood and urine sample collection and pregnancy test.
- Spirometry (FVC) measurements should always be in the allowed time window and the described order (reference visit = Visit 2)

[redacted]

- Resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated (if possible prior to blood draw).

[redacted]

Intermediate 'a-Visit' procedures

- Safety blood, pregnancy tests and urine samples will be collected and submitted to the central laboratory if needed for additional safety monitoring at the discretion of the investigator (see Section 4.2.2.2).

6.2.3 Follow-up period and trial completion

A Follow-up Visit has to be scheduled 7 days after End of Treatment Visit for all patients. This Follow-up Visit is the safety follow-up after treatment discontinuation.

- Physical examination including vital signs.
- Adverse events and concomitant therapy will be assessment since last visit.
- Local dipstick pregnancy test (if applicable).
- Spirometry (FVC) in the allowed time window will be performed.

[redacted]

Patient's participation will be concluded for all subjects who complete all treatment visits.

Trial completion

The trial completion eCRF page has to be filled-in when the patient has terminated the trial. The end of the trial for the individual patient is:

- For patients who complete all study visits, end of trial is follow-up (FU) visit (after the end of treatment visit (EOT)).
- For patients who discontinue trial medication prematurely during the study period and complete an End of Treatment (EOT) visit and a Follow-up (FU) visit 1 week later, end of trial is visit at Week 52.
- For patients who withdraw consent, end of trial is the date of consent withdrawn

Patients who prematurely discontinued trial medication

In case a patient has to permanently discontinue trial medication, for whatever reason, he/she will be encouraged to attend all future visits up to end of trial as originally planned (except for the laboratory 'a-Visits').

1. During these visits, the patient will undergo all planned examinations according to Flow Chart, especially spirometry (FVC) and [redacted] however he/she will not have to [redacted] afety laboratory.
2. These visits will be regarded as part of the trial despite the patient having discontinued trial medication.

The need for coming to future visits in case of prematurely discontinuation of trial medication will be explained to patients prior to their participation in the trial.

Vital status information

In case of premature discontinuation of trial medication, if the patient does not attend future visits as planned, every attempt will be made to get information on vital status at 52 weeks after his/her randomization and at the end of the trial for patients who have withdrawn consent.

Patients will be asked to agree to be contacted by the site personnel, which could be by telephone calls, to allow collection of the vital status.

If death occurs, the Investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary and secondary causes of death.

Collection of vital status will be performed in accordance with national ethical and regulatory guidelines.

6.2.4 Dose reduction visit / dose increase visit

If a patient experiences a drug related adverse event, the dose can be reduced and the dose can be re-increased after recovery as described in Section 4.2.1. In both cases, the patient will have to come back to a visit where the following will be performed:

- Physical examination including vital signs.
- Adverse events and concomitant therapy will be assessment since last visit.

- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- Spirometry (FVC) in the allowed time window will be performed.
- Trial medication will be collected and treatment compliance will be reviewed.
- IRT registration for reduction or increase of the dose and trial medication dispensation.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is a multi-centre, randomized, placebo-controlled, double-blind clinical trial to investigate the efficacy and safety of nintedanib at a dose of 150 mg bid, in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype over 52 weeks. Patients will be randomized to one of the treatment groups in a 2:1 ratio (nintedanib/placebo) with 60 patients in nintedanib group and 30 patients in placebo group. Randomization will be stratified by HRCT pattern: “UIP-like fibrotic pattern” vs. “other fibrotic patterns”. It is planned to randomize two thirds of patients (60 patients) with UIP-like HRCT fibrotic pattern and one thirds of patients (30 patients) with other fibrotic patterns.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis is tested.

7.2 PLANNED ANALYSES

All analyses on efficacy endpoints are exploratory including primary endpoint analysis since the objective of this study is to explore the nintedanib treatment effect in Chinese patients. Point estimate and 95% CI will be provided without statistical testing.
The efficacy and safety analyses will be conducted on the treated set (TS), which consists of patients who are randomized to a treatment group and receive at least one dose of study medication.

All analyses will be based on the treatment group (nintedanib 150 mg bid or placebo) as randomized by IRT.

No subgroup analysis is planned. All analyses will be performed on the overall population.

7.2.1 General considerations

The following analysis sets will be defined for statistical analyses:

Randomized set (RS): This patient set includes all randomized patients, whether treated or not.

Treated set (TS): This patient set includes all randomized patients who received at least one dose of trial medication.

Data from patients who are screened but not randomized will be listed but not included in any summary statistics or inferential statistics. Important protocol deviations will be summaried and all decisions concerning IPDs will be made before un-blinding.

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

7.2.2 Primary endpoint analyses

The primary endpoint is the annual rate of decline in FVC [mL] over 52 weeks. The primary analysis will be based on all randomized patients who received at least one dose of trial medication, using all available data from baseline (excluded) up to Week 52, including visits done after premature treatment discontinuation, EOT visits and follow-up visits done before Week 52 (i.e. including all measurements after first drug intake and before or on day 373). The primary analysis will use a restricted maximum likelihood (REML)-based approach with a random slope and intercept model. The analysis includes fixed effects for treatment, HRCT pattern, and baseline FVC [mL], as well as the treatment-by-time and baseline-by-time interactions. Random effects will be included for the patient response for both time and intercept. Baseline FVC in mL will be included as a covariate in the analysis model. Baseline FVC is defined as the FVC result recorded at Visit 2, unless missing in which case the screening result will be used. The HRCT pattern ("UIP-like fibrotic pattern" or "Other fibrotic patterns") will also be used as a covariate for the analysis performed. The point estimate of treatment difference between the nintedanib and placebo group will be provided as well as 95%CI. No statistical testing will be performed.

A sensitivity analysis including only on-treatment measurements of FVC (ml) will be presented. The same model as for the primary analysis will be used. This model implies that data are assumed to be missing at random (MAR) and it is implicitly supposed that patients who dropout would have behaved similarly to those who remained in the study.

[redacted]

7.2.3 Secondary endpoint analyses

Not applicable since there is no secondary endpoint.

[redacted]

7.2.5 Safety analyses

Safety data will be analyzed descriptively.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as the 7 days after the date of the last dose of trial medication. Adverse

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

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

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 highlighted in the listings.

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

7.2.6 Other Analyses

No other analysis is planned.

7.2.7 Interim Analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

For the primary endpoint, 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". Even patients with only one post-baseline assessment can be included in the model and can therefore participate in variance estimation. The statistical model assumes that patients who prematurely discontinue study participation would have behaved similarly to those who remained in the study.

For the categorical endpoints, missing data will be imputed using multiple imputation method.

7.4 RANDOMIZATION

Patients will be randomized to one of the treatment groups in a 2:1 ratio (nintedanib/placebo) with 60 patients in nintedanib group and 30 patients in the placebo group. Randomization will be stratified by HRCT pattern: "UIP-like fibrotic pattern" vs. "other fibrotic patterns". It is planned to randomize two thirds of patients (60 patients) with UIP-like HRCT fibrotic pattern and one thirds of patients (30 patients) with other fibrotic patterns.

The randomization system will include caps for the two HRCT pattern strata so that approximately two thirds of the patients are randomized to the "UIP-like fibrotic pattern" stratum and one third is randomized to the "Other fibrotic patterns" stratum.

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

7.5 DETERMINATION OF SAMPLE SIZE

The pivotal phase 3 trial 1199−0247 has confirmed the superior effect of nintedanib over placebo in terms of annual rate of FVC [mL] decline. The objective of this trial is to explore the nintedanib treatment effect in Chinese patients. The main assumption of the study is the results from trial 1199−0247 as shown in below Table 7.5:1.

Table 7.5: 1 Annual rate of decline in FVC [ml/year] over 52 Weeks

		Rate of FVC decline over 52weeks			Comparision vs. placebo			
Treatment	Number analysed	Adjusted rate	SE	95% CI	Adjusted difference	SE	95% CI	p-value
Placebo	331	-187.78	14.84	(-216.92,-158.64)				
Nintedanib 150 mg b.i.d	332	-80.82	15.07	(-110.42, -51.22)	106.96	21.15	(65.42, 148.50)	<0.0001

The sample size evaluations are conducted for several scenarios to assess the probability of the point estimate of treatment effect size from this study (Chinese patients) is equal to or greater than a critical value.

- Assuming treatment effect size (107ml/yr) is the same as observed in trial 1199−0247
- Different critical values based on percentage of treatment effect from trial 1199−0247
- Different sample sizes with 2:1 randomization ratio

With the same treatment effect size (approx. 107mL/year) as observed in trial 1199−0247, a sample size of 90 (60 vs. 30) will have 81.7% probability to observe point estimate of treatment effect size in this study is greater than or equal to 53.5 mL/year (107*50%); and 86. 0% probability to observe point estimate of treatment effect size >=42.8 mL/year (107*40%); and 89. 6% probability to oberserve point estimate of treatment effect size >=32.1 mL/year (107*30%).

