Boehringer Ingelheim

CLINICAL TRIAL PROTOCOL

	Document Number:	**c21830338-03**
EudraCT No.	2018-000525-32	
BI Trial No.	1199-0248 (INBUILD®-ON)	
BI Investigational Medicinal Product(s)	Nintedanib	
Title	An open-label extension trial of the long-term safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)	
Lay Title	A follow-up study investigating long term treatment with nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)	
Clinical Phase	III	
Trial Clinical Monitor	[redacted] Tel: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol **(Revised Protocol (based on global amendment 1))**	
Version and Date	**Version: 2.0**	**Date: 01 Sep 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	14 Jun 2018
Revision date	01 Sep 2020
BI trial number	1199-0248 (INBUILD®-ON)
Title of trial	An open-label extension trial of the long term safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)
Principal Investigator < for single-centre trial or > Coordinating Investigator< for multi-centre trial if applicable >	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s)	Multi-centre trial conducted in approximately 15 countries, sites identical to those which enrolled patients into the parent trial, 1199.247 (INBUILD®)
Clinical phase	III
Trial rationale	Extension trial to evaluate the long term tolerability and safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)
Trial objective(s)	The primary objective is to assess the long-term tolerability and safety of oral nintedanib treatment in patients with Progressive Fibrosing Interstitial Lung Disease who have completed (and did not prematurely discontinue trial medication in) the phase III parent trial, 1199.247 (INBUILD®)
Trial endpoints	The primary endpoint is the incidence of overall adverse events over the course of the extension trial
Trial design	Open label extension trial
Total number of patients entered	Approximately 480
Number of patients on each treatment	Not applicable
Diagnosis	Progressive Fibrosing Interstitial Lung Disease
Main in- and exclusion criteria	Patients who have completed the 1199.247 (INBUILD®) study and did not prematurely discontinue trial medication
Test product(s)	Nintedanib
dose	Nintedanib 150 mg bid (300mg daily) or 100 mg bid (200mg daily)
method and route of administration	p.o.
Comparator product(s)	Not applicable

dose	
method and route of administration	
Duration of treatment	Treatment duration of at least 96 weeks or until nintedanib can be made available to the patient outside of the clinical trial. Treatment will be stopped if a reason for withdrawal is met.
Statistical methods	Descriptive statistics of adverse events and other safety parameters, [redacted]

FLOWCHART

Visit*	1[2]	2	3	4	5	5a	6	6a	7	7a	8	X[7]	EOT[8]	FU[9]
	Open Label Treatment Period													FU
Week	0	2	4	8	12	18	24	30	36	42	48	60+ every 12w		
Day **Time window (days)**	1	15 ±3	29 ±3	57 ±3	85 ±3	127 ±7	169 ±7	211 ±7	253 ±7	295 ±7	337 ±7	 ±7		+28 +7
Informed consent[1]	X													
Demographics[3]	X													
Medical History[3]	X													
Baseline Conditions	X[4]													
Physical examination, vital signs	X	X	X	X	X		X		X		X	X	X	
Adverse events, conc. Therapy	X[4]	X	X	X	X		X		X		X	X	X[10]	X[10]
12-lead ECG	X						X				X			
Safety laboratory	X	X	X	X	X	X[5]	X	X[5]	X	X[5]	X	X	X	
Pregnancy test[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]	X		X		X		X		X		X	X	X	
[redacted]			X		X		X		X		X	X	X	
In-/Exclusion criteria	X													
IRT call/notification	X		X		X		X		X		X	X	X	
Dispense trial medication	X		X		X		X		X		X	X		
Collect trial medication			X		X		X		X		X	X	X	
Compliance / drug accountability			X		X		X		X		X	X	X	
Termination of trial medication													X	
Conclusion of patient participation													X	X

Footnotes:

* In case of dose change (reduction or re-escalation) additional visits may have to be scheduled (refer to section 6.2.2)

[1] The patient is required to sign informed consent prior to any trial related activities.

[2] Visit 1 will occur on the same day as EOT_B in INBUILD®. Laboratory tests, physical examination, vital signs, pregnancy test, ECG and spirometry tests are performed only once on that day as part of the EOT_B visit in INBUILD®.

[3] Demographics will be collected from the INBUILD® database. Medical History will be collected from the INBUILD® database and may be updated with relevant new information.

[4] Medical conditions that are occurring concomitantly at visit 1 will be recorded as baseline conditions in the eCRF, including any ongoing AEs from INBUILD® at the time of Visit 1.

[5] Intermediate lab tests ('a'-Visits) to be done as needed for additional safety monitoring (see sections 4.2.1.2 and 5.2.3) at the discretion of the investigator. 'a' visits do not necessarily need to be a site visit.

[6] Urine pregnancy tests should be performed in all women of childbearing potential every 4-6 weeks: at least at every visit and if necessary, additionally at home or at a local doctor / laboratory. If urine pregnancy test is not acceptable to local authorities, a blood test can be done at a local laboratory. Women of childbearing potential will be instructed accordingly.

[7] Visit X stands for Visit 9, Visit 10 etc. Visits should be repeated every 12 weeks until at least visit 12 (Week 96). Thereafter, visits will be repeated every 12 weeks until the patient's end of trial (see section 3.3.4).

[8] End of Treatment (EOT) Visit to be performed for all patients, as soon as possible after last drug intake in this extension trial (refer to section 3.3.4 and 6.2.2).

[9] A follow-up (FU) visit should be planned for 28 days (+ 7 days window) after last drug intake in case trial medication had to be discontinued permanently due to adverse events. This visit may be conducted by telephone.

[10] After the individual patient's end of the trial the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, please see section 5.2.5.2.1.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Alkaline Phosphatase
ALAT	Latin American Thoracic Association
ALT	Alanine Aminotransferase
ALCOA	Attributable Legible Contemporaneous Original Accurate
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATS/ERS	American Thoracic Society / European Respiratory Society
AUC	Area under the Curve
AZA	Azathioprine
bid	Bis In Die (twice daily dosing)
BI	Boehringer Ingelheim
CA	Competent Authority
CHP	Chronic fibrosing Hypersensitivity Pneumonitis
CK	Creatine Kinase
C_{max}	Maximum Concentration
CML	Clinical Monitor Local
CNS	Central Nervous System
CRA	Clinical Research Associate
CrCL	Creatinine Clearance
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract / Clinical Research Organization
CT	Computed Tomography
CTD	Connective Tissue Disorder
CTD-ILD	Connective Tissue Disorder- associated Interstitial Lung Disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 3A4
DDI	Drug Drug Interaction
DILI	Drug Induced Liver Injury
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EOT	End of Treatment
ERS	European Respiratory Society
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FEV1	The Forced Expiratory Volume In One Second
FGFR	Fibroblast Growth Factor Receptor
FU	Follow Up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice

GGT	Gamma-Glutamyl Transferase
GI	Gastro Intestinal
GMP	Good Manufacturing Practice
Hb	Haemoglobin
Hct	Haematocrit
HR	Hazard Ratio
HRCT	High Resolution Computerised Tomography
IB	Investigator's Brochure
ICH	International Council on Harmonization
ICH M3 (R2)	International Council on Harmonization: Guidance on M3 (R2) Nonclinical Safety Studies
IEC	Independent Ethics Committee
IIPs	Idiopathic Interstitial Pneumonias
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
iNSIP	Idiopathic Nonspecific Interstitial Pneumonia
IPF	Idiopathic Pulmonary Fibrosis
IPV	Important Protocol Violation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
I.U.	International Units
IV	Intravenous
JRS	Japanese Respiratory Society
Lck	Lymphocyte-specific Tyrosine-protein Kinase
LDH	Lactate Dehydrogenase
LPLT	Last Patient Last Treatment
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligrams
mL	Millilitres
MMF	Mycophenolate Mofetil
NAC	N-Acetylcysteine
nRTK	Non-Receptor Tyrosine Kinase
OCS	Oral Corticosteriods
OPU	Operative Unit
PAH	Pulmonary Arterial Hypertension
p.o.	per os (oral)
PDGFR	Platelet-Derived Growth Factor Receptor
P-gp	P-glycoprotein
PF-ILD	Progressive Fibrosing-Interstitial Lung Disease
PK	Pharmacokinetics
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RA-ILD	Rheumatoid Arthritis-associated Interstitial Lung Disease
RA/CTD	Rheumatoid Arthritus/Connective Tissue Disease
RBC	Red Blood cell Count

REP	Residual Effect Period
RTK	Receptor Tyrosine Kinase
s.c.	Subcutaneous
SAE	Serious Adverse Event
SMQ	Standard MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
Src	Proto-oncogene tyrosine-protein kinase src
SSc-ILD	Systemic Sclerosis-associated Interstitial Lung Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit of Normal
VEGF/R	Vascular Endothelial Growth Factor / Receptor
WHO GCP	World Health Organization Handbook For Good Clinical Practice
WOCBP	Woman Of Childbearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Based on clinical experience, there is a group of patients who, independent from the interstitial lung disease (ILD) classification, at some point in time, develop a progressive fibrosing phenotype. In this group of patients, the natural history appears to follow a course similar to idiopathic pulmonary fibrosis (IPF) with worsening of respiratory symptoms, lung function, quality of life (QoL) and functional status, as well as early mortality despite treatment with currently available non-approved immunomodulatory therapies. The proposed terminology for describing this group is progressive fibrosing interstitial lung disease (PF-ILD).

Based on expert consensus, the main fibrosing ILDs in which progressive behaviour is present include:

- Idiopathic Interstitial Pneumonias (IIPs): mainly IPF, idiopathic non-specific interstitial pneumonia (iNSIP) and unclassifiable IIP
- Chronic fibrosing hypersensitivity pneumonitis (CHP)
- Autoimmune ILDs: connective tissue disease- ILD (CTD-ILD) (mainly rheumatoid arthritis-associated ILD (RA-ILD) and systemic sclerosis-associated ILD (SSc-ILD)) and idiopathic pneumonia with autoimmune features
- Environmental/occupational fibrosing lung disease

The scientific working hypothesis is that the response to lung injury in these ILDs includes the development of fibrosis which becomes progressive, self-sustaining and independent of the original clinical association or trigger. It is postulated that, at this stage, targeted antifibrotic therapy is required to slow the progression of the disease.

Based on the similarity in both, the biologic and clinical behaviours i.e. self-sustaining fibrosis and progressive decline in lung function and early mortality, it is considered justified to group patients with PF- ILDs together regardless of their original ILD diagnosis.

Nintedanib is a kinase inhibitor indicated for the treatment of IPF, which has been shown to slow the progression of IPF. The rationale for development of nintedanib in PF-ILD is supported by the pre-clinical 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). Based on the similarity in both the underlying pathophysiology and clinical course of PF-ILD and IPF, it is anticipated that nintedanib will elicit similar effects in PF-ILD as it demonstrated in IPF.

The efficacy and safety of nintedanib in patients with PF-ILD was investigated in the INBUILD® trial (BI trial 1199.247; EudraCT no. 2015-003360-37), the parent trial to this extension trial. Patients remained in the parent trial on blinded treatment (part B) until unblinded data were available from the first database lock (after last randomised patient reached the 52-week time point) of the parent trial. If further exposure was justified by these initial results of INBUILD®, the patients were offered to participate in this extension trial without treatment interruption.

Based on the INBUILD® results, nintedanib offers a long term antifibrotic maintenance treatment option for patients with PF-ILD, a medical indication with high unmet medical need. The current trial is aimed to establish the tolerability and safety of nintedanib in patients with PF-ILD over a longer duration of treatment.

1.2 DRUG PROFILE

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) including VEGFR (vascular endothelial growth factor receptor), PDGFR (platelet-derived growth factor receptor), FGFR (fibroblast growth factor receptor), and Src family kinases (Src, Lck and Lyn belonging to a family of proto-oncogene tyrosine-protein kinases).

All of these growth factor pathways and their down-stream signal cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling.

Nintedanib inhibited the proliferation and migration of human lung fibroblasts from patients with IPF. It demonstrated anti-fibrotic and anti-inflammatory activity in three animal models of lung fibrosis and in more specific models of SSc-ILD and RA-ILD. Although the initiation of the fibrotic lung pathology in these model systems is different, progressive fibrotic lung pathology with proliferation, migration and transformation of fibroblasts to the pathogenic myofibroblast is the final common pathway. These similarities and the mode of action of nintedanib directed against the proliferation, migration and transformation of fibroblasts strongly support the rationale for the use of nintedanib in the treatment of patients with PF-ILD (U06-1451, U06-1479, U12-2437-01, U12-2066-01, n00239669, n00247887).

Pharmacokinetics

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

Nintedanib is mainly eliminated via faeces.

Co-administration of nintedanib with the P-glycoprotein (P-gp) inhibitor ketoconazole increased exposure to nintedanib by 60-70% based on area under the curve (AUC) and by 80% based on a maximum measured concentration of the analyte in plasma (Cmax) in a dedicated drug-drug interaction (DDI) trial.

In a DDI trial with the P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60. 3% based on Cmax upon coadministration with rifampicin compared to administration of nintedanib alone.

Based on population pharmacokinetic (PK) analysis, age and body weight were correlated with nintedanib exposure. However, their effects on exposure are not sufficient to warrant an a priori dose adjustment. There was no influence of sex or mild and moderate renal impairment (creatinine clearance (CrCL) > 30 mL/min) on the exposure of nintedanib. In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib was approximately 2-fold higher in volunteers with mild hepatic impairment (Child Pugh A)

and approximately 8-fold higher in volunteers with moderate hepatic impairment (Child Pugh B). Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

The Residual Effect Period (REP) of nintedanib is 28 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
Nintedanib (trade name: Ofev) is approved for the treatment of IPF and for the treatment of SSc-ILD in the US, EU, Japan and a large number of additional countries. Nintedanib is recently also approved in the US, EU, Japan, Canada and a number of other countries for the treatment of (chronic) fibrosing ILDs with a progressive phenotype.

Summary of clinical efficacy results in IPF: The clinical efficacy of nintedanib has been studied in over 1400 patients with IPF in one phase II dose finding trial (TOMORROW) including four different doses of nintedanib, and two replicate phase III trials (INPULSIS® 1 and 2). 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 of forced vital capacity (FVC) (in mL) was demonstrated in patients receiving nintedanib 150 mg twice daily (bid) compared to patients receiving placebo. The treatment effect of nintedanib compared to placebo on FVC was consistent 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 (P14-07514; P11-11216).

Summary of clinical safety results in IPF: The safety profile of nintedanib in patients with IPF has been investigated comprehensively in clinical Phase II/III trials. The most commonly reported AEs were gastrointestinal disorders. Of those, the most frequent events were diarrhoea, nausea, vomiting and abdominal pain. Most of these events were of mild or moderate intensity, reported as non-serious, and were managed by symptomatic treatment and/or temporary interruption and/or reduction of the nintedanib dose. Diarrhoea, nausea, vomiting may lead to dehydration and/or electrolyte disturbances. Weight decreased and appetite decrease are also considered adverse drug reactions of nintedanib treatment.

Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALK, GGT). Administration of nintedanib was also associated with elevations of bilirubin. The dosing regimen, that includes dose reduction and dosing interruptions, was effective in the management of liver enzyme and bilirubin elevations (see section 4.2.1). Cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. In the post-marketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment.

Based on data from clinical trials and post-marketing and supported by population pharmakokinetic models, patients with low body weight (<65 kg), Asian and female patients have a higher risk of liver enzyme elevations with nintedanib treatment.