Table 7.5: 2 Sample size assessment based on the probability to observe point estimate of annual FVC decline rate is >= K% effect size of trial 1199-0247

Treatment effect size (ml/year)	Sample size (nintedanib vs. placebo)	Prob. to observe at least 50% (107*50%) effect size of the global data in Chinese population	Prob. to observe at least 40% (107*40%) effect size of the global data in Chinese population	Prob. to observe at least 30% (107*30%) effect size of the global data in Chinese population
107	40 vs 20	0.762	0.804	0.841
	50 vs 25	0.793	0.836	0.870
	60 vs 30	0.817	0.860	0.896

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."
The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

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

8.3.1 Source documents

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

For eCRF all data need to be derived from source documents, which need to be available onsite (this could be for example physician's notes in patient files, printouts, patient diaries). In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported

data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source files (HRCT) necessary for central eligibility reads will be provided to an imaging vendor., the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will

be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor 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 contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

Not applicable due to no biological samples.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial to incorporate and consider all data in the report.

The sponsor will submit to the database a summary of the final trial results within one year from the end of a clinical trial as a whole.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

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

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

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

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

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central images service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 FVC LUNG FUNCTION CRITERIA

FVC

Predicted normal values will be calculated according to Global Lung Initiative (GLI) [R15-0845, R15-2073] at the site level, using the Spirosphere®. FVC percent predicted is a key inclusion criterion and a further endpoint using the following demographic information: race, age, gender and height.

10.2 CREATININE CLEARANCE

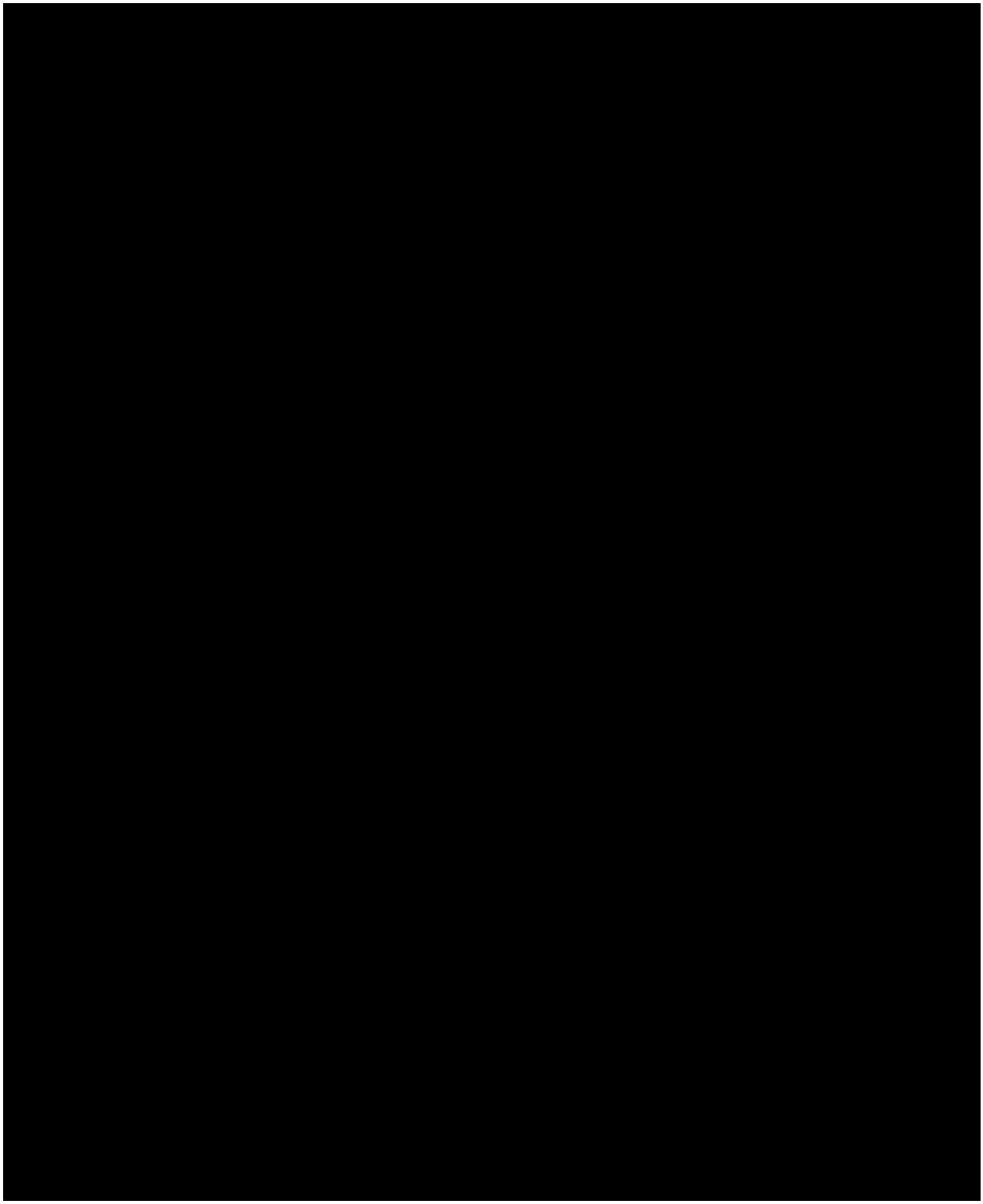
Creatinine clearance calculation is done according to Cockroft and Gault [R96-0690].

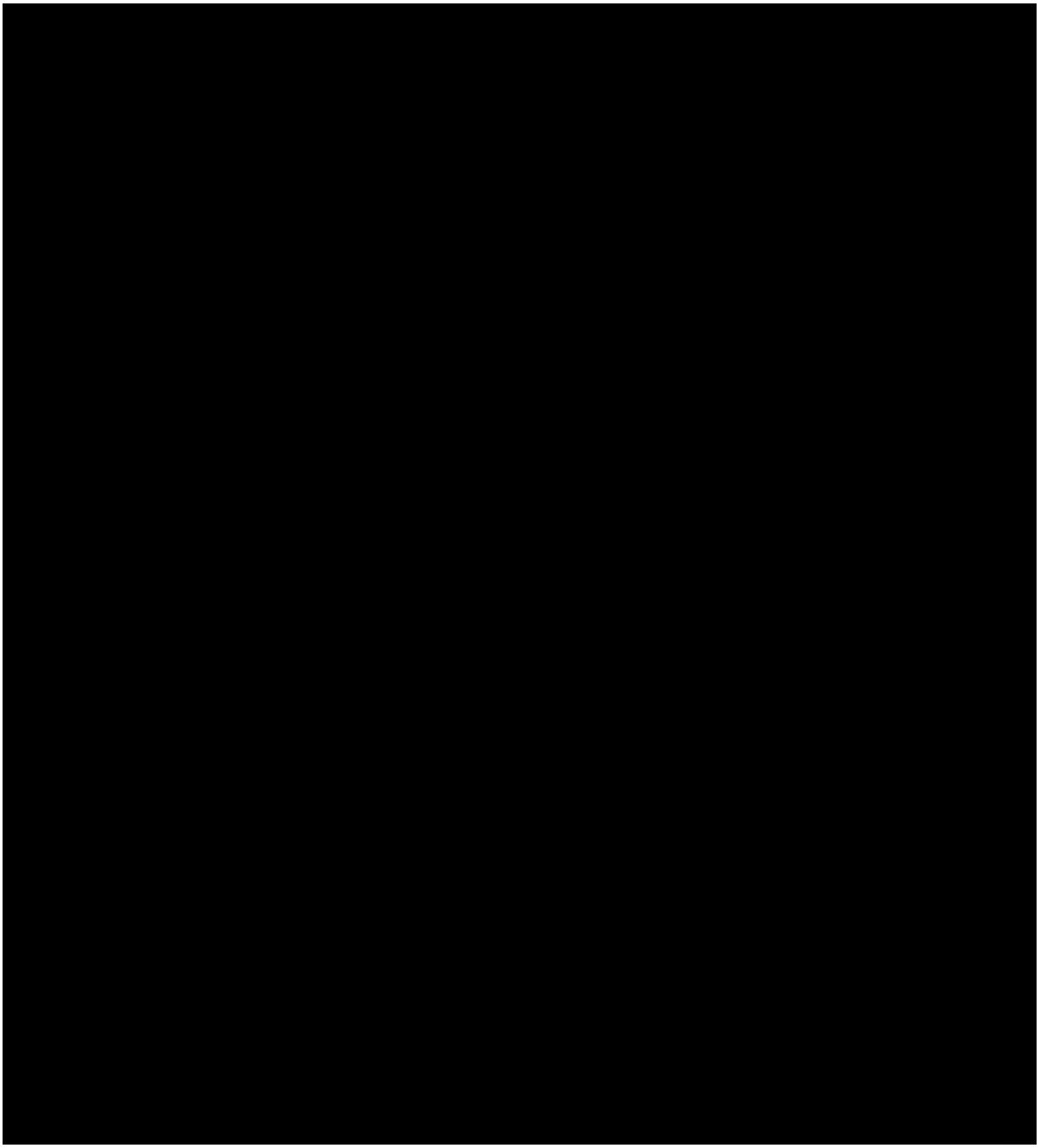
- Creatinine clearance = (140 - age) x (Weight in kg) x (0.85 if female) / (72 x serum creatinine in mg/dL)

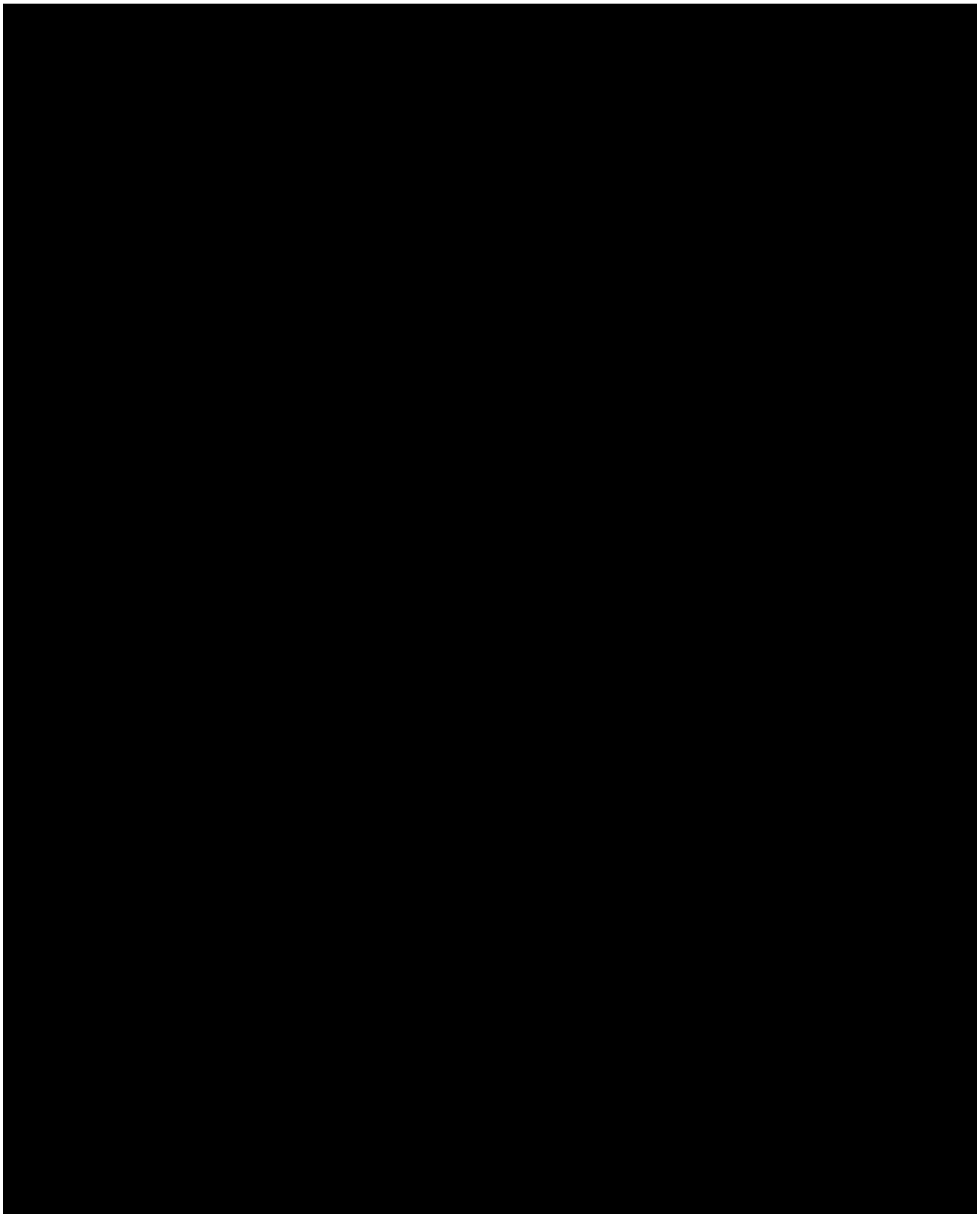
10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS

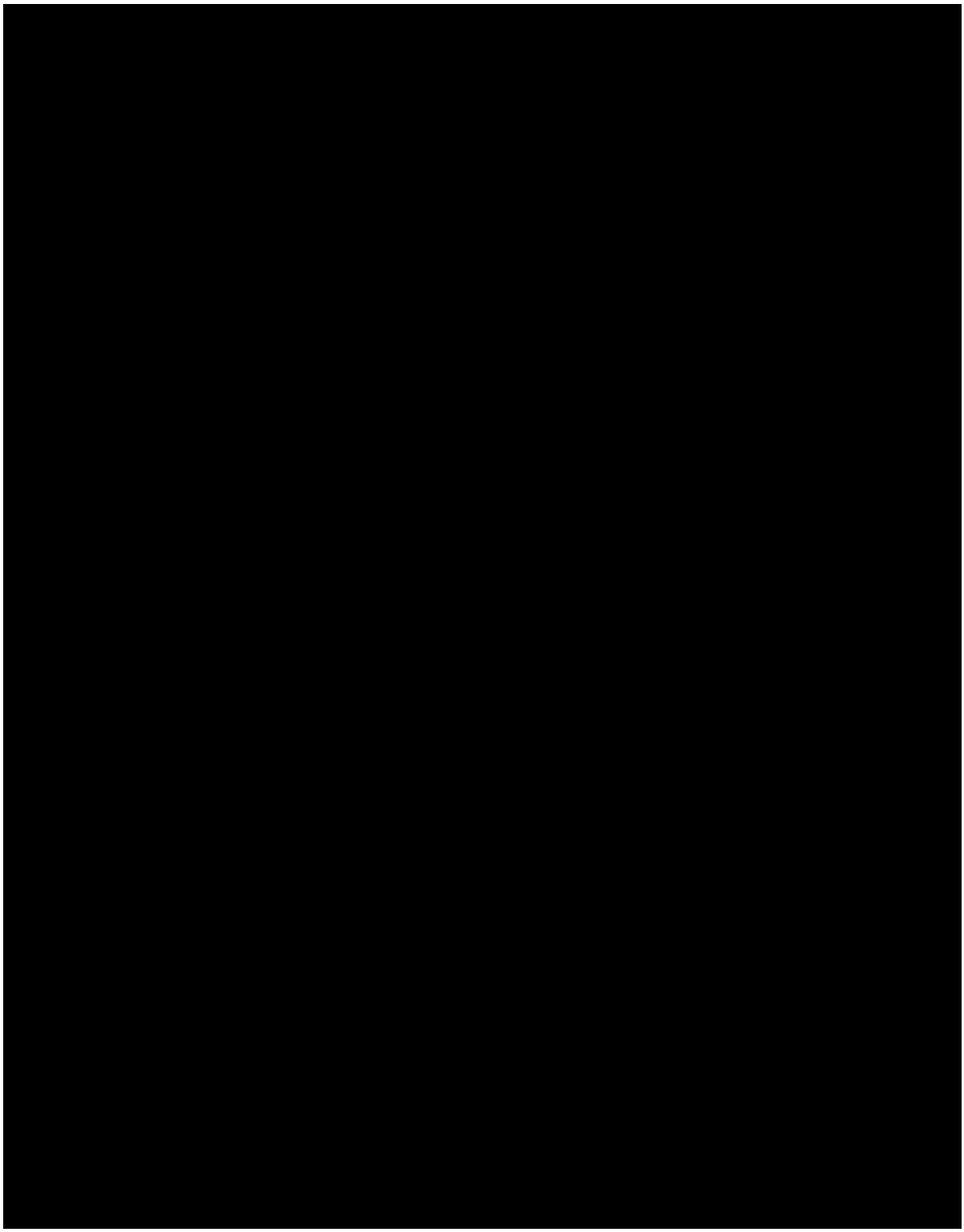
Table 10.3: 1 Equivalent Doses of Corticosteroids