Patients at known risk for bleeding or who required fibrinolysis, full-dose therapeutic anticoagulation, or high dose antiplatelet therapy were excluded from participation in the

nintedanib in IPF trials, and initiation of any of these therapies during the course of the trials required discontinuation of the study medication. In the IPF phase III trials, bleeding events were slightly more frequently reported in patients treated with nintedanib than in those receiving placebo. In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed. Considering that VEGFR inhibition might potentially be associated with an increased risk of bleeding, patients with full-dose anticoagulation should only be treated with nintedanib if the anticipated benefit outweighs the potential risk.

Thromboembolic events were more frequently reported in the nintedanib group than in the placebo group. This difference was due to arterial thromboembolic events, specifically due to myocardial infarction. The proportion of patients with cardiac adverse events and cardiac SAEs, and especially AEs reflecting ischaemic heart disease, was balanced between the nintedanib and placebo groups. Based on the available clinical data, and considering the mechanism of action of nintedanib, no definitive conclusion on the risk of thromboembolic events can be drawn. Arterial thromboembolism is considered an important potential risk of nintedanib treatment in IPF.

A slightly increased frequency of arterial hypertension, which is considered an adverse drug reaction, was observed with nintedanib in the IPF clinical trials.

Based on cumulative post-marketing safety data bleeding, pancreatitis and thrombocytopenia are included as adverse drug reactions.

In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients. Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations have been reported in the post-marketing period. Gastrointestinal perforations are considered an important potential risk of nintedanib treatment.

Summary of clinical efficacy in patients with progressive fibrosing ILD: (INBUILD® study [c26471552])

The INBUILD® study was a multicentre, randomised, placebo-controlled, double-blind Phase III clinical trial to investigate the efficacy and safety of nintedanib in patients with progressive fibrosing ILDs over 52 weeks. 663 patients were randomised, stratified by HRCT fibrotic pattern: ‘UIP-like pattern only’ (412 patients) or ‘Other fibrotic patterns’ (251 patients). Treatment with nintedanib reduced the adjusted annual rate of decline in FVC by 106.96 mL/year (95% CI 65.42, 148.50; $p < 0.0001$) in the overall population and by 128.20 mL/year (95% CI 70.81, 185.59; $p < 0.0001$) in patients with HRCT with UIP-like fibrotic pattern compared with placebo. Consistent results were observed in the complementary population of patients with other HRCT fibrotic patterns (adjusted difference 75.28 mL/year; 95% CI 15.54, 135.01). The treatment effect was independent of HRCT pattern (interaction p-value 0.2268).

Secondary and further lung function endpoints (such as categorical changes in relative FVC % predicted and absolute change from baseline in FVC % predicted) supported the primary endpoint. Time-to-event endpoints further evidenced the treatment benefit of nintedanib vs. placebo and suggested that the reduction in FVC decline translated into a reduction of clinically meaningful outcome events. Over the whole trial (Part A+B), treatment with nintedanib reduced the risk of first ILD exacerbation or death by 33% compared with

placebo, as indicated by the HR of 0.67 (95% CI 0.46, 0.98), and numerically reduced the risk of death by 22% compared with placebo (HR 0.78; 95% CI 0.50, 1.21).

Summary of clinical safety results in patients with PF-ILD (INBUILD® study [c26471552])

In the overall population over 52 weeks, adverse events in the SOC 'gastrointestinal disorders' were the most common AEs and were reported more frequently in the nintedanib group (80.7%) than in the placebo group (45.0%). The difference was mainly driven by the PTs diarrhoea (nintedanib: 66.9%, placebo: 23.9%), nausea (28.9% vs. 9.4%), vomiting (18.4% vs. 5.1%), and abdominal pain (10.2% vs. 2.4%). Almost all of these events were non-serious and of mild or moderate intensity; they led to premature treatment discontinuation in less than 10% of patients. In line with the findings for gastrointestinal disorders, the proportions of patients with decreased appetite reported as AE and weight loss reported as AE or measured as body weight were higher for nintedanib than for placebo.

Elevations of hepatic enzymes are a known side effect of nintedanib treatment. The frequencies of patients with AEs in the safety topic 'hepatic enzyme increased' were about four times higher in the nintedanib group (22.6%) than in the placebo group (5.7%). Most of the liver laboratory AEs were non-serious. In the pooled INPULSIS® trials, the frequencies of patients with AEs related to liver enzyme elevations were about five times higher in the nintedanib group than in the placebo group [U13-2683-01/ c02153150-02]. In trial 1199.247, all patients with serious hepatobiliary or liver laboratory AEs in the nintedanib group, except for 1 patient with hepatic cirrhosis, recovered from these events, in most cases after drug withdrawal or dose reduction. Clinical liver failure in terms of hepatic decompensation was not reported. The reported hepatic laboratory changes were in line with the observed liver laboratory AEs.

In the INBUILD® trial, the incidence of hypertension, a labelled side effect of nintedanib in IPF, was comparable in both treatment groups. Serious and non-serious cardiovascular AEs were reported with similar frequencies in both treatment groups. No imbalances were observed for fatal or non-fatal MACE. AEs in the safety topic 'myocardial infarction' were reported for 0.9% of patients in both treatment groups.

The proportion of patients with AEs in the safety topic 'bleeding' was similar in the nintedanib group (11.1%) and in the placebo group (12.7%). Like in the INPULSIS® trials the majority of bleeding events in trial 1199.247 were non-serious cases, and SAEs were reported for very few patients only.

In conclusion, 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. There were no new or unexpected safety concerns identified in this trial. Overall, a positive benefit-risk profile for nintedanib in patients with progressive fibrosing ILD was shown.

For a more detailed description of the nintedanib profile, please refer to the current Investigator's Brochure (IB) for nintedanib in IPF, Systemic Sclerosis and PF-ILD (c01783972-11).

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is an extension trial of the 1199.247 parent trial, INBUILD® All patients still receiving blinded treatment at the end of part B of the parent trial had the possibility to receive open label nintedanib in this extension trial.

The aim of this extension trial is to evaluate long term tolerability and safety of nintedanib in patients with PF-ILD.

1.4 BENEFIT - RISK ASSESSMENT

In the group of patients with PF-ILD 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. With the exception of nintedanib and pirfenidone, which were available for patients with IPF, there was no approved therapy for PF-ILD at the start of this trial.

Based on the efficacy and safety shown in IPF patients, and considering the similarity of the pharmacological rationale between IPF and PF-ILD, the same dose regimen of 150 mg nintedanib bid is considered appropriate.

This extension trial only started recruiting when the results from the initial database lock (i.e. the efficacy and safety results after 52 weeks of treatment) of the INBUILD® trial had been reviewed and justified the start of this extension study. This meant that the nintedanib-treated patients showed a lesser decline in lung function compared to the placebo-treated group, and that the safety and tolerability was acceptable with no new relevant safety issues identified that influenced the existing benefit-risk assessment. The first day of this extension trial was on the same day as the last visit of the parent trial to allow continuous treatment.

All patients receive active treatment in this trial.

The risks of treatment with nintedanib have been well delineated in patients with the fibrotic lung disease IPF. These risks are primarily related to the gastrointestinal tract (diarrhoea, nausea, vomiting, abdominal pain), and are usually managed with supportive therapy and with temporary or permanent dose reduction to 100 mg bid. In some cases, temporary interruption or permanent drug discontinuation is necessary. A reduction in appetite and weight decrease has also been reported in patients treated with nintedanib.

The potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. The majority of patients presented with mild to moderate liver enzyme elevation, which was in most cases transient upon dose reduction or treatment discontinuation. However, severe DILI with fatal outcome has also been reported. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. Nintedanib must be dose-reduced, or interrupted in the event of hepatic toxicity and further treatment withheld until recovery of the abnormal laboratory parameters (see also section 4.2.1.2 and 5.2.5.1.4).

Concomitant therapies with a known overlap in side effects with nintedanib (e.g. gastrointestinal [GI] adverse events, increase of AST, ALT, bilirubin) or concomitant use of therapies that interact with metabolism of nintedanib (through UGT1A1 and P-gp) should be used with caution and patients should be closely monitored (see section 4.2.2.2).