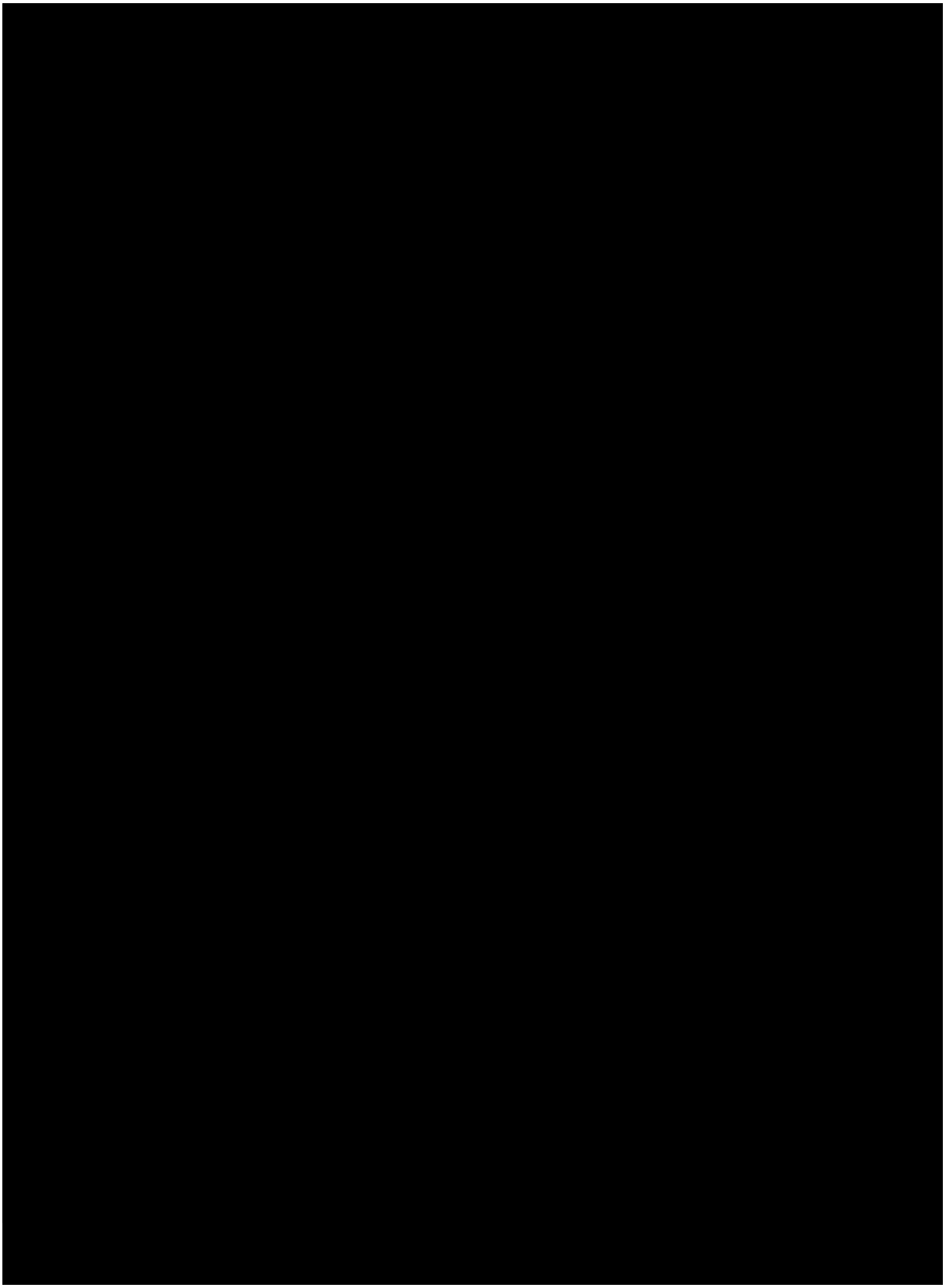
Drug	Equivalent dose (mg)	Conversion factor
Prednisone	5	x 1
Prednisolone	5	x 1
Triamcinolone	4	x 1.25
6-Methylprednisolone	4	x 1.25
Dexamethasone	1	x 5
Betamethasone	0.75	x 6.7
16-Methylprednisolone	6	x 0.8
Fluocortolon	5	x 1
Cloprednol	3,75-5	x 1.0-1.5
Deflazacort	6	x 0.8
Cortisol (hydrocortisone)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