Potential risks of nintedanib treatment also include gastrointestinal perforations and thromboembolism. Hypertension, thrombocytopenia and bleeding are considered side effects of nintedanib treatment in IPF. Therefore, the use of full dose therapeutic anticoagulation, fibrinolysis or high-dose antiplatelet therapy is not recommended during the trial, and patients requiring such a treatment should only be treated with nintedanib if the anticipated benefit outweighs the potential risks.

The mode of action of nintedanib indicates a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality. In women of childbearing potential receiving nintedanib, contraceptive measures must be employed 28 days before treatment initiation, during the treatment and for a period of 3 months after last drug intake.

The underlying diseases should be managed in accordance with current standard management practices. In some of the underlying diseases, immunosuppressive agents as well as of non-immunosuppressive therapies are commonly used to treat organ-specific manifestations, and need to be considered although appropriate randomised-controlled data for these therapies are lacking. Cautionary notes are included in the protocol (section 4.2.2.2) with regard to such therapies whose safety profile could interfere with that of nintedanib.

Safety will be closely monitored at site visits, including physical examinations, safety laboratory and specific monitoring procedures, to follow-up potential hepatic enzyme elevation and exclusion of pregnancy. In addition, safety laboratory results will be monitored at intermediate lab visits in the first year. In patients who develop severe symptoms of gastrointestinal toxicity not amenable to symptomatic treatment with standard measures or severe liver enzyme elevations or other severe adverse events as specified in section 3.3.4, treatment with nintedanib must be discontinued and appropriate therapeutic measures taken.

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 whether PF-ILD conveys a higher risk for adverse outcomes in case of COVID-19.

The trial related risk to the COVID-19 pandemic situation is the general risk of travelling to site and being at site for assessments with increased infection risk for lung function testing. Risk mitigation and possible modifications are described in Section 6.1 and in Appendix 10.3

In conclusion, the benefit-risk profile is considered appropriate for this stage of clinical development.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective is to assess long term tolerability and safety of treatment with oral nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) who have completed (and did not prematurely discontinue trial medication in) the phase III parent trial, INBUILD® (trial 1199.247).

2.1.2 Primary endpoint(s)

The primary endpoint is the incidence of overall adverse events over the course of this extension trial.

2.1.3 Secondary endpoint(s)

No secondary efficacy endpoints are defined.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, prospective, open label extension clinical trial. It is estimated that approximately 480 patients with PF-ILD will complete the INBUILD® trial 1199.247 (part A and part B) on blinded treatment. These patients will be eligible for enrolment in this extension trial. Patients who withdrew treatment prematurely in the INBUILD® trial will not be eligible for the open label extension trial (INBUILD®-ON).

At the time point when the data from the INBUILD® trial for patients with PF-ILD are available, and justify the start of the extension trial, all patients on blinded treatment at the end of the parent trial can be offered participation in the current rollover study.

After signing Informed Consent, and if all eligibility criteria are met, patients will initiate treatment with nintedanib (Visit 1) (refer to section 4.1.3). Patients will receive active drug at a dose of 150 mg bid or 100 mg bid, depending on their last dose of blinded medication in the parent trial. Patients whose last dose of blinded medication in the parent trial was 150 mg bid will receive nintedanib 150 mg bid in the extension trial. Patients who dose reduced to 100mg bid in the parent trial, can either receive nintedanib 100 mg bid or be offered nintedanib at the dose of 150 mg bid based on the judgement of the investigator.

In order to collect long-term safety data in patients with PF-ILD, all patients will be requested to stay in the trial for 96 weeks (until visit 12). At week 96, patients who can be treated with nintedanib outside the clinical trial will have their EOT visit. The remaining patients will continue in the trial until nintedanib can be made available to them outside the clinical trial. Treatment will be stopped if a reason for withdrawal is met (refer to section 3.3.4). Overall, the trial is estimated to last a total of approximately 36 months.

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

The trial will be conducted as a prospective, open-label trial. This design is appropriate for assessing the long-term tolerability and safety of nintedanib in patients with PF-ILD.
All patients eligible for this extension study will have completed the parent trial, i.e. were treated with blinded study drug (nintedanib or placebo) for at least 52 weeks and did not prematurely discontinue blinded treatment. All patients in the extension study will receive active treatment as prolonged use of placebo would not be appropriate.

3.3 SELECTION OF TRIAL POPULATION

It is anticipated that approximately 480 patients, from approximately 160 sites in about 15 countries, will complete the INBUILD® trial and will consent to participate (and thus receive treatment) in this extension trial. At the start of the open label extension trial it is not known which treatment the patients have received in INBUILD®. Patients previously on active treatment will continue treatment with nintedanib, patients who received placebo will initiate treatment with nintedanib for the first time at Visit 1 of the extension 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).

If a patient is entered 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

Only patients with PF-ILD who have completed the parent trial (INBUILD®) on treatment (i.e. did not early discontinue treatment) are eligible and will be included in this trial if they fulfil all the inclusion and do not present any of the exclusion criteria.

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. Male or female patients who completed the INBUILD® trial as planned and who did not prematurely discontinue blinded treatment.

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

3. Women of childbearing potential (WOCBP)[1] must continue 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 and in section 4.2.2.4.

3.3.3 Exclusion criteria

1. Any disease that may put the patient at risk when participating in this trial. Reconsider carefully all exclusion criteria of the INBUILD® trial (see Appendix 10.1). However, patients may qualify for participation even though exclusion criteria may have been met during the course of participation in INBUILD®, if the investigator's benefit-risk assessment remains favourable.

2. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
3. Patient not compliant in parent trial (INBUILD®), with trial medication or trial visits, according to investigator's judgement.

4. Previous enrolment in this trial.

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

5. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to complete the trial.

6. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Withdrawal of patients from treatment or assessments

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

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 the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship. These data will be included in the trial database and will be reported.

3.3.4.1 Discontinuation of trial treatment

An individual patient will permanently discontinue trial treatment if:
- The patient experiences signs of hepatic injury, defined in section 5.2.5.1.4
- In the opinion of the investigator, the patient experiences unacceptable adverse events despite dose adjustments and supportive care.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take prohibited concomitant medication as defined in section 4.2.2 "Restrictions".
- The patient can no longer receive nintedanib for medical reasons
- Pregnancy: if a patient becomes pregnant during the trial, nintedanib needs to 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 5.2.5.2.4 for detailed information on event reporting in case of pregnancy.

In the following cases discontinuation of nintedanib is highly recommended. Only in special circumstances, the investigator, upon thorough assessment of all available clinical data and taking into consideration the potential risks associated with administration of nintedanib, may decide not to withdraw the trial medication, even though one or more of the below mentioned criteria are fulfilled. 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.

- Major surgery, including any abdominal or intestinal surgery.
- Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, factor Xa inhibitors etc.), or high-dose antiplatelet therapy. (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 is allowed.).
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.

In case of a temporary interruption, trial treatment should be restarted if medically justified, please see section 4.2.1.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the options for continued follow up outside of the trial after trial discontinuation, please see section 3.3.4.1 above.

Given the patient's agreement, the patient will undergo the procedures for trial discontinuation and follow up (if applicable) as outlined in the Flowchart and section 6.2.3.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
2. Patients have alternative access to nintedanib, for example via an alternative clinical trial, marketed product, an expanded access program, named patient use program, compassionate use protocol or other means based on local regulation.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

All patients will be treated with nintedanib in this trial; there is no active comparator or placebo.

Substance:	**Nintedanib**
Pharmaceutical formulation:	Soft gelatine capsule
Source:	BI Pharma GmbH & Co. KG
Unit strength:	150mg, 100mg
Posology:	Bid
Route of administration:	Oral (swallowed)

4.1.2 Selection of doses in the trial and dose modifications

Based on the efficacy, safety and dose-finding from trials investigating nintedanib in IPF, a dose of 150 mg bid is selected for the PF-ILD program. With 150 mg bid, acceptable tolerability in PF-ILD patients is expected based on the risk profile seen in IPF patients. However to manage adverse events, the dose may be reduced to 100 mg bid temporarily or permanently (see section 4.2.1 and section 6.2.2).