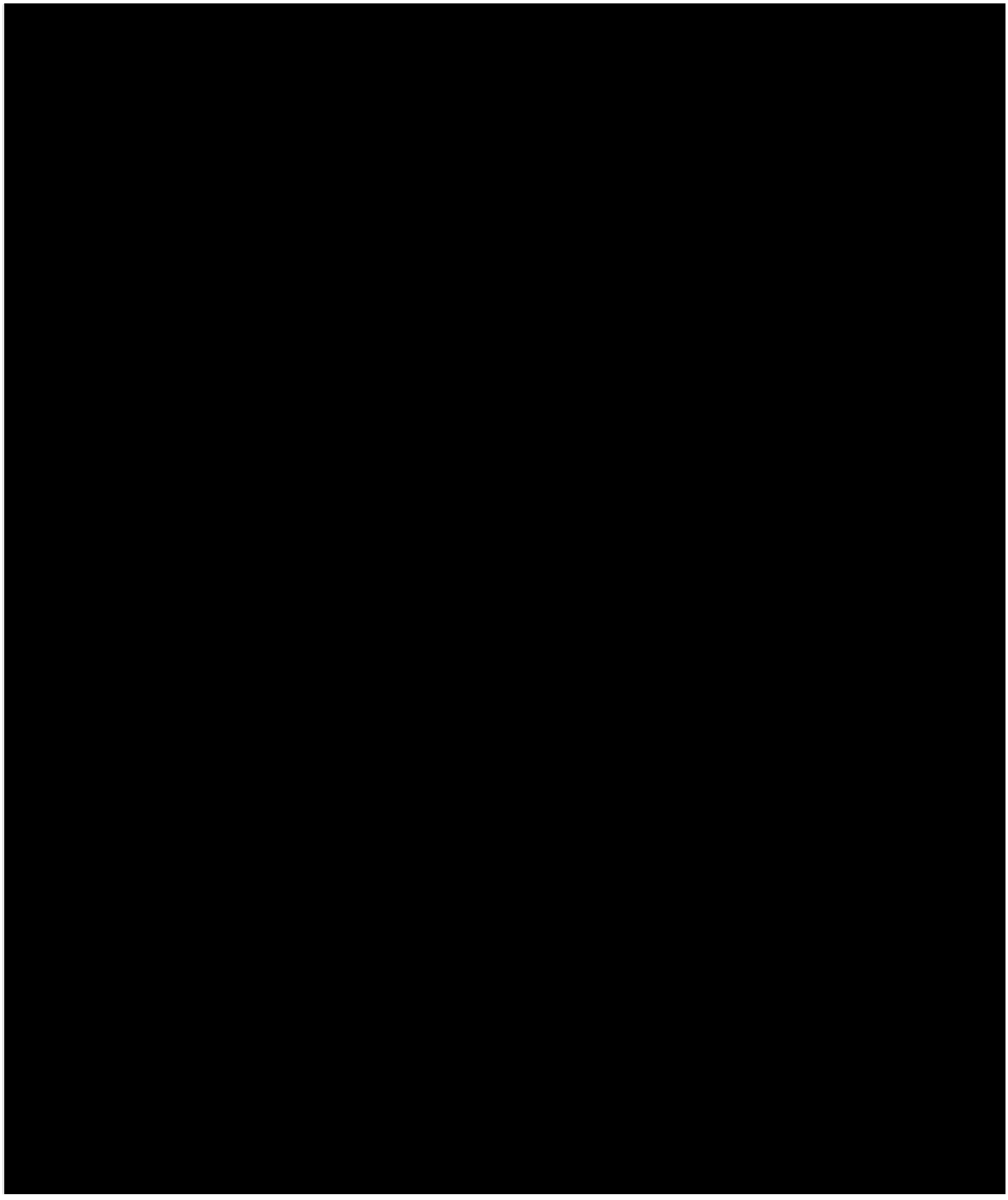


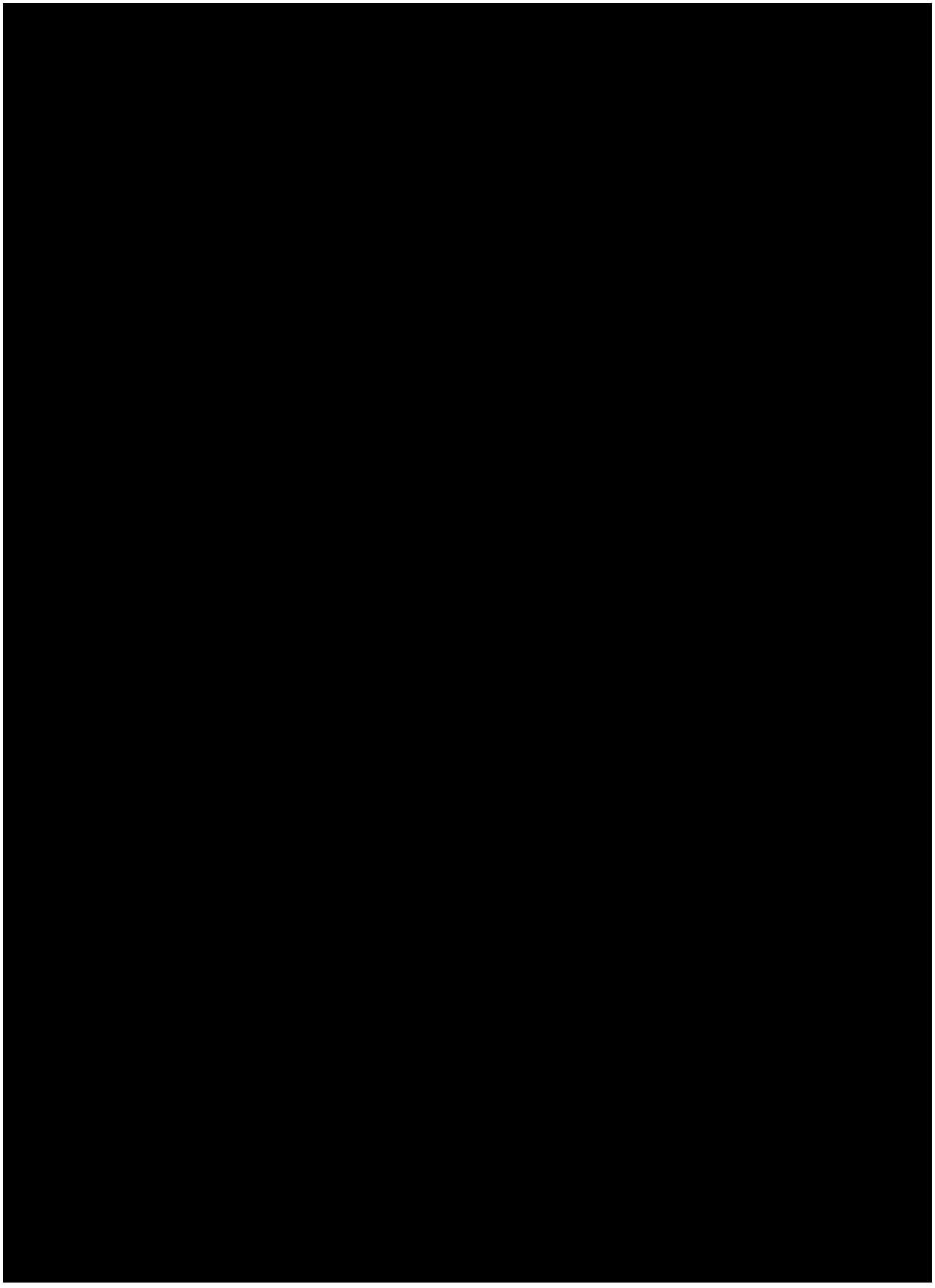


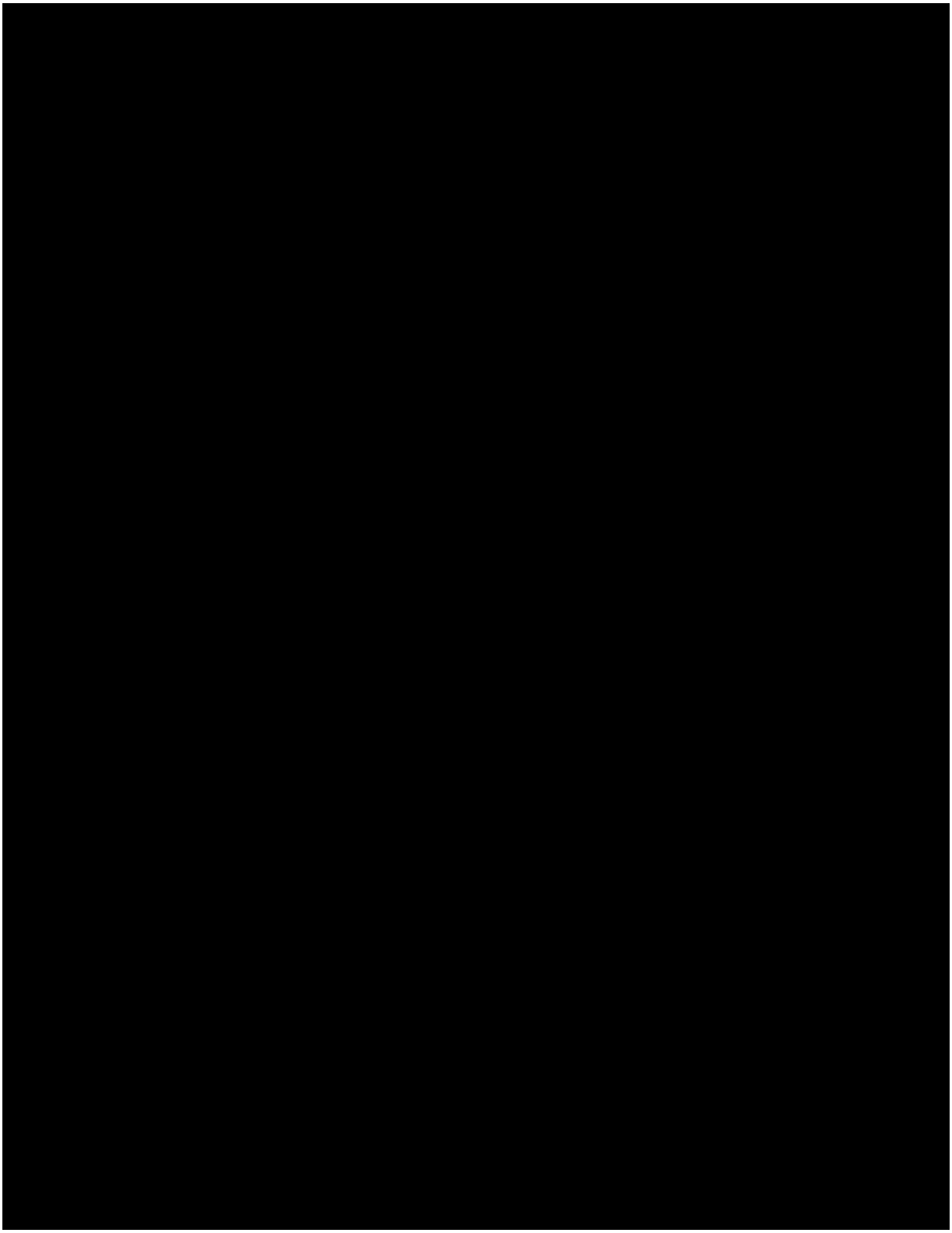


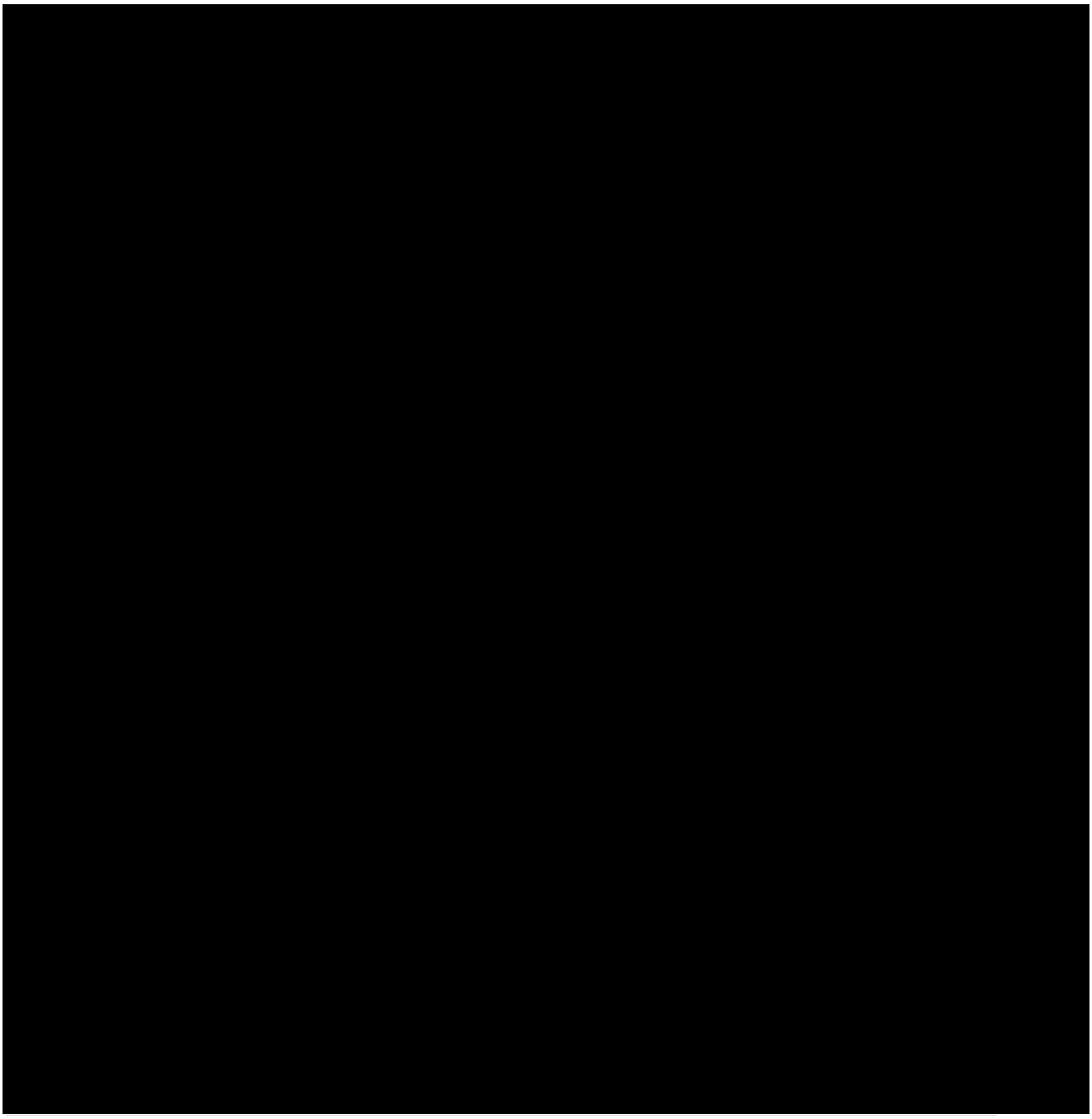


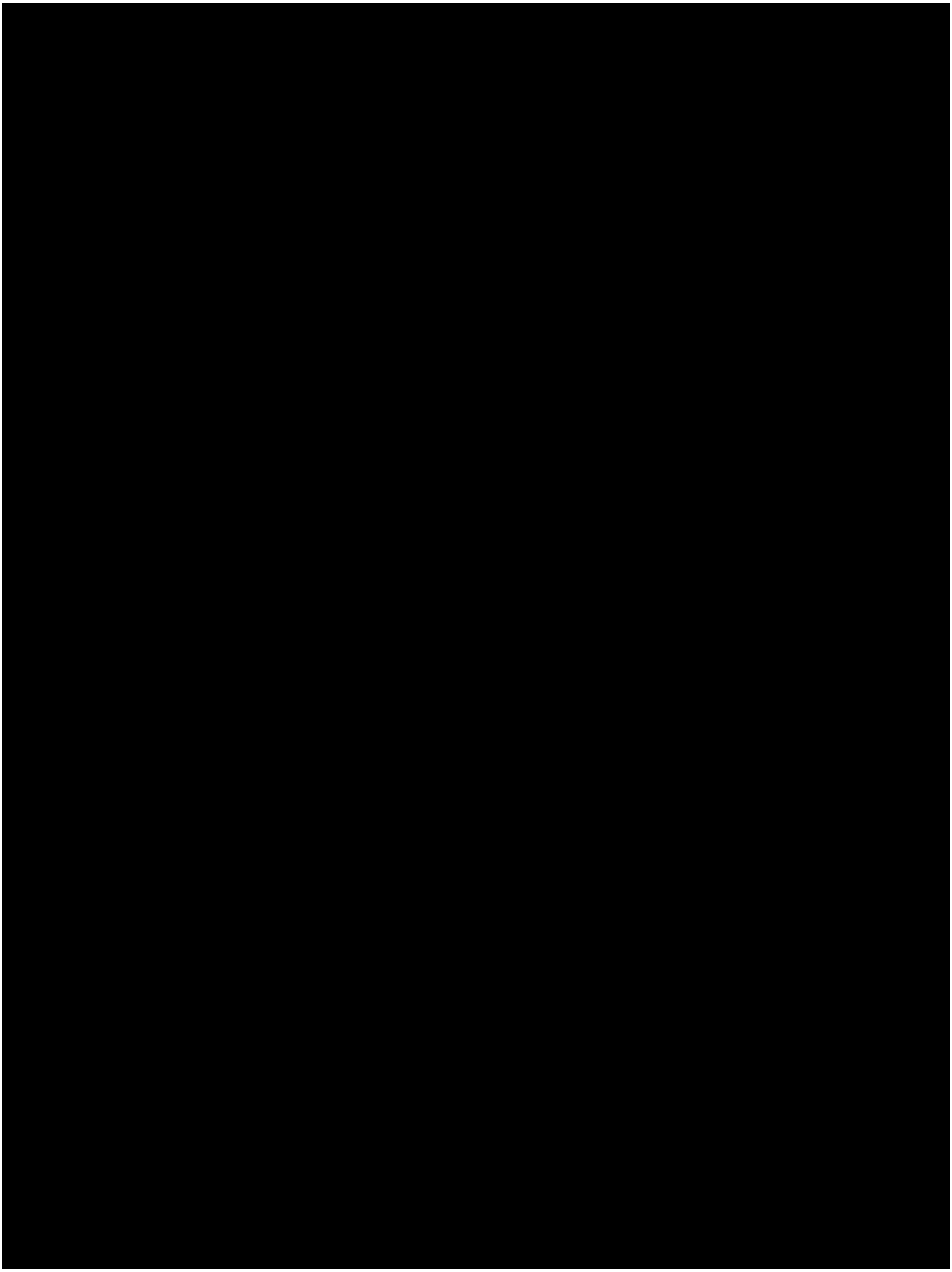












10.5 PHARMACOKINETIC METHODS AND ANALYSES

Not applicable.

10.6 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Not applicable.

10.7 TRIAL BIOMARKER PLAN

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

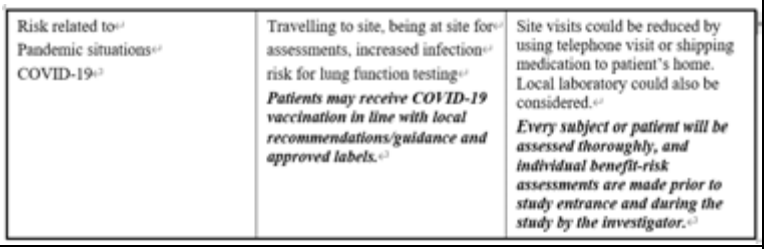
11.1 GLOBAL AMENDMENT 1

Date of amendment		22 Feb 2021
EudraCT number **EU number**		Not applicable
BI Trial number		1199-0434
BI Investigational Medicinal Product(s)		Nintedanib
Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Home page and 2nd page
Description of change		Deleted ***Principal Investigator < for single-centre trial or > and < for multi-centre trial if applicable >***
Rationale for change		To delete the excess.
Section to be changed		Trial objective(s) of Clinical trial protocol synopsis and section 2.1.1 Main objectives
Description of change		Deleted ***and safety***
Rationale for change		Safety is not a main objective and it is only a further objective.
Section to be changed		Mitigation strategy of Table 1.4.2:1 Overview over trial related risks
Description of change		Added ***and early management, guideline to liver enzyme elevations***
Rationale for change		The guideline on management of liver enzymes is also a risk mitigation strategy for DILI.
Section to be changed		4.2.2.4 Contraception requirements
Description of change		Corrected a mistake from "or 28 days before treatment initiation" to "***and*** 28 days before treatment initiation".
Rationale for change		Typo correction.