The objective of INBUILD® was to assess the efficacy and safety of a dose of 150 mg bid compared to placebo. Patients were randomised either to blinded nintedanib or to blinded placebo 150 mg bid.

Patients taking 150 mg bid blinded study medication (active drug or placebo) at the end of INBUILD® will start treatment with nintedanib 150 mg bid in the current extension trial. Patients taking 100 mg bid blinded study medication (active drug or placebo) at the end of INBUILD® will start treatment with nintedanib in the current extension trial either at 100 mg bid or at an increased dose of 150mg bid at the discretion of the investigator.

For patients who receive nintedanib 100 mg bid in the extension study, at the time of unblinding (final database lock) of the INBUILD® trial, it is allowed to increase the dose to 150 mg bid at the discretion of the investigator, based on the unblinding information. In this situation, dose increase will need to be assigned through IRT, and an additional visit might be required (refer to section 6.2.2).

Nintedanib can be interrupted or reduced without prior interruption, i.e., immediately stepping down from 150 mg bid to 100 mg bid at the discretion of the investigator to manage adverse events. Dose adjustments might require a special trial visit according to the procedures in section 6.2.2.

4.1.3 Method of assigning patients to treatment groups

All patients will receive treatment with nintedanib. Interactive Response Technology (IRT) will be used to assign medication numbers to eligible patients. Distribution of nintedanib to sites will be triggered by IRT. Details on the IRT system are provided in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

The treatment for an individual patient will be assigned by means of an IRT contact during Visits 1, 3, 5, 6, 7, 8 to X. Each patient will receive active drug at a dosage of 150mg bid or 100mg bid.

Trial medication will consist of 1 capsule twice daily throughout the trial. Wallets covering 30 days + 5 days reserve treatment will be dispensed to the patient:

- 1 wallet at Day 1 (Visit 1) (30 days plus 5 days reserve)
- 2 wallets at Visit 3 (60 days plus 10 days reserve)
- 3 wallets at Visit 5, Visit 6, Visit 7, Visit 8 and Visit X (90 days plus 15 days reserve)

Nintedanib will be administered orally on a twice daily basis (bid). The patients should swallow the trial medication unchewed together with a glass of water (~250mL), and should observe a dose interval of 12 hours. Nintedanib needs to be taken at the same times every day (between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening). Because nintedanib may cause stomach discomfort, it is recommended to take the trial medication with food.

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.

Nintedanib should only be dispensed to participating patients according to the protocol by authorised personnel as documented in the form “Trial Staff List”.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on actual treatment.

The previous treatment received in INBUILD® (active drug or placebo) will remain unknown to the investigator and patient until after the final database lock of INBUILD®. No individual unblinding regarding treatment received in INBUILD® should occur prior to this time.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated clinical research organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Initial supply and re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites, and assign treatment kits to each patient.

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

Primary trial material will be capsules containing 150 mg of nintedanib (or 100 mg of nintedanib if dose is reduced). All trial medication will be packaged in blister cards. Each blister card will contain 10 capsules. Seven blisters cards will be packaged into one child-resistant tamper-evident wallet (i.e. 70 capsules/wallet). Each wallet will be labelled with a multi-language booklet according to the requirements of the participating countries.

One wallet provides for one month of treatment.

Re-supplies of trial medication are planned due to the short expiry date and the long duration of the trial. The medication for re-supply will be packaged in an identical manner as the medication for initial supply.

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 local clinical monitor (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 a clinical research organisation (CRO) appointed by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the institutional review board (IRB) / ethics committee (EC),
- Availability of a signed and dated clinical trial contract between the sponsor and the head of 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,
- In countries where it is required, availability of the proof of a medical license for the Principal Investigator,
- In the US, availability of FDA Form 1572.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Rescue medications to reverse the action of nintedanib are not available.

There are no special emergency procedures to be followed.

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 dose. In case of persistent adverse events observed at this dose, or severe effects at 150 mg bid, permanent treatment discontinuation should be considered.

Dose reduction from 150 mg bid to 100 mg bid was possible at Visit 1 if required to manage adverse events identified at the end of the INBUILD® trial.

Treatment interruption and reduction and re-escalation are repeatedly possible.

Table 4.2.1: 1 Allowed treatment reduction / interruption periods

	AEs considered drug related	**AEs or other events not considered drug related**
Maximum interruption	4 weeks	12 weeks
Recommended restart	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	Any time to 150 mg bid	----

4.2.1.1 Management of diarrhoea

Diarrhoea is a known side effect of nintedanib treatment (see section 1.2). 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 antidiarrhoeal symptomatic treatment, e.g. loperamide.

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and dose reduction of nintedanib should be considered based on 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-diarrhoeal 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-diarrhoeal 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, hospitalisation 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 causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, bacterial overgrowth, antibiotic treatment)

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

4.2.1.2 Management of liver enzyme elevation

Evaluate the concomitant use of other drugs known to cause liver enzyme elevations. 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 Management of liver enzyme elevations

<table>
<tr><td colspan="3">AST or ALT increase to</td><td rowspan="2">Signs of hepatic injury* (section 5.2.5.1.4)</td></tr>
<tr><td>>1.5x to <3x ULN</td><td>≥3x to <5x ULN and no signs of hepatic injury (section 5.2.5.1.4)</td><td>≥5x to <8x ULN and no signs of hepatic injury (section 5.2.5.1.4)</td></tr>
<tr><td>Continue as planned[1]</td><td>Reduce dose or interrupt trial medication [2]</td><td>Interrupt trial medication</td><td>Permanently discontinue / interrupt trial medication</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">Close observation[3]

After 2 weeks or any time later</td><td rowspan="2">Close observation[3]

After 2 weeks or any time later</td><td>CLINICAL EVALUATION OF HEPATIC-INJURY[4] (section 5.2.5.1.4)</td></tr>
<tr><td colspan="3">↙ ↓ ↓ ↘</td></tr>
<tr><td><3x ULN</td><td>≥3x ULN</td><td>< 3x ULN</td><td>≥3x ULN</td></tr>
<tr><td>Reduced: return to initial dose.

Interrupted: restart at reduced dose.
Monitor every 2 weeks for at least 8 weeks</td><td>Permanently discontinue trial medication

Close observation[3]</td><td>Restart at reduced dose

Monitor weekly for 4 weeks, then every 2 weeks for at least 8 weeks</td><td>Permanently discontinue trial medication.

Close observation[3]</td></tr>
</table>

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

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

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

[4] If clear evidence for alternative cause for hepatic injury was identified and resolved (i.e. relation to trial medication excluded, hepatic injury confirmed to have alternative explanation [other than use of IMP]): return to trial medication would be possible, after consultation with the sponsor. Prior to restart, liver laboratory values must be normal. Monitor weekly for first 4 weeks of re-introduction and every 2 weeks for the following 8 weeks.

Initial assessment and blood sampling for liver enzyme elevation follow up should be performed at the investigational site. Blood samples for additional monitoring may be collected at the investigational site, primary care physician or external laboratory with specific trial lab kits and sent to the central laboratory for analysis.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Investigational therapy is not allowed during the entire study period of this open label extension trial.

There are no further restrictions for treatment of the underlying disease or other treatments for the ILD, thus allowing the underlying disease to be managed according to current standard practice (see cautionary notes below).

4.2.2.2 Cautionary notes

As nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4, concomitant use of P-gp and CYP3A4 inhibitors (e.g. erythromycin) with nintedanib may increase exposure to nintedanib. Patients taking potent P-gp inhibitors (e.g. ketoconazole, erythromycin or ciclosporine) should be monitored closely for tolerability of nintedanib. Management of adverse events may require interruption, dose reduction, or discontinuation of therapy with nintedanib.

Concomitant use of P-gp and CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's wort) with nintedanib may decrease exposure to nintedanib and should be avoided.

As the most common side effects known for nintedanib are GI effects, the concomitant use of medication with an overlapping safety profile (e.g. methotrexate, mycophenolate mofetil) should be carefully considered.

Nintedanib is 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) are recommended every 2 weeks for approximately 6 weeks, by using the intermediate (a-visit) trial lab kit.

The concomitant use of 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) is not recommended (see note section 3.3.4.1).

4.2.2.3 Restrictions on diet and life style

There are no restrictions on diet and lifestyle.

4.2.2.4 Contraception requirements

WOCBP (for the definition please refer to section 3.3.2) must continue to 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. They must use one barrier method, i.e. condom or occlusive cap with spermicide, or vasectomised partner, and one highly effective non-barrier method including oral, injected or implanted hormonal contraceptives, intrauterine device or system or bilateral tubal occlusion.

4.3 TREATMENT COMPLIANCE

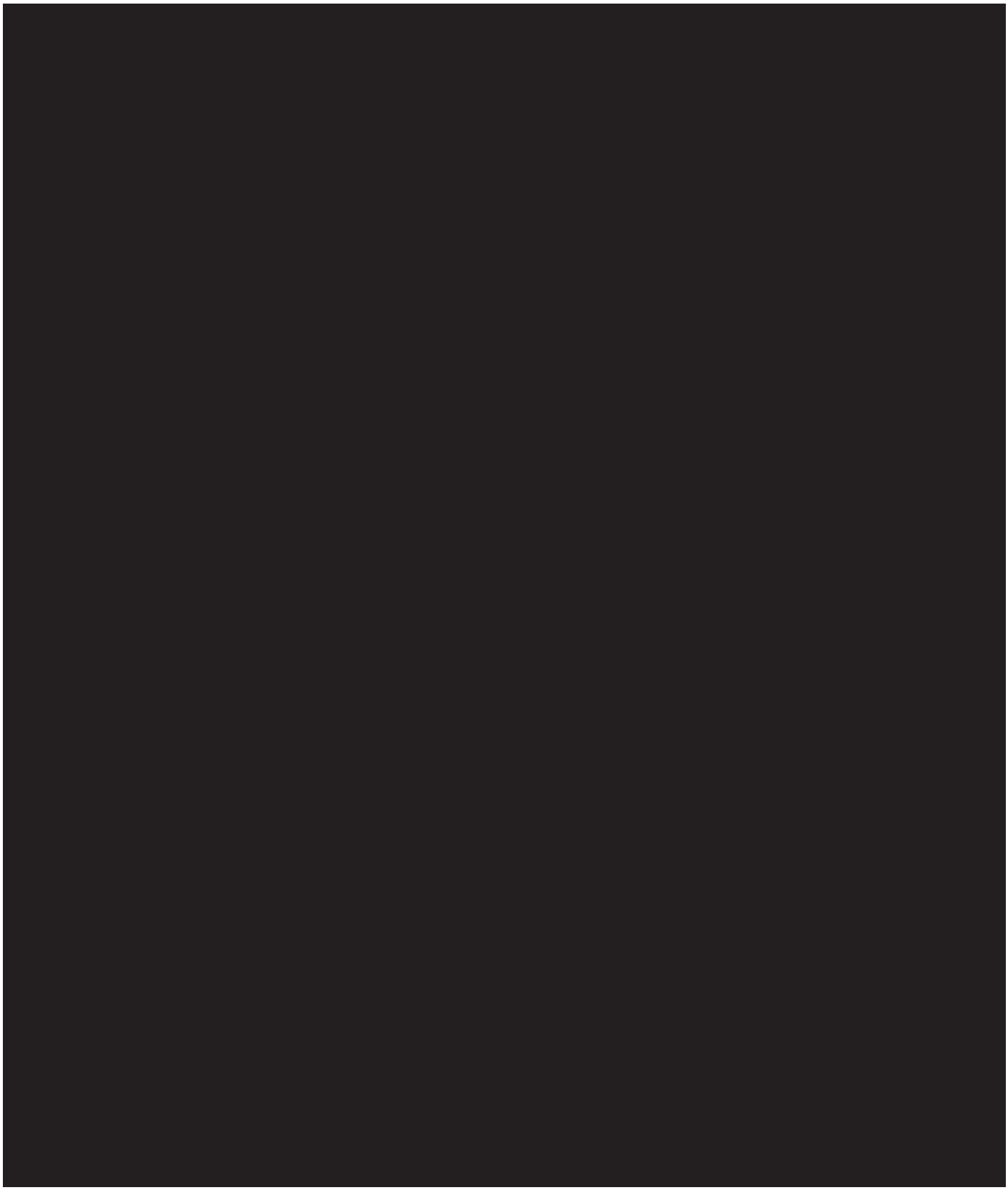
Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on capsule counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of capsules actually taken} \times 100}{\text{Number of capsules which should have been taken}}$$

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

5. ASSESSMENTS



[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination, including body weight, will be performed at the time points specified in the Flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height will be performed at Visit 1.

All abnormal findings at baseline (Visit 1) in the extension trial will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions in the extension trial detected at subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

5.2.2 Vital signs

Systolic and diastolic blood pressure and pulse rate will be measured at the time points specified in the Flowchart, ideally prior to blood sampling and with the patient seated after having rested. All abnormal findings at baseline (Visit 1) in the extension trial will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions in the extension trial detected at subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

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 Flowchart.

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. 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 lab and detailed documentation (Laboratory Manual) will be included in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.5.2).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.5.1.4 and the DILI Checklist provided in the ISF). 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.

The laboratory tests at regular site visits (Visit 1, Visit 3, Visit 5, Visit 6, Visit 7, Visit 8 to X) will include:

Table 5.2.3: 1 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 Creatinine Glucose (non fasting) Uric acid Thyroid stimulating hormone (at V1 then every 48 weeks and at EOT)
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalised ratio (INR) Partial thromboplastin time (PTT) Prothrombin time (PT)
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.	

The laboratory tests at Visit 2, Visit 4, Visit 5a, Visit 6a and Visit 7a will include:

Table 5.2.3: 2 Laboratory tests at Visit 2, Visit 4, Visit 5a, Visit 6a and Visit 7a

Category	Laboratory test
Biochemistry	Total protein, creatinine, electrolytes (sodium, potassium, calcium, chloride, inorganic phosphorus) and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin)
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.	

The laboratory samples taken at intermediate 'a' visits (Visits 5a, 6a and 7a) and any samples taken for additional safety monitoring (see section 4.2.1.2) 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. Dependent on concomitant treatments, additional safety monitoring should be considered 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 3.3.4 for withdrawal criteria.

5.2.4 Electrocardiogram

Resting 12-lead electrocardiograms (ECGs) will be conducted during the trial with site's own equipment. 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 Visit 1) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of AEs

5.2.5.1.1 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 according to the criteria in section 5.2.5.1.2):

- 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, including adverse events that started during the parent trial, INBUILD®, and that are still ongoing at the time of Visit 1 of the extension trial, they will be considered as baseline conditions and should be collected on the Baseline Condition eCRF only.

5.2.5.1.2 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,
- requires 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.

For Japan only:
The following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

5.2.5.1.3 AEs considered "Always Serious"

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 5.2.5.2, subsections "AE Collection" and "AE reporting to sponsor and timelines"**.**

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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 electronic data capture (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 above.

5.2.5.1.4 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 5.2.5.2.2.

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 lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication and need to be followed up according to the "drug-induced liver injury (DILI) checklist" provided in the ISF.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are

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.

5.2.5.1.5 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.

5.2.5.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship, 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.

5.2.5.2 Adverse event collection and reporting

5.2.5.2.1 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: 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 on the SAE form, any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however not be reported in the CRF.

5.2.5.2.2 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 reporting process 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.

5.2.5.2.3 Information required

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.

5.2.5.2.4 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.