11.2 GLOBAL AMENDMENT 2

Date of amendment		28 Jun 2021
EudraCT number **EU number**		Not applicable
BI Trial number		1199-0434
BI Investigational Medicinal Product(s)		Nintedanib

Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		The whole protocol
Description of change		Changed from ***lab*** to ***laboratory***
Rationale for change		To keep wording consistency throughout the protocol
Section to be changed		Clinical Trial Protocol Synopsis: trial design
Description of change		Added "***approximately***" before "***two thirds of patients with UIP-like HRCT fibrotic patterns, one third of patients with other fibrotic patterns***." Deleted "s" from "one third of patients with other fibrotic patterns".
Rationale for change		To make the text more precise. Typo correction.
Section to be changed		Flow Chart
Description of change		Deleted ***of treatment*** and ***0*** from Flow Chart, kept ***weeks*** and added ***D1.***
Rationale for change		According to BI standard process, Day 1 is usually the day of the first randomised treatment administration. Day 0 should not be used to describe the trial schedule.
Section to be changed		Flow Chart, section 3.1 Overall trial design, section 6.2.1 Screening period(s) and section 6.2.4 Dose reduction visit / dose increase visit
Description of change		Deleted ***call/*** from ***IRT call/notification*** in the Flow Chart. Changed from ***Interactive phone/web Response System (IRT)*** to ***Interactive web Response System (IRT)*** in section 3.1. Changed from ***Site personnel will perform a screening call in IRT to ensure in-time trial medication shipment*** to ***Site personnel will perform a screening registration in IRT to ensure in-time trial medication shipment*** in section 6.2.1. Changed from ***IRT call for reduction or increase of the dose and trial medication dispensation*** to ***IRT***

		registration for reduction or increase of the dose and trial medication dispensation in section 6.2.4.
Rationale for change		The IRT is not using phone anymore.
Section to be changed		Flow Chart, section 6.2.2 Treatment period(s) and section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		Added ***Release patient diary*** and ***Review and collect patient diary*** into the Flow Chart. Added ***Patient diary release*** and ***Patient diary will be collected & reviewed and/or dispensed according to Flow Chart*** into section 6.2.2. Added ***A patient diary will be used to record the daily intake of the trial medication*** into section 4.1.4.
Rationale for change		Patient diary will be dispensed to collect the use of drug when the patient at home.
Section to be changed		Section 1.2 Drug profile and Section 9.2 unpublished references
Description of change		Removed "-14" from index ***[c01783972-14]*** of section 1.2 and section 9.2 and changed to ***Most recent version: Investigator`s Brochure. Nintedanib (BIBF 1120)*** in section 9.2.
Rationale for change		As the most recent IB version has extension 18.
Section to be changed		Section 1.3
Description of change		Added "***l***" into "***conditionally***"
Rationale for change		Typo correction
Section to be changed		Table 1.4.2:1 Overview over trial related risks
Description of change		Added the following guidance related to COVID-19 vaccination:  Risk related to Pandemic situations COVID-19 / Travelling to site, being at site for assessments, increased infection risk for lung function testing / ***Patients may receive COVID-19 vaccination in line with local recommendations/guidance and approved labels.*** / Site visits could be reduced by using telephone visit or shipping medication to patient's home. Local laboratory could also be considered. / ***Every subject or patient will be assessed thoroughly, and individual benefit-risk assessments are made prior to study entrance and during the study by the investigator.***
Rationale for change		Updated based on the current situation of COVID-19
Section to be changed		Section 3.2 Discussion of trial design, including the choice of control group(s)
Description of change		Deleted ***12 months treatment duration for primary assessment of benefit-risk of nintedanib in Chronic Fibrosing ILDs with a Progressive Phenotype***.
Rationale for change		To delete the excess.
Section to be changed		Section 3.3.3 Exclusion criteria: article 26

Description of change		Added footnote ** for article 26: Testing for SARS-CoV-2 is not the part of this trial. If required this needs to be done per local requirements or investigator's assessment.
Rationale for change		To clarify SARS-CoV-2 testing clearly
Section to be changed		Section 3.3.3 Exclusion criteria: footnote *
Description of change		Deleted ***include hysterectomy, bilateral salpingectomy and bilateral oophorectomy***
Rationale for change		To delete the excess.
Section to be changed		Table 4.1.4: 1 Dosage and treatment schedule
Description of change		Added "n" into "morning"
Rationale for change		Typo correction.
Section to be changed		Corrected a mistake for Table 4.2.1.1: 1 Management of diarrhoea (considered related to trial medication)
Description of change		Added ***Diarrhoea with increase of ≥7 stools per day over baseline1; stool incontinence, or life threatening consequences.***
Rationale for change		A mistake correction.
Section to be changed		Table 4.2.1.2: 1 Recommendations for managing liver enzyme elevations
Description of change		Added ***Close observation[4]***
Rationale for change		Close observation is still required for patient safety.
Section to be changed		Section 5.2.4 Electrocardiogram
Description of change		Deleted ***Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate***.
Rationale for change		To delete the excess.
Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		Added ***Adverse events relating to gastrointestinal perforation and hepatic injury will be considered AESIs.***
Rationale for change		According to nintedanib previous trials, gastrointestinal perforation is also thought as AESIs.
Section to be changed		5.2.6.2.2 AE reporting to the sponsor and timelines
Description of change		To delete "via fax"
Rationale for change		The AE reporting method is not limited to fax
Section to be changed		Section 6.1 Visit schedule
Description of change		Changed from ***The maximum duration is expected to be 434 days*** to ***The maximum duration is expected to be 437 days***.
Rationale for change		A mistake correction.
Section to be changed		Section 6.1 Visit schedule
Description of change		Deleted ***of the participating country***
Rationale for change		The trial is only conducted in China.
Section to be changed		Section 6.2.1 Screening period(s) and the footnotes of Flow Chart

Description of change		Deleted ***Patients will be asked to give informed consent about COVID-19*** from section 6.2.1 and added ***Patients will be asked to give informed consent about COVID-19 if necessary*** into the footnotes of Flow Chart.
Rationale for change		The outbreak is well under control in China. The site can assess whether or not ICF about COVID-19 needs to be signed based on the actual situation, so this ICF signature is not a general rule at Visit 1.
Section to be changed		[redacted]
Description of change		
Rationale for change		

11.3 GLOBAL AMENDMENT 3

Date of amendment		31 May 2022
EudraCT number **EU number**		Not applicable
BI Trial number		1199-0434
BI Investigational Medicinal Product(s)		Nintedanib
Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**3.3.4 imaging criteria**
Description of change		Added section 3.3.4 imaging criteria as below: ***Patients with original physician diagnosis of different fibrosing ILDs, e.g. CTD-ILD, chronic fibrosing HP, iNSIP, unclassifiable IIP and environmental/ occupational fibrosing lung disease will be included if they meet the protocol criteria for PF-ILD. While the clinical ILD diagnosis will not be verified, central review of the screening HRCT images will ensure that relevant***

		lung fibrosis is present and the HRCT pattern is not indicative of other causes of progression. ***At screening the recent (not older than 12 months at screening) HRCT image of the patient will be evaluated; previous HRCT images will not be collected or reviewed. Hence inclusion based on increasing extent of fibrotic changes on chest imaging within 24 months will reflect the investigator's judgement.*** ***Eligible patients will have fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing with disease extent of >10%.*** ***The following co-existing features will be accepted:*** • ***Ground glass opacity*** • ***Upper lung or peribronchovascular predominance*** • ***Mosaic attenuation*** • ***Air trapping*** • ***Centrilobular nodules*** ***The following co-existing features will not be allowed:*** • ***Widespread consolidation*** • ***Progressive massive fibrosis*** ***In addition, determination of the HRCT pattern will also be done by central review and will be used for randomization stratification. The study will be enriched for patients meeting either criteria A, B and C, criteria A and C, or criteria B and C as described below. These patients will be referred to as "patients with HRCT with UIP-like fibrotic pattern only".*** ***Patients with PF-ILD who do not meet these criteria will be referred to as "patients with other HRCT fibrotic patterns".*** ***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***

<table>
<tr><td></td><td></td><td>Specifications for the HRCT acquisition will be provided in the ISF. Screening HRCT can be performed as part of the study in case the available HRCT does not meet the required image acquisition specifications.</td></tr>
<tr><td>Rationale for change</td><td></td><td>HRCT imaging requirements are clearly provided for the investigator as a reference.</td></tr>
<tr><td>Section to be changed</td><td></td><td>5.1.1 FVC</td></tr>
<tr><td>Description of change</td><td></td><td>Added “Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with preferably a maximum of five manoeuvres.”</td></tr>
<tr><td>Rationale for change</td><td></td><td>To make the text more precise.</td></tr>
<tr><td>Section to be changed</td><td></td><td>5.2.3 Safety laboratory parameters</td></tr>
<tr><td>Description of change</td><td></td><td>Added the below content:
The laboratory tests at intermediate ‘a’ visits will include:
<table>
<tr><td>Category</td><td>Laboratory test</td></tr>
<tr><td>Biochemistry</td><td>Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)</td></tr>
<tr><td>Urinalysis</td><td>pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++)</td></tr>
<tr><td colspan="2">Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.</td></tr>
</table>
The samples and pregnancy tests may be collected at the office of a local doctor using trial specific lab kits that will be sent to a central laboratory for analyses. These kits will be provided to patients at study visits as applicable.

Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2).</td></tr>
</table>

		If laboratory values indicate abnormality, adequate and more frequent blood sampling may be performed at the discretion of the Investigator. ***In case of liver function value elevations, close monitoring must be ensured by the Investigator. Refer to Section 4.2.1.2 for monitoring elevations and Section 3.3.5 for withdrawal criteria.*** ***Laboratory analysis will be done using central laboratory services. Venous whole blood will be collected in appropriate syringes provided by the Sponsor through the assigned central laboratory. Details regarding centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the Sponsor. The Investigators will be informed and instructed by the central laboratory and detailed documentation will be included in the ISF.***
Rationale for change		To refine and supplement relevant information
Section to be changed		**6.1 VISIT SCHEDULE**
Description of change		Added the below description: ***Except for visit 1, visit 2 and EOT visit, in the event of force majeure or other disrupting circumstances the other visits may have to be performed at the patient's home after alignment with sponsor, remotely (by phone) or as a combination of home and remote visits. At these visits, the following assessments can be performed at the*** ***Patient's home or remotely:*** • ***Concomitant therapy*** • ***Pregnancy testing (urine) if need*** • ***review results if some assessments can be done at local hospital except for FVC, please refer to Flow Chart for more details.*** • ***all AEs / SAEs / AESIs*** • ***IRT call after completing the above assessment, include the test results review from local laboratory*** • ***Dispense trial medication*** • ***compliance check*** ***Trial medication will not be collected at visits performed remotely. Instead, the medication should be collected when the patient next visits the site, or when a visit is performed at the patient's home (see below).***

		The following assessments can be performed at the patient's home: • ***vital signs*** • ***physical examination if possible*** • ***resting 12-lead ECG (using a portable ECG machine) if possible*** • ***safety laboratory sampling and review of results if possible*** • ***collect trial medication*** ***If safety laboratory sampling via the central laboratory is not possible from the investigational site (and is instead performed at the patient's home or local hospital), analyses can be performed at a local laboratory. The results of the safety laboratory tests must be transferred to the Investigator who must ensure a medical review and document any clinically relevant safety issues as AEs. For a list of "minimum required safety laboratory parameters" refer to Section 5.2.3 and Table 5.2.3: 1.*** ***When scheduling such visits every effort should be made to ensure a continuous supply of trial medication for the patient, whilst also taking into account that the next kit(s) of trial medication may need to be shipped from the site to the patient's home and, that medical pre-requisites should be performed and confirmed prior to shipment of new supplies.*** ***The investigators should ensure as much as possible that FVC assessment can be finished on site for every visit.*** ***All deviations from the original schedule of assessments as defined in the Flow Chart will be documented and the implications considered for the analysis of the trial data.***
Rationale for change		Updated based on the current situation of COVID-19
Section to be changed		**9.1 PUBLISHED REFERENCES**
Description of change		Added ***"R96-0690 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976. 16(1):31-41."***
Rationale for change		Added a published reference.
Section to be changed		**10.2 CREATININE CLEARANCE**

Description of change		Deleted ***Table 10.2:1 Equivalent Doses of Corticosteroids*** and added: ***Creatinine clearance calculation is done according to Cockroft and Gault [R96-0690].*** • ***Creatinine clearance = (140 - age) x (Weight in kg) x (0.85 if female) / (72 x serum creatinine in mg/dL)***
Rationale for change		An error was corrected in order to be consistent with article 3 of the Exclusion Criteria

11.4 GLOBAL AMENDMENT 4

Date of amendment		18 Sep 2023
EudraCT number **EU number**		Not applicable
BI Trial number		1199-0434
BI Investigational Medicinal Product(s)		Nintedanib
Title of protocol		A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in Chinese patients with Chronic Fibrosing ILDs with a Progressive Phenotype
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title Page: Clinical Trial Leader
Description of change		• The name of Clinical Trial Leader "[redacted]" was changed into "[redacted] • The address of Clinical Trial Lead was changed to [redacted] • The phone number of Clinical Trial Leader was changed to [redacted]"
Rationale for change		CTL handover
Section to be changed		**Flow Chart** Footnote 10
Description of change		Updated the text as following (See text in bold): • Footnote10: Conclusion of **trial** participation is ~~only applicable for subjects who withdraw consent~~ **for all subjects who complete all treatment visits.**
Rationale for change		Conclusion of participation needs to be checked at the follow up visit for all subjects who complete all treatment visits. These revisions have been clarified in the Protocol Administrative Letter (date: on 28 June 2023).

Section to be changed		**Section 4.1.4 Drug assignment and administration of doses for each patient**
Description of change		Updated the text as following (See text in bold): • The patients should take the trial medication with food, swallow whole with water, and should not be chewed or crushed because of a bitter taste, and should observe a dose interval of 12 hours **as far as possible**. Effort should be made to ensure that drug administration occurs at the same time every day +/- 30 min (between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening). **A forgotten dose should be skipped if the time window to the next dose is less than 8 hours. The next dose should be taken as scheduled. The recommended maximum daily dose of 300 mg should not be exceeded.** • The dose may be reduced to 100 mg bid due to AE after the investigator assessment. The investigator can dispense new medication kits with 100mg to the patient via IRT system. ~~• If a dose is missed, administration should resume at the next scheduled time point at the recommended dose. If a dose is missed the patient should not take an additional dose. The recommended maximum daily dose of 300 mg should not be exceeded.~~
Rationale for change		Texts were added to avoid potential side effects of accumulating exposure to the drug if the interval between morning dose and evening dose becomes too short. Clarification about the actions if the time window to the next dose is less than 8 hours. These revisions have been clarified in the Protocol Administrative Letter (date: on 28 July 2022).
Section to be changed		**Section 5.2.3 Safety laboratory parameters**
Description of change		Updated the text as following (See text in bold): ~~• eGFR will be analysed and calculated by the central laboratory at the same timepoints as other safety laboratory parameters (see in the Flow Chart).~~ • Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2).

		…….Venous whole blood will be collected **through the assigned central laboratory** ~~in appropriate syringes provided by the Sponsor through the assigned central laboratory~~.
Rationale for change		For clarification and consistency. This revision has been clarified in the Protocol Administrative Letter (date: on 25 Apr 2023).
Section to be changed		**Section 6.2.2 Treatment period(s)**
Description of change		Updated the text as following (See text in bold): *General rules* …Drug intake at ~~visit days~~ Visit 7 should always be performed at site and after blood and urine sample collection and pregnancy test.
Rationale for change		Clarification
Section to be changed		**Section 6.2.3 Follow-up period and trial completion**
Description of change		Updated the text as following (See text in bold): A Follow-up Visit has to be scheduled 7 days after End of Treatment Visit for all patients. This Follow-up Visit is the safety follow-up after treatment discontinuation. • Physical examination including vital signs. • Adverse events and concomitant therapy will be assessment since last visit. • Local dipstick pregnancy test (if applicable). • Spirometry (FVC) in the allowed time window will be performed. • Acute ILD exacerbations will be recorded. Patient's participation will be concluded for ~~patients who withdraw consent and do not attend future visits~~ **all subjects who complete all treatment visits.** **<u>Trial completion</u>** The trial completion eCRF page has to be filled-in when the patient has terminated the trial. The end of the trial for the individual patient is: • For patients who complete all study visits, end of trial is ~~EOT~~ **follow-up (FU) visit (after the end of treatment visit (EOT)).** ~~• For patients who withdraw consent~~ ~~– at time of trial medication discontinuation, end of trial is an EOT visit followed by a follow-up visit.~~

		~~- after EOT was already completed, then the patient should have a final visit based on their scheduled study visit.~~ • **For patients who discontinue trial medication prematurely during the study period and complete an End of Treatment (EOT) visit and a Follow-up (FU) visit 1 week later, end of trial is visit at Week 52.** • **For patients who withdraw consent, end of trial is the date of consent withdrawn** **<u>Vital status information</u>** In case of premature discontinuation of trial medication, if the patient does not attend future visits as planned, every attempt will be made to get information on vital status at 52 weeks after his/her randomization~~, at the time of data cut-off for the primary analysis~~ and at the end of the trial for patients who have withdrawn consent.
Rationale for change		To keep consistent with the change of footnote 10. "A Follow-up Visit has to be scheduled 7 days after End of Treatment Visit for all patients", the trial completion description for patients completed all study visits is corrected. Correct the end of trial description for patients who withdraw consent. These revisions (except the revision of vital status information) have been clarified in the Protocol Administrative Letter (date: on 28 June 2023).