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 Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (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 Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.5.2.5 Safety monitoring and adverse events with additional information collection

Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse event 'Diarrhoea' and the adverse events in the subordinate Standard MedDRA Query (SMQ) 'Haemorrhage terms, excluding laboratory terms'.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Not applicable

5.3.2 Methods of sample collection

Not applicable

5.3.3 Analytical determinations

Not applicable

5.3.4 Pharmacokinetic – pharmacodynamic relationship

Not applicable

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable

5.5 BIOBANKING

Not applicable

5.5.1 Methods and timing of sample collection

Not applicable

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and ECG. These endpoints are standard and accepted for evaluation of safety and tolerability of an oral drug, and they are widely used in this kind of study. The timing of all measurements is presented in the Flowchart.

Spirometry is a validated and well-established measurement tool for lung function testing (P05-12782).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flowchart. Some flexibility is allowed in scheduling the visits according to visit time windows as specified in the Flowchart. The trial medication kits contain sufficient medication to allow for these time windows. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule (calculated from Visit 1). All deviations from the planned visit schedule will be documented. In case of a missed visit, the investigator should contact the local clinical monitor, these will be addressed on a case by case basis.

All patients that complete the INBUILD® trial and did not prematurely discontinue blinded treatment may be eligible for this trial. After giving informed consent (at the latest before any procedure related to this study 1199-0248 is performed), and if all inclusion criteria and none of the exclusion criteria are met, patients enter the trial on the same day as the EOT_B visit in the parent trial, INBUILD®.

Patients will be requested to stay in the trial for 96 weeks (until visit 12). At week 96, patients who can be treated with nintedanib outside the clinical trial will have their EOT visit. The remaining patients will continue in the trial until nintedanib can be made available to them outside the clinical trial. Treatment will be stopped if a reason for withdrawal is met (refer to section 3.3.4).

In exceptional circumstances, when it is impossible to conduct study visits at the study site, study visits may be performed at the patient's home or remotely (via telephone and/or internet based means of communication). The visit may also be performed as a hybrid of home and remote visit. All home/remote visits need to be discussed and approved by the sponsor's trial team. Local regulatory and legal requirements of the participating country still apply. The trial team's decision will be based on a thorough benefit-risk evaluation.

The procedures performed during a home/remote visit may be adjusted as compared to a regular visit, as detailed in Appendix 10.3.

If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF. Minimum required safety lab parameters are AST, ALT, GGT, ALK and Total bilirubin. For patients who have been in the trial for at least 36 weeks, the maximum interval between two lab measurements for these parameters is 16 weeks. If the interval is more than 16 weeks, trial treatment should be interrupted (refer to section 4.2.1). These measures relating to lab sampling were not possible early in the trial when frequent monitoring was mandatory.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations and assessments will be performed as outlined in the Flowchart and as per the descriptions listed below.

6.2.1 Screening and run-in period(s)

Visit 1 will be conducted on the same day as EOT_B of the parent trial, INBUILD® so that there is no interruption of treatment. The trial will be explained to all patients who completed INBUILD® (who didn't discontinue treatment) and are willing to continue or start treatment with nintedanib. This may be done prior to Visit 1, however no trial related procedure or data collection should be performed until the patient has signed the Informed Consent for the extension trial at Visit 1.

Upon obtaining informed consent, the investigator will register the patient in the IRT system and the patient will receive a trial identification card.

Assessments conducted as part of EOT_B of the INBUILD® trial do not need to be repeated for Visit 1 of this extension trial.

If the patient has been determined eligible by the investigator to enter the trial (refer to section 3.3), medication will be assigned to the patient via the IRT system (refer to section 4.1.3). First dose of nintedanib within INBUILD®-ON will be administered in the clinic at Visit 1. Data from the EOT_B assessments will be transferred to INBUILD®-ON as baseline data. All AEs ongoing at the EOT_B visit of INBUILD® will be recorded as baseline conditions in INBUILD®-ON.

6.2.2 Treatment period(s)

Subsequent clinic visits will be scheduled after 2, 4, 8, 12, 24, 36 and 48 weeks of treatment (Visits 2- 8). After the first 48 weeks of treatment (Visit 8), complete clinic visits will be scheduled every 12 weeks until at least Week 96 (Visit 12) and thereafter until the patient's end of trial.

Intermediate lab tests ('a' visits) will be performed if needed at 18, 30 and 42 weeks (Visits 5a, 6a and 7a) at the discretion of the investigator. The laboratory samples taken at these visits and any samples taken for additional safety monitoring (see sections 4.2.1.2 and 5.2.3) 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.

If possible, ECG should be performed prior to blood draw.

For detailed description of the trial procedures at each visit and dispensing schedule, please refer to section 5 and the Flowchart.

Dose Modification Visit
If the dose is reduced or increased (refer to section 4.1.3) patients may need to come to the investigational site for a dose modification visit where the following will be performed:

- Physical examination including weight
- Vital signs

- Assessment of adverse events and concomitant therapy since last visit
- Assignment of new dose in IRT and trial medication dispensation
- Trial medication will be collected and drug accountability and treatment compliance will be reviewed

End of Treatment (EOT)

If a reason for drug discontinuation is met or when the trial is terminated due to one of the reasons mentioned in section 3.3.4, an End of Treatment Visit (EOT) should be scheduled as soon as possible after last drug intake for all patients. Reason for discontinuation must be documented in the eCRF. IRT should always be notified on end of treatment (EOT).

Adverse events that are ongoing at EOT should be followed up according to section 5.2.5.2.3.

For detailed description of the trial procedures at the EOT visit, please refer to the Flowchart.

6.2.3 Follow up period and trial completion

A follow-up (FU) visit must be conducted 28 days after last drug intake if trial medication was discontinued permanently due to adverse events. A FU visit does not need to be conducted for patients who stop for any other reason.

For detailed description of the trial procedures at the FU visit, please refer to the Flowchart.

If the reason for removal of a patient from the treatment is an adverse event, the patient must be followed until complete resolution or stabilization of the event for at least 28 days after the onset of the event or until follow-up is considered adequate by the investigator and clinical monitor.

A patient will be lost to follow-up if the investigator is not able to contact him/her despite multiple attempts. Every effort must be made; at least 2 telephone contacts plus 1 mailing should be documented. The site must notify the clinical monitor prior to designating a patient as lost to follow up.

For patients who permanently discontinue nintedanib due to adverse events, the FU Visit will be the trial completion visit. For all other patients the EOT visit will be the trial completion visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a multi-centre, multi-national, open-label clinical trial to investigate the long-term tolerability and safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) previously treated in a double-blind phase III placebo controlled trial (INBUILD®).

As the main objective of this extension trial is to study long-term tolerability and safety, only descriptive statistics will be used. Some limitations due to the nature of the extension trial should be considered when interpreting the data (bias in the selection of the population, no comparative arm). Further endpoints are considered as exploratory only.

This statistical paragraph deals with the analyses to be performed on the extension trial only. Although data of the parent trial will not be described in the scope of these analyses, they will be taken into account for adverse events analyses, as well as other evaluations.

7.2 NULL AND ALTERNATIVE HYPOTHESES

All analyses in this trial are descriptive and exploratory in nature. No formal statistical inferences are foreseen.

7.3 PLANNED ANALYSES

All evaluations will be based on the treated set (TS), unless otherwise stated. The TS will consist of all patients who are documented to have received and taken at least one dose of open-label trial medication.

The definition of important protocol violations (IPV) will be specified in the trial statistical analysis plan (TSAP). These IPV definitions will include consideration of important violations of entry criteria, treatment non-compliance, restricted medications and inadequate follow-up of hepatic events.

Patients will be analysed according to their randomised treatment group in the previous trial (INBUILD®) and overall.

Values collected at Visit 1 will be considered as the baseline, for this extension trial.

The main statistical analyses as described below will be performed based on all data collected during the on treatment period.

7.3.1 Primary endpoint analyses

The primary objective of the study is to assess the tolerability and safety of nintedanib, so please refer to section 7.3.4. Number of patients and % will be presented over the extension trial by category for adverse events overall.

7.3.2 Secondary endpoint analyses

Not applicable.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

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. No hypothesis testing is planned.

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

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

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

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Not applicable.

7.4 INTERIM ANALYSES

Interim analyses could be performed upon request from Health Authorities or for publication purpose. All the above mentioned analyses may be presented at each interim analysis.

7.5 HANDLING OF MISSING DATA

Missing or incomplete AE dates will be imputed according to BI rules. No imputation is planned for other safety criteria.

Missing or incomplete data for survival are managed by censored data analyses. No specific procedures need to be specified to handle them.

[redacted]

7.6 RANDOMISATION

Not applicable as this is an extension trial.

7.7 DETERMINATION OF SAMPLE SIZE

Not applicable as this is an extension trial. The number of patients included in this trial will correspond to the number of patients who have completed INBUILD® and did not prematurely discontinue trial medication, who fulfil the eligibility in this trial and are willing to participate.

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles.

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 finalization of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan 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. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

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.

Source documents in addition to the patient file are:

- [redacted]
- Laboratory reports

- ECG results (original or copies of printouts)

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

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.7.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

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 clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Trial Clinical Monitor (TCM), 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 Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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, [redacted] and an IRT vendor will be used in this trial. Details will be provided in the Central Laboratory Manual, Spirometry Manual and IRT Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

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n00239669 [redacted] Evaluation of Nintedanib in preclinical model systems of systemic sclerosis. Study number Dist-GvHD-Tsk-1-Fra-2. 26 September 2014. This was submitted to IND 124707 on January 15, 2015 (Sequence 0001/Serial Number Not Applicable), Module 4.2.1.1.

n00247887 [redacted] Evaluation of the therapeutic efficacy of Nintedanib in a model of rheumatoid arthritis-associated intersitial lung disease. 11 Feb 2016.

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10. APPENDICES

10.1 1199.247 (INBUILD®) EXCLUSION CRITERIA (BASED ON FINAL PROTOCOL VERSION 2 DATED 21 DEC 2016)

1. AST, 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 (refer to Appendix 10.2).
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.
   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
8. Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 Guidelines (P11-07084).
9. 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
10. Primary obstructive airway physiology (pre-bronchodilator FEV1/FVC < 0.7 at Visit 1).
11. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
12. Major extrapulmonary physiological restriction (e.g. chest wall abnormality, large pleural effusion)
13. 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
14. 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.

15. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1.
16. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin)
17. Patients with peanut allergy.
18. 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.
19. Life expectancy for disease other than ILD < 2.5 years (Investigator assessment).
20. Planned major surgical procedures.
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
22. 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.
23. In the opinion of the Investigator, active alcohol or drug abuse.
24. Patients not able to understand or follow trial procedures including completion of self-administered questionnaires without help.

10.2 CREATININE CLEARANCE

Creatinine clearance calculation is done according to Cockcroft 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 VISIT MODIFICATION IN EXCEPTIONAL CIRCUMSTANCES

INITIAL	MODIFIED or ADDED
Face-to-face patient visit performed by a physician/under the responsibility of a physician on site.	Remote or home visit performed by the investigational site physician/under the responsibility of the investigational site physician to ensure the wellbeing of a patient and to collect at least: **Adverse Events** / **Concomitant Treatments and Drug Interruption**
Regular on-site safety lab test using central lab kits: • Haematology, Biochemistry, Electrolytes, Coagulation, Urinalysis every 12 weeks; additional liver enzyme monitoring optional in between • Pregnancy every 4-6 weeks (possible at home)	• Under treatment with nintedanib, regular liver enzyme monitoring is required and needs to be ensured by the investigational site, but can be done at a local lab / local doctor. The investigator has to ensure medical review and proper documentation in the eCRF. Minimum required safety lab parameters are AST, ALT, GGT, ALK and Total bilirubin. • Urine pregnancy tests (for women of childbearing potential only) are regularly required and may be done at local lab / local doctor, or at home. • For patients who have been in the trial for at least 36 weeks, the maximum interval between two lab measurements for these parameters is 16 weeks. If the interval is more than 16 weeks, trial treatment should be interrupted. These measures relating to lab sampling were not possible early in the trial when frequent monitoring was mandatory. Decision whether to continue nintedanib treatment should be made based on an individual risk assessment for that individual patient and weigh up the benefits of an extended lab interval to maximum 16 weeks versus an interruption of treatment. • Medical decision has to be documented in patient's source notes. If remote patient visits and/or local liver enzyme monitoring cannot be performed, nintedanib treatment needs to be interrupted.
If liver function tests are out of the range, the per protocol rules apply => dose reduction	If the patient cannot come to site to receive new dose treatment and/ or patient safety and follow up safety lab testing cannot be guaranteed, treatment needs to be interrupted.
Dispensation of study treatment on site	• Site / depot to patient IMP shipments • Patients must consent to providing contact details for shipping purposes • Patients should retain all unused IMP and packaging, and return it when they are able to return to the site.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		01 Sep 2020
EudraCT number **EU number**		2018-000525-32
BI Trial number		1199-0248
BI Investigational Medicinal Product(s)		Nintedanib
Title of protocol		An open-label extension trial of the long-term safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		1. Introduction
Description of change		Section 1 was updated to ensure that current knowledge and recent data are reflected in the indroduction section.
Rationale for change		New data of pivotal trial (1199-0248) available.
Section to be changed		1.4 Benefit Risk Assessment
Description of change		Risk assessment due to COVID-19 pandemic situation added
Rationale for change		New information on benefit/risk due to COVID-19 pandemic situation.
Section to be changed		4.2.1 Other treatment and emergency procedures
Description of change		Clarification that dose reduction is possible at Visit 1 if required to manage adverse events identified at the end of the INBUILD® trial.
Rationale for change		Clarification that dose reduction rules also apply to Visit 1.
Section to be changed		4.2.1.2 Management of liver enzyme elevations
Description of change		The wording regarding withdrawal and interruption of trial medication was revised for clarification. Furthermore it was added that trial medication may be resumed in the case that clear evidence for an alternative cause for the hepatic injury was identified and resolved. It was specified that this is only possible after consultation with the sponsor and if prior to restart, liver laboratory values are normal. Liver laboratory values should be

		monitored weekly for first 4 weeks of re-introduction and every 2 weeks for the following 8 weeks.
Rationale for change		Revision of the recommendations for hepatic injury.
Section to be changed		[redacted]
[redacted]		[redacted]
Rationale for change		Correction of typo
Section to be changed		5.2.2 Vital Signs
Description of change		Clarification that blood pressure and pulse rate should ideally be taken prior to blood sampling.
Rationale for change		Clarification that it is not mandatory for blood pressure and pulse to be taken before blood sampling.
Section to be changed		5.2.5.2.2 AE reporting to sponsor and timelines
Description of change		Removal of the requirement to report SAEs by fax, and that SAEs should be reported according to the country-specific reporting process.
Rationale for change		In some countries SAEs can now be reported by other methods than fax.
Section to be changed		6.1 Visit schedule Appendix 10.3 Visit modification in exceptional circumstances
Description of change		Specification that and how in exceptional circumstances (as e.g. in pandemic situations), when it is impossible to conduct study visits at the study site, study visits may be performed at patient's home or remotely combined by using local laboratories.
Rationale for change		Experiences from the COVID-19 first wave situation; to allow flexibility in visit conduct in case required due to pandemic or other exceptional situations to ensure patients safety by ensuring continuous treatment.

APPROVAL / SIGNATURE PAGE

Document Number: c21830338 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-02

Title: An open-label extension trial of the long-term safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	01 Sep 2020 15:51 CEST
Author-Clinical Trial Leader		01 Sep 2020 16:15 CEST
Approval-Team Member Medicine		15 Sep 2020 23:48 CEST
Verification-Paper Signature Completion		16 Sep 2020 12:48 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed