CLINICAL TRIAL PROTOCOL

	Document Number:	**c03495745-05**
EudraCT No.:	2015-003148-38	
BI Trial No.:	1199.227	
BI Investigational Product(s):	Ofev®, nintedanib	
Title:	A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.	
Brief Title:	Effect of nintedanib on biomarkers of ECM turnover in patients with IPF and limited FVC impairment	
Clinical Phase:	IV	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	, Phone: Fax:	
Status:	Final Protocol (Revised Protocol (based on global amendment 4))	
Version and Date:	**Version: 5.0**	**Date: 09 Jul 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product: Ofev®			
Name of active ingredient: Nintedanib			
Protocol date: 11 Feb 2016	**Trial number:** 1199.227		**Revision date:** 09 Jul 2018

Title of trial:	A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.
Coordinating Investigator:	
Trial site(s):	Multi-centre, multi-national trial
Clinical phase:	IV
Objective(s):	To investigate the effect of nintedanib on various extracellular matrix (ECM) turnover biomarkers and the predictive value of change in those ECM biomarkers on disease progression.
Methodology:	12-week randomised, double blind, parallel group, placebo controlled phase followed by a single active arm phase of 40 weeks
No. of patients:	~490 enrolled (screened) patients
total entered:	~350 entered (randomised) patients
each treatment:	Nintedanib: 117 Placebo: 233 * **applicable to 12-week randomised part of the trial*
Diagnosis :	Idiopathic Pulmonary Fibrosis (IPF)
Main criteria for inclusion:	Male or female patients aged ≥40 years at Visit 1 (screening); IPF diagnosis based upon ATS/ERS/JRS/ALAT 2011 guideline within 3 years of Visit 0; HRCT

Name of company:		**Boehringer Ingelheim**	
Name of finished product: Ofev®			
Name of active ingredient: Nintedanib			
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	performed within 18 months of Visit 0; confirmation of diagnosis by central review of chest HRCT and surgical lung biopsy (later if available) prior to randomisation; FVC ≥ 80% predicted of normal at Visit 1 (screening)
Test product(s):	Nintedanib
dose:	300 mg daily (150 mg bid) with possibility to reduce total daily dose to 200 mg (100 mg bid) to manage adverse events (AEs)
mode of administration:	oral
Comparator products:	Placebo matching Nintedanib
dose:	Not applicable
mode of administration:	oral
Duration of treatment:	52 weeks
Endpoints	Primary Endpoint: • Rate of change (slope) in blood CRPM from baseline to week 12 Key Secondary Endpoint: • Proportion of patients with disease progression as defined by absolute FVC (% predicted) decline ≥10% or death until week 52 Secondary Endpoints: • Rate of change (slope) in blood C1M from baseline to week 12 • Rate of change (slope) in blood C3M from baseline to week 12 Further Endpoints (selected):

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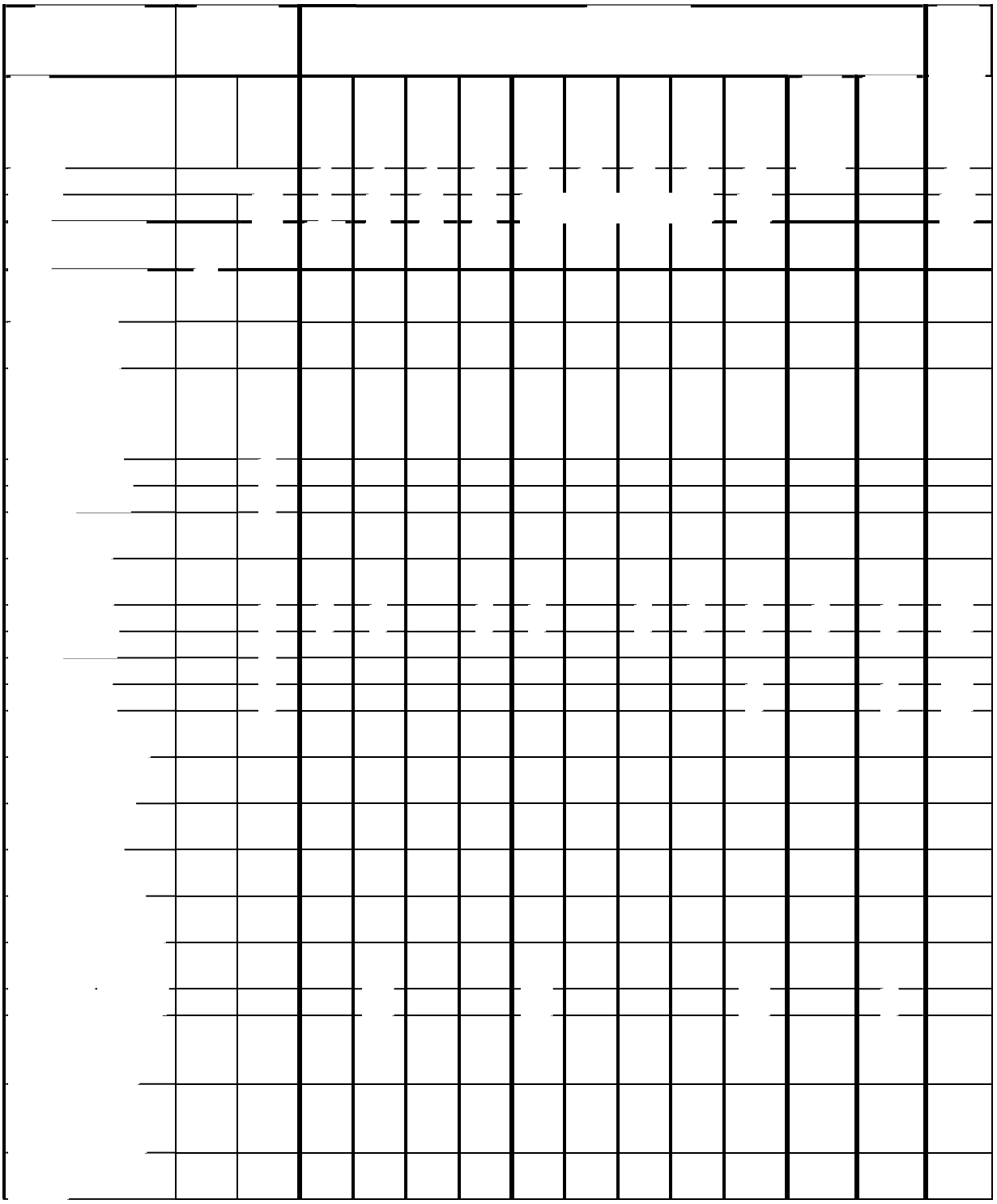
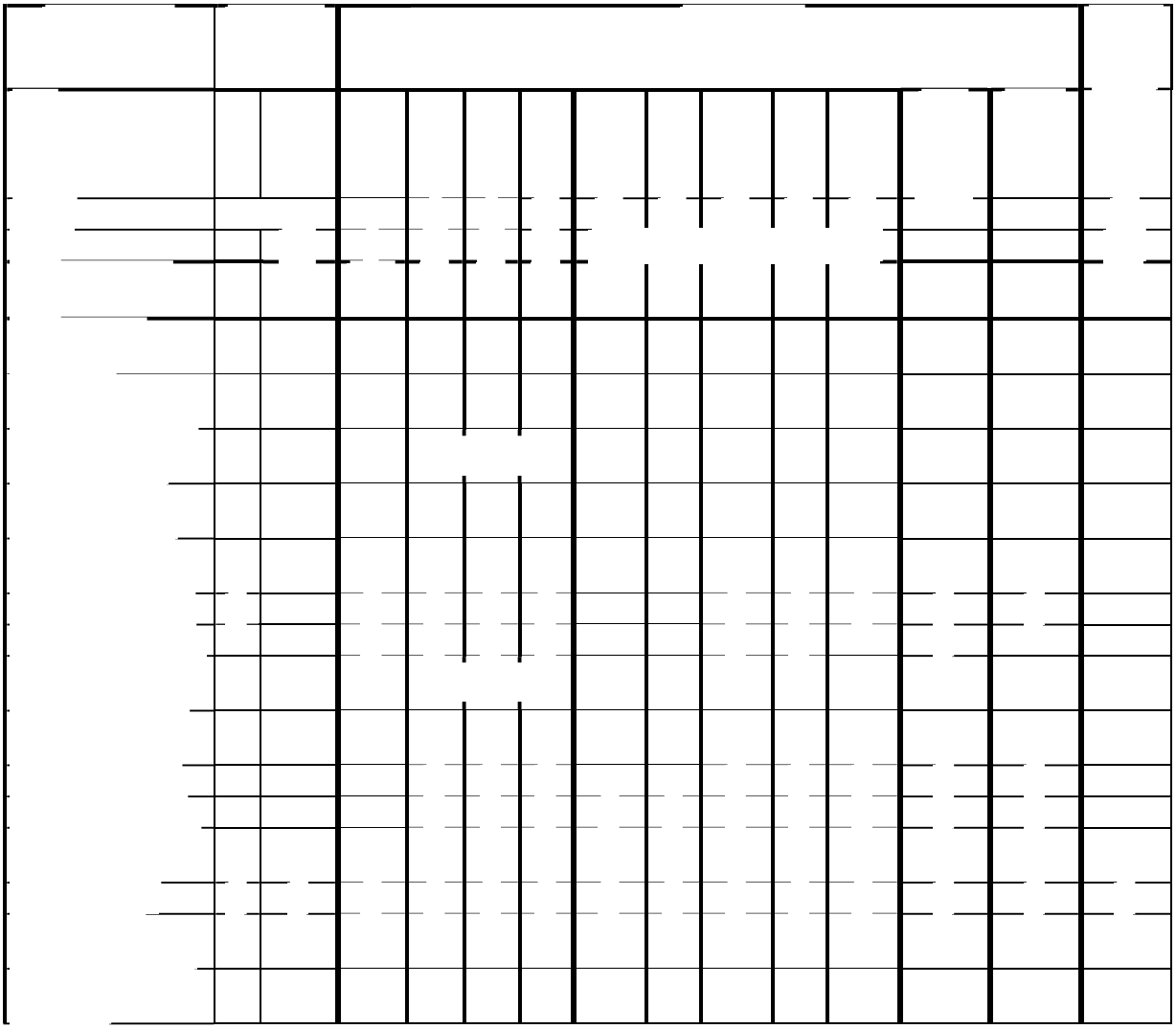
Safety criteria:	Adverse events (especially SAE and other significant AE), physical examination, weight measurements, 12 lead electrocardiogram, vital signs and laboratory evaluations.
Statistical methods:	Random coefficient regression models for continuous endpoints, Log rank tests, Kaplan-Meier plots and Cox regressions for time to event endpoints, logistic regression models or other appropriate methods for binary endpoints





1. Informed consent should be obtained before any study procedure including the shipment of the HRCT image and biopsy sample (if available) for central review.
2. At visit 1, height measurement should be included.
3. PK samples will be taken at Visits 3, 6 and 10 just prior to drug administration. Patients will be provided with a PK card/diary to support the record of the exact clock time of medication intake three days prior to PK sampling.
4. Blood samples for serum banking and pharmacogenetics may be drawn from all randomised patients who received at least one dose of trial medication and who gave a separate informed consent. Patients will be asked to participate in the biobanking subset, i.e. pharmacogenetic and serum biobanking. Still, the participation is voluntarily and not a pre-requisite for participation in the trial. The **single** pharmacogenetic sample will be drawn at Visit 2 or at any other subsequent visit after randomisation. Serum banking samples shall be drawn as per Flow Chart.
5. SGRQ, UCSD-SOBQ: the first procedure at the clinic.
6. Patient diary will be issued at Visit 2 and will be reviewed at each clinic visit up until Visit 10. Content to be discussed and reviewed by the site staff as it pertains to AEs and concomitant therapy and times of drug intake three days prior to the PK sampling.
7. Including acute IPF exacerbations
8. Patients who prematurely discontinue from the trial and don't accept to attend all planned visits will be contacted for vital status collection at week 52.
9. No fasting required.
10. If performance compliance is below 80% or as deemed necessary by the site.

11. To be performed **after** pre-dose PK sample (if applicable) and **after** current visit exams.
12. Perform only if abnormal or findings needing follow-up recorded at Visit 10.
13. Visit 1 should only be conducted after IPF diagnosis has been confirmed by central review.
14. In case of dose change of nintedanib (reduction or re-escalation), dose adjustment visit must be conducted to allow dispensing of new medication kit.
15. Early end of treatment visit to be completed for all patients who withdraw or discontinue study treatment prematurely. Patients who prematurely discontinue treatment will then be invited to attend all visits as planned until week 52 (Visit 10).
16. Screening period (period between Visit 1 and 2) should last 14 days (2 weeks). The screening period may be prolonged by additional 2 week for any reasons, i.e. total 28 days (4 weeks). Eligible patients can be randomised once central lab results have been received and are found to be consistent with eligibility criteria.
17. 4 days prior to planned PK sampling site should preferably contact the patient to record times of drug intake within patient diary. Patient should record times of drug intake three days prior to the PK sampling.
18. In women of childbearing potential.
19. Applicable only if patient doesn't accept to attend remaining scheduled visits.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	Latin American Thoracic Association
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BS	Biomarker Set
C1M	Collagen 1 degraded by MMP-2/9/13
C3M	Collagen 3 degraded by MMP-9
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CRPM	C-reactive protein degraded by MMP-1/8
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DDI	Drug-drug interaction
DEDP	Drug exposure during pregnancy
DILI	Drug induced liver injury
DLCO	Carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Reported Outcome
ECG	Electrocardiogram
ECM	Extracellular matrix
EDC	Electronic Data Capture
EDTA	Ethylendiamintetraacetate
EOT	End of treatment

ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor/receptor
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
ß-HCG	β-human Chorionic Gonadotropin
HPC	Human Pharmacology Center
HRCT	High Resolution Computer Tomography
IB	Investigator's Brochure
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IEC	Independent Ethics Committee
INR	International normalised ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
JRS	Japanese Respiratory Society
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LoEE	List of Essential Element
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMPs	Metalloproteinases
MMRM	Mixed Effects Model for Repeated Measures
MST	Medical Sub team
N/A	Not Applicable
NAC	n-acetylcysteine
nRTKs	Non-receptor tyrosine kinases
OPU	Operative Unit
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PD	Pharmacodynamic/ Pharmacodynamics
PDGFR	Platelet derived growth factor/receptor

PFT	Pulmonary Function Test
PG	Pharmacogenetics
PK	Pharmacokinetic Set
PKS	Pharmacokinetic/ Pharmacokinetics
PT	Prothrombin time
PTT	Partial thromboplastin time
q.d.	quaque die (once a day)
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RS	Randomised Set
RTKs	Receptor tyrosine kinases
SAE	Serious Adverse Event
s.c.	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SP-D	Surfactant Associated Protein-D
SpO2	Oxygen Saturation
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TMW	Trial Medical Writer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid stimulating hormone
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit Normal
UCSD-SOBQ	UCSD Shortness of Breath Questionnaire
VEGFR	Vascular endothelial growth factor/receptor

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown aetiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency [P11-07084].

The course of the disease in individual patients is variable: some patients progress rapidly, others have periods of relative stability punctuated by acute exacerbations and others progress relatively slowly. Acute exacerbations of IPF are events of respiratory deterioration of unidentified cause that occur in 5–10% of patients annually and are associated with a very poor outcome [R12-2786].

IPF is most prevalent in middle aged and elderly patients, and usually presents between the ages of 40 and 70 years. The median life expectancy in IPF patients after diagnosis is 2 to 3 years [P11-07084].

The latest update on clinical practice guideline for the treatment of IPF, jointly issued in 2015 by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) has provided a conditional recommendation for treatment with nintedanib or pirfenidone for the majority of IPF patients, taking into account individual patient values and preferences [P15-07362]. Conventional IPF treatments such as n-acetylcysteine (NAC), corticosteroids, cyclophosphamide, cyclosporine and azathioprine are not approved treatments for IPF, and their efficacy is questionable or even harmful [P15-07362; P12-06085; P14-07665]. Non-pharmacological therapies such as pulmonary rehabilitation and long-term oxygen therapy are recommended for some patients, but their efficacy in patients with IPF has not been established. Lung transplant has been shown to positively impact survival in patients with IPF. [R11-5086; R12-2785]. Although the number of patients transplanted due to IPF has increased steadily over the last years, the scarce availability of donor organs, as well as the comorbidities and advanced age preclude many patients from referral to lung transplant [R12-3676; R12-3474].

Pirfenidone, a compound which demonstrated anti-fibrotic activity in non-clinical models, was first licensed in Japan in 2008 based on two local trials which showed a reduced decline of vital capacity under treatment with the compound [R06-2070; R10-4316]. In the international Phase III CAPACITY program, pirfenidone demonstrated efficacy on the primary FVC lung function endpoint in only one of two confirmatory trials [R11-4827]. The additional confirmatory ASCEND Phase III trial requested by FDA met the primary endpoint of change from baseline FVC % predicted [R14-2103]. Pirfenidone is also licensed since February 2011 for the treatment of mild to moderate IPF in the European Union and since October 2014 for the treatment of IPF in the United States of America. It is also licensed in several other countries.

Nintedanib is a small molecule intracellular tyrosine kinase inhibitor which has demonstrated anti-fibrotic and anti-inflammatory activity in preclinical models [P08-08684; P14-02860]. The two replicate Phase III INPULSIS trials and the Phase II TOMORROW trial consistently showed positive results for the efficacy of nintedanib 150 mg twice daily versus placebo in

patients with IPF. Both INPULSIS trials showed that nintedanib reduced the annual rate of decline in FVC (mL/year) by approximately 50%, consistent with slowing disease progression [P14-07514; P11-11216]. Based on these three clinical trials, nintedanib was approved for the treatment of IPF in the USA in October 2014, in the European Union in January 2015 and in Japan in July 2015. As of 20 October 2015, nintedanib has also been approved in Canada, Switzerland, Russia, Australia, Chile, Ecuador and Taiwan and it has been submitted for marketing authorization in other countries across the world.

Although nintedanib and pirfenidone can be considered a standard of care for patients diagnosed with IPF, it remains unclear when to start and when to stop treatment with either of the drugs, given the unpredictability of clinical course in the individual patient as well as the lack of biomarkers to inform patient management and therapeutic response.

With the introduction of nintedanib in the treatment algorithm of IPF, there is an additional need to further characterize its profile in patients at an early disease stage, i.e. in patients with limited lung volume impairment, and to address the question when to start treatment in these patients. Currently, many physicians apply a wait and watch strategy for these patients as there are no markers to predict the individual course in a given patient or response to treatment which may result in a delay of treatment initiation. Identifying biomarkers to predict the clinical course and benefits of therapy for a given patient early in the course of the disease remains one of the most urgent and relevant challenges in patient management

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) at pharmacologically relevant concentrations. Among them, FGFR (fibroblast growth factor/receptor), PDGFR (platelet derived growth factor/receptor) and VEGFR (vascular endothelial growth factor/receptor) have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology [P08-08684; P14-02860].

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 reached at the latest within one week of dosing. After food intake, a trend towards an increased systemic exposure (around 15 to 20%) and a delayed absorption was observed compared to administration under fasted conditions. Nintedanib is recommended to be taken with food. Nintedanib is preferentially distributed in plasma, with a blood to plasma ratio of 0.87; the terminal half-life is in the range of 7 to 19 h. 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) study. Patients taking potent P-gp inhibitors (e.g ketoconazole, erythromycin or cyclosporine) should be monitored closely for tolerability of nintedanib.

In a DDI study with the P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on Cmax upon co-administration compared to administration of nintedanib alone. Since potent P-gp inducers may decrease exposure to nintedanib, selection of alternative treatment with no or minimal P-gp induction should be considered.

The clinical efficacy of nintedanib has been studied in over 1400 patients with IPF in one phase II dose finding study (TOMORROW) including four different doses of nintedanib, and two replicate phase III (INPULSIS 1 and 2) trials. These were randomised, double-blind, placebo-controlled studies comparing treatment with nintedanib twice daily to placebo for 52 weeks. A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving nintedanib 150 mg bid compared to patients receiving placebo. The treatment effect on FVC was consistent in all 3 studies, i.e. a relative reduction of approximately 50% between nintedanib and placebo. Furthermore, 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 adjudicated confirmed/suspected acute exacerbations by 68% in a pre-specified sensitivity analysis of pooled data from the INPULSIS® trials, supporting the effect of nintedanib on slowing disease progression [P14-07514; P11-11216].

The safety profile of nintedanib has been investigated comprehensively. The proportion of patients with serious adverse events was similar in the nintedanib and placebo groups.

The risks of treatment with nintedanib in adult patients are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhea, abdominal pain) and to increases in liver enzymes aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin. The most frequently reported adverse event was diarrhea which was mild to moderate in intensity for the vast majority of patients and lead to treatment discontinuation in less than five percent of patients treated with nintedanib. Weight decrease and decreased appetite have also frequently been reported in studies with nintedanib.

Potential risks of nintedanib treatment also include arterial hypertension, GI perforations, thromboembolism and bleeding. Patients treated with full-dose anticoagulation or at known risk for bleeding were excluded from the INPULSIS trials. This has led to recommendations stating that patients at known risk for bleeding should be treated with nintedanib only if the anticipated benefit outweighs the potential risk. Although cardiac disorder AEs were balanced between the nintedanib and placebo groups, a higher proportion of patients in the nintedanib groups had myocardial infarctions. Conversely, a lower proportion of patients in the nintedanib groups had other ischemic heart disease. ‘Other ischemic heart disease’ was a pre-defined category including terms such as coronary artery disease, angina pectoris, coronary angioplasty, coronary artery stenosis, myocardial ischemia, coronary artery stent insertion, electrocardiogram (ECG) ST segment depression. The clinical significance of this finding is unknown, and further observation is needed.

For patients finalizing the 52 week study treatment in the TOMORROW and INPULSIS trials, participation in open label extension trials (1199.35 and 1199.33) was offered. Long term treatment in these still ongoing open label extension trials confirm the safety profile observed in the phase II and III trials [P15-09876].

Nintedanib has also demonstrated efficacy and tolerable safety in patients with non-small cell lung cancer who failed first line treatment [P11-00203], as well as in patients with advanced renal cell cancer [P13-06268], ovarian cancer [P11-10116] and hepatocellular carcinoma [P13-12693]. Furthermore, nintedanib is also being investigated in other oncological indications, such as mesothelioma [P14-08020].

For a more detailed description of the drug profile, refer to the current Investigator's Brochure (IB) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Until recently, IPF was essentially an untreatable disease. With the availability of specific antifibrotic drugs like nintedanib and pirfenidone, a major advance in the management of IPF has been achieved. However, based on the heterogeneity of disease progression and the lack of validated prognostic biomarkers, the clinical course in an individual patient remains unpredictable which is also true for the individual response to treatments.
Retrospective studies have identified several factors at a single point in time (baseline factors) or over time (longitudinal factors) that are associated with increased mortality in IPF. Change in physiologic measures over time, such as absolute decline in FVC % predicted normal by 10% or more, are associated with reduced survival; This association is only seen after a minimum of 6-12 months [R06-4127; R10-6539; P05-02699; R06-4126]. However, change in pulmonary function in the prior year does not predict the subsequent change in pulmonary function in the following year [R14-1149]. In addition, none of these markers has been validated prospectively. Several serum proteins at baseline (e.g. KL-6, MMP-7, surfactant protein D) have also been shown to weakly correlate with the clinical course of the disease [R15-4126 ; R10-6378 ; R15-4125], but none of these markers have been assessed longitudinally.
A key hallmark in the pathology of IPF is dysregulation in connective tissue turnover within the lungs, resulting in excessive accumulation of distorted extracellular matrix and scarring which is considered a final common pathway in lung fibrosis. This deranged equilibrium is determined by several components including fibroblast proliferation, migration and differentiation, ECM synthesis by active myofibroblasts, collagen cross-linking and matrix degradation by various enzymes like metalloproteinases (MMPs).
The prospective observational PROFILE study [R15-1220] has recently shown that disease progression and prognosis can be determined through temporal changes in extracellular biomarkers indicating the defective and excessive matrix turnover potentially directly reflecting disease activity. In addition, the magnitude of change in ECM biomarkers related to the subsequent risk of disease progression and these changes provided the ability to predict outcome at an earlier stage (after 3 months) compared to physiologic measures of lung function. It remains to be determined whether baseline or change in ECM biomarkers will predict response to treatment.

Identifying biomarkers to predict the clinical course and benefits of nintedanib therapy, e.g. effect of nintedanib on surrogate biomarkers early in the course of the disease remains one of the most urgent and relevant challenges to improve overall patient management, prevent treatment delay or overtreatment.

This study is conducted to examine for the first time the treatment effect of nintedanib on change of biomarkers indicative of extracellular matrix turnover which have been shown recently to predict disease progression in the PROFILE study [R15-1220].

This study further aims to confirm the association of biomarker course during the first three months of treatment and disease progression as observed in PROFILE and to assess whether nintedanib treatment during the first 12 weeks alters this association or not.

2.2 TRIAL OBJECTIVES

The primary objective of the trial will be to assess the effect of nintedanib on rate of change in extracellular matrix (ECM) turnover biomarker CRPM over 12 weeks which has shown to strongly associate with disease progression in patients with IPF in the PROFILE cohort [R15-1220].

A secondary objective is to confirm the observed results from the PROFILE cohort, i.e. to assess the predictive value of change in extracellular matrix (ECM) biomarkers CRPM, C1M and C3M over 12 weeks for disease progression as defined by FVC decline ≥10% or death over 52 weeks [R15-1220].This will be done primarily within patients randomised to 12 weeks placebo treatment, since placebo treatment is expected not to impact change in extracellular matrix (ECM) biomarkers CRPM, C1M and C3M over 12 weeks nor disease progression which will facilitate interpretation of obtained results.

Additionally, a further secondary objective will be to assess how nintedanib treatment during the first 12 weeks of the trial affects the association between change in extracellular matrix (ECM) biomarkers CRPM, C1M and C3M over 12 weeks and disease progression. The corresponding analyses will comprise all patients treated with nintedanib including patients who are initially on placebo.

Analyses related to both primary and secondary objectives need to be considered as a whole in order to understand the complex network of associations between biomarkers, their change over time, the potential impact of treatment and the ultimate outcome of disease progression.

Further objectives are to assess the effect of nintedanib on rate of change in additional ECM turnover biomarkers and (based on the main and secondary objective) the predictive value of the corresponding rate of change for disease progression. Furthermore, the trial will evaluate changes in pulmonary function over time using home and standard in clinic spirometry and their correlation.

2.3 BENEFIT - RISK ASSESSMENT

The favourable benefit-risk ratio based on the so far acquired knowledge about nintedanib is the rationale to conduct further studies with nintedanib in idiopathic pulmonary fibrosis.

As described in Section 1, patients with IPF, including patients with only limited FVC impairment, may benefit from lesser decline in lung function and hence slower disease progression as a result of treatment with nintedanib [P15-09946]. In addition, nintedanib significantly reduced the risk of first acute exacerbation in 2 out of 3 clinical trials [P11-11216, P14-07514].

Two thirds of the patients in this trial will be treated with placebo for the first 12 weeks of the trial. A 1:2 randomization (nintedanib:placebo) increases the number of patients treated with placebo during the first 12 weeks and consequently increases the power of assessing the association between change in the extracellular matrix (ECM) biomarker CRPM over 12 weeks and disease progression in placebo treated patients. Change in the extracellular matrix (ECM) biomarker CRPM over 12 weeks will be classified as stable or falling [≤ 0 ng/ml/month] or rising [> 0 ng/ml/month] in line with the PROFILE cohort [R15-1220]. A 12 week placebo period is considered acceptable given that the in- and exclusion criteria assure inclusion of patients with mostly preserved lung function at baseline. In addition, it is unclear if patients would even receive antifibrotic treatment as in clinical practice. IPF patients with limited lung function impairment might not be reimbursed in some countries depending on a FVC % predicted threshold (e.g. >80%predicted).
Following the 12 week placebo controlled period all patients in this trial will continue further treatment with nintedanib. This will allow active treatment also to patients previously on placebo. In the subgroup of patients by baseline FVC (>80% versus ≤ 80% predicted) in the pooled INPULSIS data set, the risk of disease progression (time to FVC decline >10% or death) up to 12 weeks was low and similar in patients treated with placebo and nintedanib (approximately 10% of patients, respectively), although there was a risk reduction in favour of nintedanib by approx. 40% in the end of the 52 week treatment period for both subgroups and a consistent effect on reducing the annual rate of decline by 50%, similar to the primary outcome in the overall population [P15-09946].

The risks of treatment with nintedanib are described in Section 1.2. The most common side effects of nintedanib are of gastrointestinal nature (diarrhea, nausea, vomiting, abdominal pain), as well as liver enzyme elevations.

Safety monitoring in this trial will consist of regular visits to the investigational site, timely blood analyses and specific monitoring procedures to follow-up potential hepatic enzyme elevation (potential for drug-induced liver injury), see also Section 5.3.6.1.
In case of lack of tolerability, symptomatic treatment, dose adjustments and/or interruptions of trial drugs (at the discretion of the investigator) should be considered to allow for resolution of the symptoms (Section 4.2.1).

Based on the mode of action of nintedanib, especially on the inhibition of VEGF or VEGF receptors, arterial hypertension, gastrointestinal perforations, thromboembolism and bleeding have been identified as potential risks of nintedanib treatment. Therefore, patients requiring full dose concomitant anticoagulation, fibrinolysis or high-dose antiplatelet therapy will be excluded from this trial.
The mode of action of nintedanib indicates a high potential for teratogenicity and/or embryotoxicity, including fetotoxicity/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.

Overall, the clinical safety profile of nintedanib as established during the development programs including patients with less advanced disease is interpreted as favourable for the intended indication of IPF.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multinational, prospective trial. The trial comprises two periods. The first period is a 12 week, randomised, double blind, placebo controlled, parallel group period to assess the effect of nintedanib 150 mg bid on change of ECM biomarker turnover indicative of disease progression compared to placebo. The second period is a single arm, open label, active treatment period (nintedanib 150 mg bid) of 40 weeks duration. The total treatment period duration is 52 weeks. (Table 3.1:1).

Table 3.1:1 Summary of treatments

	Number of patients per treatment arm	Treatment period	
		Period 1 12 week, randomised, double blind, placebo controlled, parallel group	Period 2 40 week, single arm, open label, active treatment period
Treatment	~117	nintedanib 150 mg bid*	nintedanib 150 mg bid*
Treatment	~233	placebo matching nintedanib 150 mg bid*	nintedanib 150 mg bid*
Total number of patients	~350		

**Permanent or intermittent dose reduction to a total daily dose of nintedanib 200 mg as well as subsequent re-escalation are allowed, further details are described in Section 4.2.1.*

The overall trial scheme is presented in Figure 3.1:1.

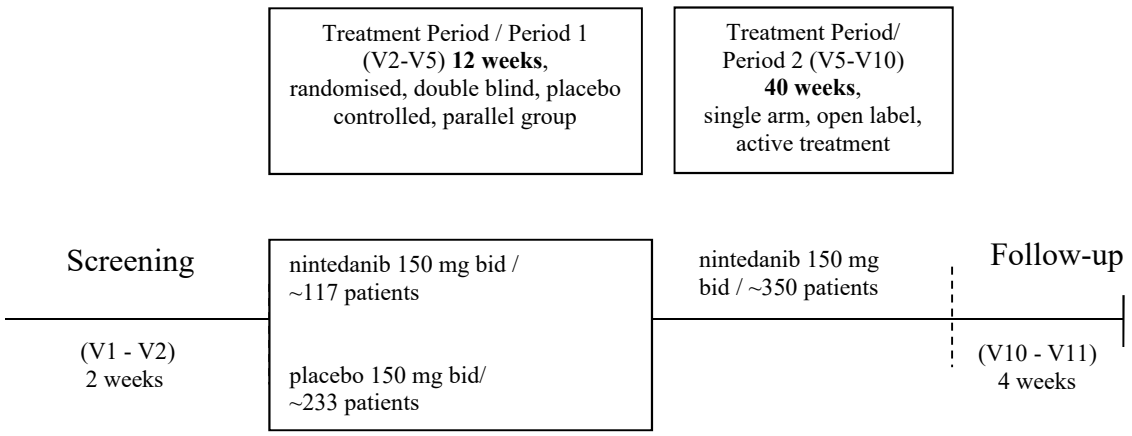


Figure 3.1:1 Trial scheme

After signing the informed consent (prior to any trial related procedures including any medication washout), the HRCT scan and surgical lung biopsy sample (later if available) will be sent for central review. Screening visit (Visit 1) should only be performed after the diagnosis of IPF has been confirmed by the central review. The screening period, i.e. period between Visit 1 and 2 should last from 14 days (2 weeks) to a maximum of 28 days (4 weeks).

Patients whose central lab results are available and who meet all inclusion and none of the exclusion criteria may be randomised into the 12-week, double-blind treatment period in which they will be receiving either of two possible treatments: nintedanib of total daily dose 300 mg administered twice daily, 150 mg in the morning and 150 mg in the evening or equivalent placebo bid in double-blind fashion. The chance of receiving either of the above mentioned treatments will be 1 (active treatment): 2 (placebo). Randomisation will be performed using an Interactive Response Technology System (IRT). Following the randomised, double blind, placebo controlled treatment period, all patients will enter the single arm, open label, active treatment period of 40 weeks. All patients previously receiving placebo will start taking nintedanib. During the trial patients will be returning to the clinic for the visits as per Flow Chart for the assessment of efficacy and safety parameters as well as assessment of compliance with the study drug.

Dose adjustment visits may occur at any time to manage adverse events. Permanent or intermittent dose reduction to a total daily dose of nintedanib 200 mg, i.e. 100 mg bid and drug interruptions are allowed to manage AEs as described in Section 4.2.1. Re-escalation to nintedanib 150 mg bid is allowed as described in Section 4.2.1. Each time a dose reduction or re-escalation is made, the patient must return for an unscheduled visit.

Upon completion of the 52 week treatment period (12 weeks Part 1 and 40 weeks Part 2), patients will enter a 28 day (4 week) Follow-Up period. Each patient will attend a total of 12 scheduled visits (Visit 0 and Visits 1 to 11 scheduled as per Flow Chart). Patients, who prematurely and permanently discontinue study treatment prior to 52 weeks, will be asked to return to the clinic and attend all visits as originally planned per protocol Flow Chart.

Each patient’s participation in the trial is estimated to last a total of approximately 58 weeks.

Depending on patient's informed consent, a blood sample for pharmacogenetics should be drawn at Visit 2 or at any subsequent visit from any randomised patients who received at least one dose of trial medication.

For an overview plan of procedures please refer to the Flow Chart at the beginning of this protocol.
Adverse events will be collected, documented and reported from the time the patient signs an Informed Consent up until 28 days after the last dose of study medication.

3.1.1 Administrative structure of the trial

The sponsor of this trial is Boehringer Ingelheim (BI). Clinical trial drug supplies, i.e. trial medication will be provided by the sponsor.

Boehringer Ingelheim has appointed the Trial Clinical Monitor, 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 to Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

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

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

A Coordinating Investigator has been nominated and will be responsible to coordinate investigators at different centres participating in this multicentre trial. The Coordinating investigator was selected by the sponsor. will review the trial protocol, any subsequent amendments to the protocol and the (draft) Clinical Trial Report (CTR). will provide signature on the final protocol signature page and amendments and will provide signature on the CTR indicating that, to the best of the co-ordinator's knowledge, the final CTR accurately describes the conduct and results of the trial.

Sites selected for participation will consist of centres experienced in the treatment and management of IPF.

The following local facilities/equipment along with the medically needed equipment to routinely treat patients are required at the trial site:

- equipment for measuring body height
- scales for measuring patient weight
- sphygmomanometer (blood pressure instrument)
- 12-lead ECG device
- refrigerator
- freezer (-20°C)
- laboratory tabletop centrifuge (ambient)
- equipment for DLCO measurements (or availability to perform measurements if not available directly at the site)
- device for pulse oximetry measurement
- premises for performing PFTs, blood and/or urine sampling and handling of samples (PK/PD/PG/ biomarker and or safety)
- weather station (to measure atmospheric temperature, barometric pressure and humidity), all parameters will be needed for spirometer calibration

- internet access
- analogue fax line

CROs:

- CRO for provision of in clinic spirometers and home spirometry devices.
- CRO/s for HRCT and surgical lung biopsy reviews
- CRO for central laboratory for safety laboratory, biomarkers, PK and pharmacogenetic sampling logistics.
- CROs for provision of CRAs.

IRT: An IRT (IVRS/IWRS, ie Interactive Voice/Web Response System) will be used for randomisation in this trial and for appropriate re-supply and assignments of trial medication to patients during treatment period. The ability to unblind will be available via the IRT.

Relevant documentation on the participating (Principal) Investigators and other important participants will be filed in the trial master file (TMF) in accordance with BI SOPs

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

Patients with idiopathic pulmonary fibrosis having a FVC of at least 80% of the predicted normal value at baseline will be eligible for participation in this trial. It is considered acceptable in this patient population to include a 12 week placebo-controlled treatment phase (refer to Section 2.3) in order to compare the effect of nintedanib versus placebo on change in ECM biomarker turnover.

In the PROFILE study [R15-1220], these biomarkers have shown their predictive potential for disease progression as early as after the period of 3 months.

A 1:2 randomisation (nintedanib:placebo) increases the number of patients treated with placebo during the first 12 weeks and consequently increases the power of assessing the association between change in the extracellular matrix (ECM) biomarker CRPM over 12 weeks and disease progression in placebo treated patients. Change in the extracellular matrix (ECM) biomarker CRPM over 12 weeks will be classified as stable or falling [≤ 0 ng/ml/month] or rising [> 0 ng/ml/month] in line with the PROFILE cohort [R15-1220].

Fibrotic remodelling of the lung interstitial tissue with subsequent restrictive ventilatory defect represents the core element of the histopathology of IPF. Therefore, FVC decline is considered a marker of disease progression and will be assessed via supervised spirometry at regular clinic visits as well as via home spirometry. Home spirometry may allow a more sensitive estimate of lung function decline based on more points of measurement resulting in higher accuracy and/or less variability in calculating the slope. Consequently, this study will also provide the opportunity to compare changes in FVC over the course of the study using standard clinic spirometry compared to home measurements, i.e. generate data on the general feasibility and validity of home spirometry in IPF.

After 12 weeks of double-blind treatment, all patients will enter the 40 week single active arm phase of the trial to potentially benefit from nintedanib treatment. Total treatment duration of 52 weeks is considered adequate to assess disease progression and the predictive value of ECM biomarker turnover in this patient population.

The most frequent symptoms in patients with IPF are dyspnoea and cough. These symptoms substantially reduce the quality of life and cause major restriction in everyday life, as well as incapacity in many patients with IPF. Therefore, a number of patient-reported outcome instruments (questionnaires) will be used to document the effect of nintedanib on symptoms (shortness of breath) and patient's health related quality of life.
The frequency of visits will allow close monitoring of adverse events, as well as control of liver enzyme values, consistent with the recommendations of the prescribing information for nintedanib.

3.3 SELECTION OF TRIAL POPULATION

Participation in this trial will be available to patients with IPF who meet the eligibility requirements specified in this protocol.

Recruitment will be competitive. The patients will be recruited from approximately 100 trial sites. Additional sites may be initiated to ensure trial recruitment as well as sponsor timelines.

Every effort should be made to keep patients in the study until completion of all study related procedures described in the clinical trial protocol.

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

3.3.1 Main diagnosis for trial entry

Any patients with confirmed diagnosis of IPF and who comply with eligibility requirements may qualify for participation in the trial.

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

3.3.2 Inclusion criteria

1. Written informed consent consistent with ICH-GCP and local laws, signed prior to participation in the trial including any study related procedures being performed [including any required washout as well as sending HRCT and lung biopsies (the latter if available)];

2. Male or female patients aged ≥ 40 years at Visit 1;
3. A clinical diagnosis of IPF within the last 3 years from Visit 0, based upon the ATS/ERS/JRS/ALAT 2011 guideline (P11-07084);
4. Chest high resolution computed tomography (HRCT) scan performed within 18 months of Visit 0;
5. Combination of HRCT pattern and surgical lung biopsy pattern (the latter if available) as assessed by central review are consistent with the diagnosis of IPF (Appendix 10.1);
6. FVC ≥ 80% of predicted normal at visit 1. NOTE: If this is not achieved at the screening visit, the visit may be repeated once within two weeks.

3.3.3 Exclusion criteria

1. ALT, AST > 1.5 fold upper limit of normal (ULN) at Visit 1[1];
2. Total bilirubin > 1.5 fold ULN at Visit 1[1];
3. Patients with underlying *chronic* liver disease (Child Pugh A, *B or C* hepatic impairment;
4. Relevant airways obstruction [i.e. pre-bronchodilator FEV1/FVC < 0.70 (i.e. 70%) at Visit 1];
5. History of myocardial infarction within 6 months of visit 1 or unstable angina within 1 month of Visit 1;
6. Bleeding Risk:
   - Known genetic predisposition to bleeding;
   - Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin etc.) or high dose antiplatelet therapy[2];
   - History of haemorrhagic central nervous system (CNS) event within 12 months prior to Visit 1;
   - History of haemoptysis or haematuria, active gastro-intestinal bleeding or ulcers and/or major injury or surgery within 3 months prior to Visit 1;
   - International normalised ratio (INR) > 2 at Visit 1[1];
   - Prothrombin time (PT) and partial thromboplastin time (PTT) > 150% of ULN at Visit 1[1];
7. Planned major[3] surgery during the trial participation, including lung transplantation, major abdominal or major intestinal surgery;
8. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1;

9. Creatinine clearance < 30 mL/min calculated by Cockcroft–Gault formula at Visit 1 (Appendix 10.2);

10. Treatment with nintedanib, pirfenidone, azathioprine, cyclophosphamide, cyclosporine, any other investigational drug, n-acetylcysteine, prednisone/prednisolone >15 mg daily or >30 mg every 2 days OR use of other systemic corticosteroids as well as any investigational drugs within 4 weeks of Visit 2;

11. Known hypersensitivity to nintedanib, peanut, soya or to any other components of the study medication;

12. Prior discontinuation of nintedanib treatment due to intolerability/ adverse events considered drug related;

13. A disease or condition which in the opinion of the investigator may interfere with testing procedures or put the patient at risk when participating in this trial;

14. Alcohol or drug abuse which in the opinion of the treating physician would interfere with the treatment and would affect patient's ability to participate in this trial;

15. Patients not able to understand and follow any study procedures such as but not limited to home spirometry[6], including completion of self-administered questionnaires without help;

16. Women who are pregnant, nursing, who plan to become pregnant while in the trial or female patients with positive pregnancy (ß-HCG) test at Visit 1 and/or Visit 2;

17. Women of childbearing potential[4] 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[5].
NOTE: ***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;***

18. Patients with acute IPF exacerbation or any respiratory tract infection in the four weeks prior to Visit 1 or during the screening period.
Visit 1 and/or Visit 2 should be postponed in case of an IPF exacerbation or respiratory tract infection. Refer to Section 6.1 for information on re-scheduling of visits;

19. Patients who are or have been participating in another trial with investigational

drug/s within one month prior to Visit 1 and patients who have previously been enrolled in this trial.

[1]Laboratory parameters found abnormal at visit 1 may be re-tested once prior to Visit 2.

[2]Exceptions: prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g., enoxaparin 4000 IU s.c. per day) and prophylactic use of antiplatelet therapy (e.g., acetyl salicylic acid up to 325 mg/d, **and**/or clopidogrel at 75 mg/d, **and**/or equivalent doses of other antiplatelet therapy).

[3]Definition of major is per investigator judgement.

[4]Women of childbearing potential are defined as: Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

[5]A list of contraception methods meeting these criteria is provided in the patient information.

[6]Patient will need to perform at least one home spirometry manoeuvre between Visit 1 and Visit 2 (in order to obtain baseline PFT values) to be eligible for the trial.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from trial treatment if:

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision;
- The patient needs to take concomitant drugs that interfere with the investigational product (Section 4.2.2);
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy);
  If a patient becomes pregnant or pregnancy is suspected during the trial, the patient will be permanently discontinued from the study treatment and will be followed up until birth or otherwise termination of pregnancy, please see Section 5.3.7.
- The patient experiences signs and symptoms of acute myocardial ischemia or stroke;
- The patient experiences hepatic injury defined as follows:
  - 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 and tenderness, fever and/or rash.
- For potential drug induced liver injury (DILI) follow up requirements please see Sections 4.2.1.3 and 5.3.6.1.
- The patient experiences unacceptable toxicity despite dose adjustments and supportive care
- Gastrointestinal perforation;
- Major surgery including abdominal or intestinal surgery;
- Signs or symptoms of acute myocardial ischemia, stroke, deep vein thrombosis and pulmonary embolism

In addition, permanent discontinuation of nintedanib should be considered in the following situations:

- Patients who require full dose therapeutic anticoagulation or high dose antiplatelet therapy;
- Increased risk of bleeding (e.g. gross/ frank haemoptysis or haematuria, active gastro-intestinal bleeding or ulcers).

In such cases, continuation of nintedanib should be discussed with the patient and the decision based on an individual benefit-risk assessment documented in the source data.

If a patient permanently discontinues a study drug, he/she will undergo procedures for early treatment discontinuation and will be invited to attend all planned study visits until week 56 as outlined in the flow chart.

For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of good clinical practice (GCP), the clinical trial protocol (CTP), or the contract disturbing 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 TREATMENTS TO BE ADMINISTERED

Patients will be randomised 1:2 to 300 mg nintedanib daily (i.e. one capsule of nintedanib 150 mg in the morning and one capsule of nintedanib 150 mg in the evening) or matching placebo (i.e. one capsule of matching placebo in the morning and one in the evening) during the first 12 weeks of the treatment period. For the subsequent 40 weeks all randomised patients will enter the single active arm treatment. All patients previously receiving placebo will start taking nintedanib.

During the trial, permanent or intermittent dose reduction to a total daily dose of nintedanib 200 mg, i.e. 100 mg bid and intermittent drug interruptions are allowed to manage AEs as described in Section 4.2.1. Re-escalation to nintedanib 150 mg bid is also allowed as described in Section 4.2.1.

Trial medication will be provided as a medication kit. One medication kit will contain seven blister cards each containing 10 soft gelatin capsules of either blinded nintedanib 150 mg, or blinded nintedanib 100 mg, or matching placebo (for blinded part of the trial) and open label nintedanib 150 mg, or open label nintedanib 100 mg (for the open label part) thus allowing sufficient amount of medication for approximately one month. Sufficient amount of kits, each identified with a unique medication number, will be dispensed to each patient throughout the trial via IRT. No active comparator is used in this trial.

Trial medication is manufactured by Boehringer Ingelheim.

4.1.1 Identity of BI investigational product(s) and comparator product(s)

Table 4.1.1: 1 Nintedanib:

Substance:	Nintedanib (Ofev®)
Pharmaceutical formulation:	Soft gelatin capsule
Source:	BI Pharma GmbH & Co. KG
Unit strength:	150 mg, 100mg
Posology	1 capsule, bid
Route of administration:	Oral (swallowed)

Table 4.1.1: 2 Placebo matching Nintedanib

Substance:	N/A
Pharmaceutical formulation:	Soft gelatin capsule
Source:	BI Pharma GmbH & Co. KG
Unit strength:	N/A
Posology	1 capsule, bid
Route of administration:	Oral (swallowed)

4.1.2 Method of assigning patients to treatment groups

To guarantee the double-blind design of the study, all treatments will be indistinguishable for the patient as well as for the investigator.
After final assessment of all inclusion and exclusion criteria, each eligible patient will be randomly assigned in 1:2 ratio (treatment: placebo) to one of the two treatment options at Visit 2 (double blind phase applicable to the first 12 weeks only). An interactive voice response system (IRT) will be used for randomisation to a specific treatment group in this trial and for the appropriate supply and re-supply of study medication to patients throughout the trial. Patients will be randomised to receive either an active drug at a dosage of 150 mg bid or matching placebo.

Documents such as but not limited to user guides, instructions, worksheets on the IRT will be stored in the ISF.

Note that the medication number is different from the patient number (the latter one is assigned after the informed consent process has been completed).

4.1.3 Selection of doses in the trial

A dose of nintedanib 150 mg bid (total daily dose of 300 mg) was selected for this trial as this is the recommended dose based on prescribing information in participating countries as well as the dose that has shown to be efficacious in two replicate phase III trials.
Dose adjustments are permitted as per Section 4.2.

4.1.4 Drug assignment and administration of doses for each patient

Drug assignment

Dosage for an individual patient will be assigned by means of an IRT at Visit 2. Patients will be randomised to receive either an active drug at a dosage of 150 mg bid or matching placebo.

At Visit 5, all patients will start receiving open label nintedanib for the remainder of the trial. Patients previously receiving placebo will now start receiving nintedanib. All patients will remain on the same dose they were previously receiving unless prescribed otherwise by the investigator. Patients, site staff and trial team will remain blinded to patient's previously randomised treatment group.

Study treatment will comprise of 1 capsule twice daily throughout the trial (refer to Section 4.1). Treatment kits containing 4 weeks + 1 week reserve treatment (one treatment kit containing 7 blister cards each having 10 capsules) will be dispensed to the patients.

To ensure patients receive adequate supply of study medication, kits will be dispensed at clinic visits in quantities outlined in Table 4.1.4: 1. Unscheduled re-supplies with additional medication kits will be possible via the IRT.

Table 4.1.4: 1 Quantity of medication kits dispensed

Visit	Week	Number of medication kits
2	0	1*
3	4	1*
4	8	1*
5	12	3**
8	24	3**
9	36	4**

* Double-blind study drug
**Open label active treatment study drug

The investigational product should only be dispensed to participating patients according to the protocol by authorised personnel as documented on the Investigator's Trial Staff List. All unused medication must be returned to the Sponsor. Receipt, usage and return must be documented on the respective forms. Any discrepancies must be accounted for.

Drug administration

- Study drug will be administered orally on a twice daily basis (bid). **At all clinic visits the study drug will be administered at the study site (after any sampling procedures and PFTs).** The patients should swallow the study medication unchewed together with a glass of water (~250 mL), and should observe a dose interval of approximately 12 hours. Study drug needs to be taken at approximately the same time every day (preferably 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 administered drug after the meal.
- If a dose of nintedanib is missed, i.e. not taken between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening, administration should resume at the next scheduled time at the recommended dose. No catch up of missed doses is permitted.

Patients experiencing adverse effects requiring temporary drug discontinuation (refer to Section 4.2.1 and 4.2.2) may start to receive study drug at 100 mg bid. The dose can also be reduced without prior discontinuation, i.e. immediately stepping down from 150 mg bid to 100 mg bid if necessary. In the case of severe toxicity or when the reduced dose is again not tolerated, drug treatment must be stopped and cannot be restarted. All dose reductions must be approved by the Investigator or delegated site staff at the site (during the scheduled or unscheduled visit) and the reason for reduction must be documented.

In case of adverse events requiring dose reduction (refer to Sections 4.2.1 and 4.2.2), 100 mg bid (or matching placebo) will be assigned by IRT upon call of the Investigator. The colour of the 150 mg capsules and the 100 mg capsules will be slightly different; the packaging will remain the same (same number of capsules per blister, same number of blisters per box).

If the reduced dose is well tolerated, re-escalation to 150 mg bid is possible, according to procedures described in Section 4.2.1.1.

The amount of study drug dispensed at the time of dose reduction and dose re-escalation is dependent upon the amount of time between the unscheduled visit and the next planned study visit. Therefore at unscheduled visits for dose reductions and dose re-escalations, IRT will assign only the number of boxes of study medication needed until the next predicted planned patient visit as noted within the IRT system.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.
The randomisation code will be kept secret by Clinical Trial Support up to database lock.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

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

4.1.6 Packaging, labelling, and re-supply

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

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

All used and unused trial medication must be returned to the sponsor. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

The Investigator and/or Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- 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
- Availability of the proof of a medical license for the principal Investigator
- Availability of Form 1572 (as applicable)

The Investigator and/or Pharmacist and/or investigational drug storage manager 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 alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor and/or appointed CRO, the Investigator / Pharmacist / investigational drug storage manager 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 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

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

4.2.1.1 Recommendations for managing adverse events (exceptions include diarrhea and liver enzyme elevations)

- If a patient experiences adverse events considered related to the trial medication, symptomatic treatment should be initiated (e.g. anti-emetic treatment such as dimenhydrinat if appropriate).
- Patients experiencing adverse events considered related to nintedanib may require drug interruption or reduction of dose (at the discretion of the investigator) to allow for resolution of symptoms.
- After resolution of AE, nintedanib may be reintroduced and re-escalated to the higher dose (at the discretion of the investigator):

- If dose has been reduced, consider re-escalation to 150 mg bid
- If treatment was temporarily interrupted, resume treatment at the full dose (150 mg bid), or at the reduced dose (100 mg bid), which subsequently may be re-escalated to the full dose (150 mg bid).

- For adverse events not related to the trial medications, treatment interruptions are allowed. Nintedanib should then be resumed at the same dose taken prior to interruption.
- In the occurrence of acute IPF exacerbations all treatment options considered adequate by the investigator are allowed, except concomitant treatment with pirfenidone.

4.2.1.2 Recommendations for management of diarrhea

The Common Terminology Criteria for Adverse Events (CTCAE Version 4.0) grading will be used to grade the severity of all AEs and SAEs of diarrhea. Management recommendations for diarrhea are based on the CTCAE grades.

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

The medical judgement should be used in decision of the use preventive treatment with loperamide after the first episode of diarrhea.

If diarrhea persists despite optimal symptomatic treatment, treatment interruption (for a maximum of 4 weeks) and dose reduction of nintedanib should be considered based on the recommendations described in Table 4.2.1.2: 1

Table 4.2.1.2: 1 Recommendations for management of diarrhea

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

[1]Refer to national prescribing information

4.2.1.3 Recommendations for management of liver enzyme elevation

For a detailed guidance on how to manage liver enzyme elevations, please refer to table 4.2.1.3: 1

Table 4.2.1.3: 1 Recommendations for managing liver enzyme elevations

<table>
<tr><th colspan="2">AST /ALT ≥3 but <5 x ULN</th><th colspan="2">AST /ALT ≥5 but <8 x ULN</th><th>Signs of hepatic injury [2]</th></tr>
<tr><td colspan="2">Reduce study medication to 100 mg bid or interrupt (at the discretion of the investigator)
Repeat Lab tests[1] in 48/72 hours, at week 1 and week 2</td><td colspan="2">Interrupt study medication
Repeat Lab tests[1] in 48/72 hours, at week 1 and week 2</td><td>Permanently discontinue study medication</td></tr>
<tr><th>If AST /ALT < 3 x ULN within 2 weeks</th><th>If AST /ALT ≥3 ULN at 2 weeks</th><th>If AST /ALT < 3 x ULN within 2 weeks</th><th>If AST /ALT ≥3 ULN at 2 weeks</th><td rowspan="2"></td></tr>
<tr><td>Re-escalate study medication to 150 mg bid if reduced; restart at 100 mg bid if interrupted
Repeat Lab tests[1] in 2 and 4 weeks</td><td>Interrupt study medication
Repeat Lab tests[1] in 1 and 2 weeks</td><td>Reintroduce study medication at 100 mg bid
Lab tests[1] in 1, 2 and 4 weeks</td><td>Permanently discontinue study medication</td></tr>
<tr><th>If AST / ALT ≥ 3 x ULN within 2 weeks</th><th>If at 2 weeks</th><th>If AST / ALT ≥ 3 x ULN within 2 weeks</th><td colspan="2" rowspan="2"></td></tr>
<tr><td>Permanently discontinue study medication</td><td>AST / ALT < 3 x ULN reintroduce study medication; lab tests[1] every week as needed

If AST / ALT ≥ 3 x ULN permanently discontinue study medication</td><td>Permanently discontinue study medication</td></tr>
</table>

[1]Laboratory tests include ALT, AST, total bilirubin, eosinophils, INR

[2] 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.

For potential drug induced liver injury (DILI) follow up requirements please see Section 5.3.6.1.

Immediately refer to Section 5.3.6.1 in case AST and/or ALT ≥3 fold ULN is combined with total bilirubin ≥2 fold ULN.

4.2.1.4 Management of acute IPF exacerbations and acute deteriorations

In case of acute IPF exacerbation, all treatment options considered adequate by the Investigator / caregiver are allowed, except concomitant treatment with pirfenidone. Although it is not generally recommended, the patient may interrupt study treatment if this is considered necessary (e.g., if short-term full anticoagulation is performed). In case of significant deterioration (absolute FVC decline >10%, DLCO >15%) all approved medications can be freely initiated or increased at the investigator‘s discretion.

Definition of Acute IPF Exacerbations

Otherwise unexplained clinical features within one month, including all of the following:

- Unexplained worsening or development of dyspnoea within 30 days;
- New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit;
- Exclusion of infection as per routine clinical practice and microbiological studies;
- Exclusion of alternative causes as per routine clinical practice, including:
  - Left heart failure
  - Pulmonary embolism
  - Identifiable cause of acute lung injury

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant medications (or therapy) to provide adequate care may be given as clinically necessary. If restricted concomitant therapy is necessary treatment with study medication should be permanently discontinued (except in case of acute IPF exacerbations – refer to Section 4.2.1.1).

Table 4.2.2.1: 1 Permitted and Restricted Concomitant therapy

	Prior to randomisation	**During treatment period**	**After EOT (Follow-up Period)**	**After early EOT[5]**
Nintedanib	Not permitted in the 4 weeks prior to visit 2 [1]	Study medication	Permitted	Permited[6]
Pirfenidone, N-acetylcysteine, Azathioprine, Cyclophosphamide, Cyclosporine	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted
Prednisone/ Prednisolone and/or other systemic corticosteroid[2]	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted
Investigational Medication	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Not permitted
Anticoagulation at full dose[3], antiplatelet therapy at high dose [4], fibrinolysis	Permitted	Not permitted	Not permitted	Permitted

1. Washout should not occur before the patient has signed informed consent
2. Prednisone/ Prednisolone >15 mg daily or >30 mg every 2 days OR use of other systemic corticosteroids within 4 weeks of visit 2.
3. Anticoagulation at full dose (vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin, etc). Exceptions: 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)
4. Antiplatelet therapy at high dose. Exceptions: prophylactic use of antiplatelet therapy (e.g. acetylsalicylic acid up to 325 mg/day and/or clopidrogrel at 75 mg/day and/or equivalent doses of other antiplatelet therapy) is allowed
5. For patients who withdrew study medication before the planned EOT date and decide to attend all remaining study planned visits.
6. At the discretion of the treating physician.

4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and life style.

4.2.2.3 Restrictions regarding women of childbearing potential

The anti-angiogenic properties of nintedanib indicate a high potential for teratogenicity and/or embryotoxicity, including fetotoxicity/lethality. In women of childbearing potential receiving nintedanib, contraceptive measures must be employed 28 days before treatment initiation, during the trial and for a period of 3 months after last drug intake.

4.3 TREATMENT COMPLIANCE

The Investigator will maintain accurate records of receipt of all study medication, including dates of receipt. In addition, accurate records will be kept regarding when and how much of each study medication is dispensed to, and used by each individual patient in the study. Reasons for deviating from the expected dispensing regimen must be recorded. A Drug Accountability Form, provided for this purpose, will be signed by the Investigator or delegate at the conclusion of the study. At the completion of the study, in order to satisfy regulatory requirements regarding drug accountability and destruction, all used and unused packages must be returned to the Sponsor or its designee.

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. A compliance worksheet will be provided in the ISF.

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

If the number of doses taken is not between 80-120% without identified cause like AE or consent withdrawal, site staff will explain to the patient the importance of treatment compliance.

Compliance will be verified by the on-site monitor authorised by the Sponsor.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

Note that all endpoints based on spirometry are measured by clinic spirometry unless explicitly stated otherwise.

5.1.1 Primary Endpoint

The primary endpoint is the rate of change (slope) in blood CRPM from baseline to week 12.

5.1.2 Secondary Endpoints

The key secondary endpoint is the proportion of patients with disease progression as defined by absolute FVC (% predicted) decline ≥10% or death until week 52 based on in clinic supervised spirometry.

Secondary endpoints are the rate of change (slope) in blood C1M from baseline to week 12 and the rate of change (slope) in blood C3M from baseline to week 12.

5.2 ASSESSMENT OF EFFICACY

Measurements of biomarkers

Blood samples collected from patients at visits will allow measurement of following concentrations: collagen 1 degraded by MMP-2/9/13 (C1M), collagen 3 degraded by MMP-9 (C3M),

C-reactive protein degraded by MMP-1/8 (CRPM), and citrullinated vimentin

Sample collection is described in Section 5.5. More details of sample collection and processing will be given in a lab manual.

Measurements of in clinic FVC

Spirometry devices for in clinic measurements as well as devices for home spirometry will be supplied by a central vendor to all participating sites.

In clinic spirometry performance will be centrally reviewed. On-going feedback and training will be provided. Predicted normal values shall be calculated according to ECSC [R94-1408].

The spirometers and their use, including daily calibration, must meet ATS/ ERS criteria (P05-12782). Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate and selection of the best result done according to the guidelines. Spirometric results will be electronically transmitted and confirmed by central reading. Further details on in clinic spirometry shall be provided in the ISF.

For each patient, pulmonary function testing will always start at approximately the same time of the day within ±90 minutes maximum difference from measurement time at Visit 1.

On days of clinic visits (including the screening visit), patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing.

Smoking should be discouraged throughout the study day (clinic visit) and will not be permitted in the 30-minute period prior to spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes).

Washout of bronchodilators (betamimetics and anticholinergics) need to be observed prior to in clinic spirometry (8 hours for short acting and 24 hours for long acting bronchodilators).

Carbon Monoxide Diffusion Capacity and Oxygen Saturation.

The site will use its own carbon monoxide diffusion capacity (DLCO) equipment and conduct all measurements with the same equipment (e.g. if several devices would be available at the site). Single-breath DLCO will be carried out according to the ATS / ERS guideline on DLCO measurements [R06-2002]. Before beginning the test, the manoeuvers should be demonstrated and the subject carefully instructed. Please refer to Appendix 10.5 for additional information. The DLCO assessment should be performed after the FVC assessment.

Oxygen saturation (SpO2) will be measured at rest by standard pulse oximetry (unaffected skin of earlobe or fingertip or forehead) and the recorded value will be entered in eCRF.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Physical examination includes assessment of heart, lung, abdomen and measurement of weight. Height will also be measured at Visit 1. Abnormal finding at the time of screening will be recorded as baseline conditions on the appropriate eCRF page. New abnormal

findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.3.2 Vital Signs

Vital signs including measurements of systolic and diastolic blood pressure and pulse rate, will be measured with the patient seated after having rested for at least 5 minutes at each on site visit.

5.3.3 Safety laboratory parameters

The laboratory tests will include:

- Haematology: complete blood count with platelet count and automated differential.

- Chemistry: sodium, potassium, creatinine, creatinine clearance calculated by Cockcroft–Gault formula, aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), total protein, alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), creatinine kinase and thyroid stimulating hormone (TSH).

- Coagulation: International normalized ratio (INR) and partial thromboplastin time (PTT).

- Urine: pregnancy testing

If laboratory values indicate toxicity, adequate and more frequent blood sampling will be performed at the discretion of the investigator.

Laboratory analysis during main visits will be done using central laboratory services. Venous whole blood will be collected in appropriate syringes provided by the sponsor through the assigned central laboratory. No fasting is required. Details regarding centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the sponsor. The investigators will be informed and instructed by the central laboratory and detailed documentation will be included in the ISF.

In case of liver enzymes elevation, close monitoring must be ensured by the investigator (Section 4.2.1.3).

5.3.4 Electrocardiogram

12-lead ECGs are to be conducted with site equipment as specified in the Flow Chart. Changes should be examined, compared to previous test, and assessed for clinical relevance. Clinically relevant findings at Visit 1 will be recorded as baseline conditions, new abnormal findings thereafter will be recorded as adverse events.

5.3.5 Other safety parameters

Medical history

All active and relevant historical disorders will be recorded on the Medical History/Baseline Conditions eCRF page at the screening visit (Visit 1).

A patient diary will be used by all patients in this trial. The diary will be used to prompt patient recollection during adverse event, concomitant therapies and times of drug intake three days prior to the PK sampling. Instructions for use of the diary will be provided in the ISF.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize 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. Any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction.

Life-threatening in this context 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.

For Japan only: The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

AEs considered "Always Serious"
Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
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 given above.

The latest list of "Always Serious AEs" can be found in the RDC system. These events should always be reported as SAEs as described in Section 5.3.7.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs: adverse events relating to gastrointestinal perforation and hepatic injury.

Hepatic Injury

In this study protocol, hepatic injury is defined as follows:

- 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 be followed up according to the "DILI checklist" provided in the ISF.

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

Intensity of AEs
The intensity of the AE should be judged based on the following:

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

The intensity of **diarrhea adverse events** should in addition be classified and recorded in the (e)CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 [R10-4848].

Table 5.3.6.1:1 CTCAE Categorization for diarrhea

CTCAE Grade	
1	Increase of <4 stools per day over baseline
2	Increase of 4 to 6 stools per day over baseline
3	Increase of ≥7 stools per day over baseline; incontinence
4	Life threatening consequences
5	Death

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.
Medical judgment 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. preexisting 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 diminished).

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; 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 study drug treatment continues or remains unchanged.

For Japan only: The reason for the decision on causal relationship for unlisted AEs needs to be provided in the eCRF.

5.3.7 Adverse event collection and reporting

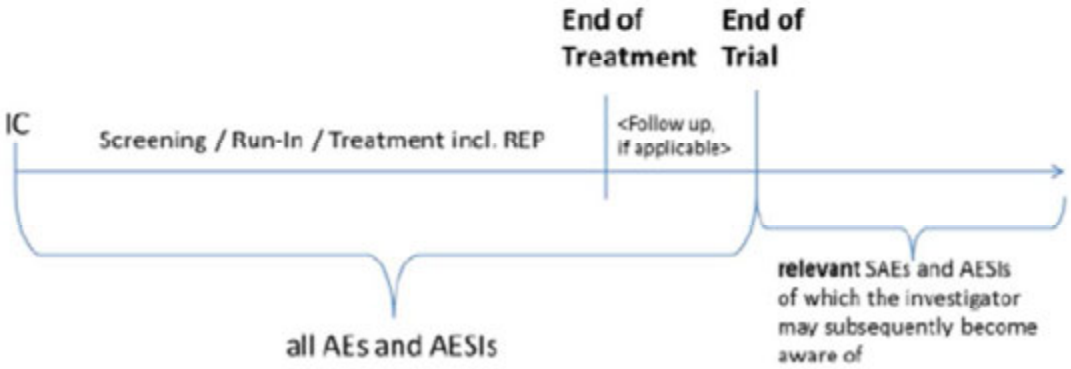
AE Collection

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

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial:
  -all AEs (serious and non-serious) and all AESIs.

  However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs.

- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.



The Residual Effect Period (REP) is defined as 28 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

AE reporting to 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 via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF).

The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

For Japan only: All SAEs must be reported immediately to the head of the trial site.

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.

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

Blood samples will be taken according to the Flow Chart for the analysis of exploratory biomarkers.
These samples will be stored for up to 3 years after the end of the clinical trial.
Samples will be shipped from the sites to a central laboratory for short-term storage. These samples will be shipped in batches from the central laboratory to Boehringer Ingelheim or to another location for biomarker analyses or long-term storage.
In order to better understand the effects of nintedanib on the disease, mechanistic and disease related biomarkers will be assessed in peripheral blood of randomised patients.

The assessment of exploratory biomarkers is a key feature of this clinical trial with the aim to better characterise and understand the disease, as well as their potential predictive value for treatment response. All biomarkers related to IPF pathology will be explored pre during and post treatment with nintedanib or placebo in serum and plasma and will be correlated with the clinical endpoints.

Methods and timing of sample collection

Whole blood will be collected for the preparation of serum, plasma and
Collection time points are outlined in the Flowchart and respective footnotes. Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis.
A detailed description of biomarker sample collection and sample handling is provided in the ISF.

The samples will be shipped to the central laboratory and later analysed at the sponsor or a contractor of the sponsor.

5.5.1 Analytical determinations

The analytical methods for the analysis of biomarkers from blood will be given in detail in a analytical biomarker report.

5.5.2 Biobanking

To allow for future scientific analyses, all patients will be asked for additional samples. Only if a separate specific informed consent is given in accordance with local ethical and regulatory requirements, DNA and/or serum banking samples will be taken, processed and stored. Participation in the DNA and/or serum banking part is voluntary and not a prerequisite for participation in the study.

Serum banking
To enable future not yet specified biomarker analyses additional blood will be collected into serum collection tubes. This sample will be collected according to the Flow Chart. Details on sample collection and processing will be given in the ISF. This sample will be stored up to 15 years after the end of the trial and may be used for further characterization of IPF patients. Approximately 100 mL of blood will be collected for serum banking. Detailed instructions for serum banking sampling, handling and shipment of samples are provided in the ISF.

DNA banking
The DNA sample derived from the original blood sample will be stored by Boehringer Ingelheim for up to 15 years after the end of the clinical trial or until there is no more material available for tests. The stored DNA may be used at a later time for pharmacogenomic analyses.

Methods and timing of DNA banking sample collection
An amount of approximately 8.5 mL blood will be collected per PaxGene DNA blood sampling tube for those patients who signed a separate informed consent concerning the Sample DNA banking part with any other blood sampling after randomisation. The Paxgene Blood DNA tubes can be stored and shipped at room temperature within 14 days. If a longer storage and shipment period for Paxgene Blood DNA tubes is necessary, the blood samples have to be stored at a temperature of approximately -20°C or below.
Once frozen, thawing of the samples should be avoided except for analysis.
Detailed instructions for pharmacogenomics sampling, handling and shipment of samples are provided in the ISF.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted in the trial are using standard methods.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This trial starts with Visit 0 during which informed consent process shall be undergone HRCT scans and biopsies (later if available) shall be sent for central review to confirm the diagnosis of IPF. Further the trial consists of screening visit (Visit 1) and screening period lasting 14 days (2 weeks), treatment period lasting 52 weeks and follow-up period lasting 28 days (4 weeks). The treatment period will consist of two parts. At Visit 2 patients will be randomised into double-blind portion of the study. Additional clinic visits of the double blind period will be scheduled at week 4, 8 and 12 (Visits 3, 4 and 5). At Visit 5, i.e. after completing the randomised, double blind treatment all patients will enter the single arm, open label, active treatment period. During this period patients will visit the clinic for scheduled visits at week 16, 20, 24, 36 and 52 (Visits 6, 7, 8, 9 and 10). The follow-up visit (Visit 11) will be scheduled 28 days post-treatment. Unscheduled visits may be conducted anytime if deemed necessary.

Time windows to be adhered to for scheduling of visits are shown in the Flow Chart. Sites should make every attempt to adhere to the protocol time windows as close as possible. The screening period (between Visit 1 and Visit 2) may be extended by additional 2 weeks (i.e. 28 day total) for any reasons (e.g. exacerbation, lab results receipt, etc.). All onsite visits from Visits 1 to Visit 11 will be scheduled in the morning, in order to guarantee start of pulmonary function testing at approximately the same time of the day (recommended time for PFTs from 8:00 till 11.00 a.m.; any subsequent PFTs should preferably be done within ± 90 minutes from the measurement at Visit 1). Patients should make every attempt to complete the study as specified. Investigators should encourage patient treatment compliance and adherence to other protocol specific activities.

All deviations from the planned visit schedule will be documented.

Rescheduling prior to randomisation.

• if a patient experiences acute IPF exacerbation or respiratory tract infection between Visit 0 and Visit 1, the Visit 1 will be postponed until complete recovery from the infection or exacerbation, preferably 4 weeks following the recovery from the infection or exacerbation.

• laboratory parameters found abnormal at visit 1 may be re-tested once prior to Visit 2.

• if the screening period (2 weeks and 2 additional weeks for administrative reasons) needs to be extended further (counted from Visit 1), the clinical monitor should be contacted. Reasoned prolongation of the screening period may be allowed by the clinical monitor.

• if a patient experiences an IPF exacerbation or respiratory tract infection during the screening period (2 weeks) between Visit1 and Visit 2, the Visit 2 will be postponed until complete recovery from the infection or exacerbation, preferably 4 weeks following the recovery from the infection or exacerbation.

Patients should make every attempt to adhere to the protocol. Investigators should encourage patient treatment compliance and adherence to other protocol related activities.

Subsequent visits should always be planned to take place at scheduled dates in line with the protocol Flow Chart.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Visit 0

Informed consent will be obtained prior to patient participation in the trial, which includes any study related procedures, medication washout procedures or restrictions. Furthermore, the patient will be asked to give informed consent to the pharmacogenomic (optional DNA and serum banking sample) analyses. HRCT and biopsy tissue samples (later if available) shall be sent for central review. Call the IRT to register a new patient into the study.

Visit 1

Visit 1 may only be performed once the central HRCT and biopsy tissue sample reading confirm the IPF diagnosis

At Visit 1:

- Verify medication washout compliance

- Record demographic data

- Conduct relevant medical history and physical examination including height and weight measurements, vital signs (blood pressure and pulse rate), pulse oximetry ($Sp0_2$) and 12-lead ECG. The vital signs (seated), pulse oximetry and ECG should be conducted following five minutes rest and prior to screening pulmonary function testing and DLCO measurement

- Perform blood collections for haematology, serum chemistry, coagulation panel and urine pregnancy test (if applicable). *Blood samples shall be sent to central laboratory; for further information refer to Laboratory Manual in the ISF*

- Perform **pulmonary function testing** in the morning preferably between 08:00 – 11:00. Patients must demonstrate FVC ≥ 80% to be eligible.

- Perform DLCO measurement

- Review and record all adverse events experienced since signed informed consent

- Record concomitant therapy for the previous 3 months in the eCRF as described in Section 4.2.

- Review inclusion and exclusion criteria

- Instruct and train patients on how to perform and record PFTs at home

- Give instructions on medication restrictions and washout requirements for the screening period and subsequent visits

- Instruct patients to bring all study-related equipment to the clinic at each visit

- Schedule the next clinic visit in 14 days (2 weeks), additional 2 weeks are allowed for administrative reasons

Screening period

6.2.2 Treatment period(s)

The order of procedures should be as follows: patient self-administered questionnaires (if applicable), blood collections (as per Flow Chart), vital signs and ECG (if applicable), PFTs, medication administration (if applicable).

Observations / Procedures

Visit 2 (randomisation visit)

Optional - Call the patient the day before the clinic visit to remind the clinic visit next day. Remind the patient medication washout requirements (if applicable) and to bring all study related supplies (home spirometer) to the clinic visit.

- Review and record all adverse events experienced and changes in concomitant therapy.

- Review all inclusion and exclusion criteria

- Perform blood collections for haematology, serum chemistry, coagulation panel and urine pregnancy test (if applicable) including biomarker serum and plasma samples, biomarker RNA sample, optional serum banking sample and optional DNA banking sample if applicable (later sample may be collected at any time as of Visit 2). For further details on safety lab collections refer to Section 5.3.3. For further details on biomarker related collections refer to Section 5.5. *Blood samples shall be sent to central laboratory; for further information follow Laboratory Manual in the ISF*

- Record vital signs (blood pressure and pulse rate) before PFTs and with the patient seated and rested for at least five minutes

- Record patient weight

- Perform supervised PFTs

- Perform randomisation in case patient is eligible

- Call IRT to randomise the patient and dispense the first blinded medication kit (period between Visit 2 and Visit 3)

- Instruct patient to take the first capsule at the clinic under trial staff supervision. Refer to Section 4.1.4. Instruct patient on further medication intake, please refer to Section 4.2 regarding possible dose reductions, interruptions and management of drug relates AEs

- Dispense the Patient Diary and instruct the patient on its use

- Schedule next planned clinic visit. Instruct patients to bring all study related treatments to the next clinic visit

Visits 3 and 4

Optional - Call the patient the day before the clinic visit to remind the clinic visit next day. Remind the patient medication washout requirements (if applicable) and to bring all study related supplies (home spirometer, patient diary, treatments, etc.) to the clinic visit.

- Review and discuss new Patient Diary entries with the patient

- Review and record all adverse events experienced and changes in concomitant therapy

- Perform blood collections and urine pregnancy test (if applicable). Refer to Section 5.3.3

- Collect biomarker serum and plasma samples, optional serum banking sample and optional DNA banking sample if applicable (later sample may be collected at any time as of Visit 2). Refer to Section 5.5

- Record vital signs (blood pressure and pulse rate) before PFTs and with the patient seated and rested for at least five minutes (at Visit 3 only)

- Record patient weight

- Perform supervised PFTs

- Perform Study Drug Compliance Check

- Call IRT to dispense the blinded medication kits (for further details refer to Section 4.1.4)

- Administer morning dose of the trial drug from newly dispensed kit at the site

- Schedule next planned clinic visit. Instruct patients to bring all study related treatments to the next clinic visit

Visit 5

Optional - Call the patient the day before the clinic visit to remind the clinic visit next day. Remind the patient medication washout requirements (if applicable) and to bring all study related supplies (patient diary, treatments, etc.) to the clinic visit.

- Review and discuss new Patient Diary entries with the patient

- Review and record all adverse events experienced and changes in concomitant therapy

- Record vital signs (blood pressure and pulse rate) before PFTs and with the patient seated and rested for at least five minutes

- Record patient weight

- Perform safety laboratory collections and urine pregnancy test (if applicable). For further details refer to Section 5.3.3

- Collect biomarker serum and plasma samples, optional serum banking sample and optional DNA banking sample if applicable (later sample may be collected at any time as of Visit 2). Refer to Section 5.5

Section 5.5

- Perform supervised PFTs

- Perform Study Drug Compliance Check

- Call IRT to dispense the open label medication kits (for further details refer to Section 4.1.4)

- Instruct patient to take the first capsule of open label medication at the clinic under trial staff supervision. Refer to Section 4.1.4 Instruct patient on further medication intake, please refer to Section 4.2 regarding possible dose reductions, interruptions and management of drug relates AEs.

- Schedule next planned clinic visit. Instruct patients to bring all study related treatments to the next clinic visit.

Visits 6, 7, 8 and 9

Optional - Call the patient the day before the clinic visit to remind the clinic visit next day. Remind the patient medication washout requirements (if applicable) and to bring all study related supplies (, patient diary, treatments, etc.) to the clinic visit.

- Review and discuss new Patient Diary entries with the patient

- Review and record all adverse events experienced and changes in concomitant therapy

- Record vital signs (blood pressure and pulse rate) before PFTs and with the patient seated and rested for at least five minutes (Visit 6, 8 and 9)

- Record patient weight

- Perform safety laboratory collections and urine pregnancy test. For further details refer to Section 5.3.3.

- Collect biomarker serum and plasma samples, optional serum banking sample and optional DNA banking sample if applicable (later sample may be collected at any time as of Visit 2). Refer to Section 5.5

- Perform supervised PFTs.

- Perform Study Drug Compliance Check

- Call IRT to dispense the open label medication kits (for further details refer to Section 4.1.4) (not applicable at Visit 6 and 7)

- Administer morning dose of the trial drug from the newly dispensed kits at the site (not applicable at Visit 6 and 7, as kits dispensed at Visit 5 will be used at these visits)

- Schedule next planned clinic visit. Instruct patients to bring all study related treatments to the next clinic visit

Visit 10 (End of treatment visit)

Optional - Call the patient the day before the clinic visit to remind the clinic visit next day. Remind the patient medication washout requirements (if applicable) and to bring all study related supplies (home spirometer, patient diary, treatments, etc.) to the clinic visit.

- Review and discuss new Patient Diary entries with the patient

- Review and record all adverse events experienced and changes in concomitant therapy

- Perform blood collections for haematology, serum chemistry, coagulation panel and urine pregnancy test (if applicable), including biomarker serum and plasma samples, biomarker RNA sample, optional serum banking sample and optional DNA banking sample if applicable (later sample may be collected at any time as of Visit 2). For further details on safety lab collections refer to Section 5.3.3. For further details on biomarker related collections refer to Section 5.5. *Blood samples shall be sent to central laboratory; for further information follow Laboratory Manual in the ISF.*

- Perform physical examination including vital signs (blood pressure and pulse rate) and perform 12-lead ECG before PFTs with the patient seated and rested for at least five minutes.

- Record patient weight

- Perform supervised PFTs

- Perform Study Drug Compliance Check

- Administer the last morning dose of the trial drug at the site. Collect remaining study drug. After the last dose of trial medication the Investigator / the treating physician may initiate further IPF treatment in line with the protocol Section 4.2.2.

- Call IRT to record End of Treatment

- Schedule next planned clinic visit (the Follow-up visit). Instruct patients to bring all remaining study supplies to the next clinic visit

6.2.3 Follow Up Period and Trial Completion

Visit 11 (Follow-up Visit)

Patients will be contacted once at the end of the follow up period. Adverse events and concomitant therapies will be reviewed and recorded. Urine pregnancy test will be performed in applicable patients. A 12-lead ECG and physical examination including vital signs should be performed if these were abnormal at Visit 10. Remaining trial supplies should be collected.

Premature withdrawal

Patients who prematurely discontinue study drugs (refer to Section 3.3.4) before the planned end of treatment at Visit 10, should come to the clinic as soon as possible after last drug intake for an early EOT visit. Reason for discontinuation must be documented in the eCRF. For detailed description of the trial procedures at this visit, please refer to the Flow Chart.

In addition patients will be invited to attend all remaining planned visits and perform all study procedures If a patient doesn't accept to attend remaining study visits, collect the home spirometer and any trial related supplies and contact patient for vital status collection at week 52.The need to come to remaining scheduled visits in case of prematurely discontinuation of trial medication will be explained to patients prior to their participation in the trial.

Vital status information

In case of an early discontinuation of trial medication, if the patient does not agree to come to future visits as planned, any attempt will be made to get information on vital status at Week 52 (refer to Flow Chart).

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

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

Collection of vital status will be performed in accordance with national ethical and regulatory guidelines. The need for vital status information will be explained to patients prior to their participation in the trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, placebo controlled, multi-centre, multinational, prospective, double blind trial to investigate the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and preserved forced vital capacity (FVC).
The primary endpoint is the rate of change (slope) in blood CRPM from baseline to week 12. Therefore, the rate of change (slope) in blood CRPM will be analyzed using random coefficient regression (random slopes and intercepts) model including gender, age and height as covariates.
The secondary endpoint, proportion of patients with disease progression defined by FVC decline ≥10% or death, will be analysed using logistic regression models or other appropriate methods.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The objective of this study, demonstrating a treatment effect of nintedanib at a dose of 150 mg bid compared to placebo for the rate of change (slope) in blood CRPM, will be tested using the following null hypothesis.

> H_0: No difference in the rate of change (slope) in blood CRPM evaluated from baseline until 12 weeks of treatment between nintedanib mg bid and placebo.

The alternative hypothesis is

> H_a: The rate of change (slope) in blood CRPM is different for patients taking nintedanib 150 mg bid than those taking placebo.

The hypothesis will be tested using 5% level of significance (two-sided test).

7.3 PLANNED ANALYSES

The statistical analysis will be based on the following populations.

Treated Set (TS):
The treated set (TS) consists of patients who are randomised to a treatment group and receive at least one dose of study medication

Randomised Set (RS):

The Randomised set (RS), consists of those patients who were randomised to a treatment group.

The efficacy and safety analysis will be conducted on the TS. Efficacy parameters will be analysed from an as randomised perspective and safety parameters from an as treated perspective, respectively. For efficacy analysis, all measurement performed within the first 12 weeks will be used. Efficacy evaluations done after lung transplant will not be used for the efficacy analyses; sensitivity analyses will be performed including these data.
Although there is no per protocol data set in the study, reasons for important protocol violations will be specified in the Trial Statistical Analysis Plan (TSAP). Patients with potential important protocol violations (those that relate to patient safety or efficacy) will be identified at Blinded Review Planning Meetings and listed in the clinical trial report.

7.3.1 Primary endpoint analyses

The primary endpoint is the rate of change (slope) in blood CRPM evaluated from baseline over 12 weeks (expressed in ng/mL/month) estimated from measurements taken over 12 weeks of treatment. The rate of change (slope) in blood CRPM is assumed to be linear within each subject over the 12 weeks period. The intercepts and slopes will be assumed to be normally distributed with arbitrary covariance matrix. Gender, age and height which are usual predictors of FVC will also be included in the model. Baseline blood CRPM will be measured at visit 2. No imputation is planned if this assessment is not available for a patient. The within patient error will be assumed to be independent and normally distributed with mean zero and a common variance. The Kenward-Roger approximation will be used to estimate denominators degrees of freedom. Significance tests will be based on least-squares means using a two-sided α=0.05 (two-sided 95% confidence intervals). Analyses will be implemented using SAS® Version 9.4.
The linearity assumption for the rate of change (slope) in blood CRPM will be tested and sensitivity analysis will be done with alternative models described in the Trial Statistical Analysis Plan (TSAP). The effect of missing data will be investigated using pattern-mixture models. Depending on the pattern of the missingness in the data, multiple imputation methods may also be considered.

7.3.2 Secondary endpoint analyses

For the key secondary endpoint, proportion of patients with disease progression as defined by FVC decline ≥10% or death over week 52, two main analyses are planned.
Firstly, in order to assess the predictive value of change in extracellular matrix (ECM) biomarker CRPM over 12 weeks for disease progression as defined by FVC decline ≥10% or

death over 52 weeks, a logistic regression (or a similar appropriate) analysis including baseline blood CRPM and the rate of change (slope) in blood CRPM over the first 12 weeks as covariates will be applied for the placebo treated patients only.
Secondly, in order to assess how nintedanib treatment during the first 12 weeks affects the association between change in extracellular matrix (ECM) biomarker CRPM over 12 weeks and disease progression, a logistic regression (or a similar appropriate) analysis including baseline blood CRPM, rate of change (slope) in blood CRPM over the first 12 weeks, treatment and treatment CRPM slope interaction as covariates will be applied. The interaction term will be of primary interest within this analysis. More details will be given in the TSAP.
Both analyses will be repeated for rate of change (slope) in the biomarkers C1M and C3M defined as secondary endpoints. Reasonably, baseline CRPM as covariate will be replaced by baseline C1M/C3M in these analyses.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 28 days
after the last dose of trial medication, will be assigned to the 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. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as 28 days. 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).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. 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.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Efficacy endpoints

In efficacy analyses of continuous endpoints, missing data will not be imputed. In the analyses of the time-to-event endpoints, missing or incomplete data are managed by standard survival analysis techniques. These will be described in detail in the TSAP.
In the analyses of the categorical endpoints, missing data will be imputed using the worst case.

7.5.2 Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards. With respect to other safety evaluations, it is not planned to impute missing values.

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment with an unequal probability 1 to 2 of assignment to nintedanib and placebo. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented. All members of the Medical Project Team will remain blinded to the randomisation schedule until after the final database is locked.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on change relative to baseline in biomarker levels of serum CRPM, serum C1M and serum C3M (unpublished data, no reference available). The sample size calculations are based on two-sided tests (α =0.05) to detect a difference in means of two independent samples with a 1:2 randomisation ratio nintedanib:placebo in the samples with a power of 90%. No multiplicity adjustments are made as part of the power calculation, and no adjustment is made for a potential subject withdrawal. Sample size calculations are performed for assumed differences between treatment group and placebo of 20% and 30% difference. Due to the lack of data from respective IPF patients and since there is no evidence biomarker courses are principally different across both indications, data from two studies of RA patients are used to estimate the standard deviation over time in biomarker values relative to baseline: Study A) RA patients including a placebo group and a treatment group with measurements of serum CRPM, serum C1M and serum C3M at baseline, weeks 4, 16, and 24; and Study B) RA patients including a placebo group and a treatment group with measurements of serum CRPM, serum C1M and serum C3M at baseline, weeks 4, and 12.

The hypothesis to be tested can be formulated as:

H_0: $\mu_{Treatment} = \mu_{Placebo}$

tested confirmatively against the alternative

H_a: $\mu_{Treatment} \neq \mu_{Placebo}$

where $\mu_{Treatment}$ is the change in biomarker relative to baseline in the treatment group, and $\mu_{Placebo}$ is the change relative to baseline in the placebo group.

Table 7.7:1 Data of standard deviation over time in changes relative to baseline

Data of standard deviation over time in changes relative to baseline						
	CRPM		C1M		C3M	
	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment
Study A						
Week 4	42% (n=100)	34% (n=143)	44% (n=116)	41% (n=176)	38% (n=116)	31% (n=176)
Week 16	33% (n=88)	36% (n=128)	42% (n=102)	58% (n=156)	32% (n=102)	27% (n=156)
Week 24	31% (n=83)	32% (n=131)	53% (n=97)	53% (n=162)	33% (n=97)	31% (n=162)
Study B						
Week 4	40% (n=71)	25% (n=66)	48% (n=76)	68% (n=75)	43% (n=71)	66% (n=67)
Week 12	43% (n=52)	47% (n=68)	45% (n=54)	55% (n=73)	44% (n=50)	44% (n=68)

Based on Table 7.7:1, sample sizes will be calculated for a range of common standard deviations of 30%; 40% and 50%.

Table 2 gives the calculated sample size numbers for assumed relative treatment differences of 20 and 30 percent.

Table 7.7:2 Sample sizes for common standard deviations of 30%, 40%, and 50%; significance level 5%; power 90% with a 1:2 randomisation ratio nintedanib:placebo

Sample sizes for common standard deviations of 30%, 40%, and 50%; significance level 5%; power 90% with a 1:2 randomisation ratio nintedanib:placebo									
	Common STD 30%			Common STD 40%			Common STD 50%		
	n			n			n		
	nintedanib	placebo	total	nintedanib	placebo	total	nintedanib	placebo	total
20%	37	73	110	64	128	192	100	199	299
30%	17	33	50	29	58	87	45	89	134

If the true standard deviation of change in CRPM relative to baseline lies between 30 and 50 percent, a total number of patients between 110 and 300 would be needed to detect a

treatment group difference of 20% with a power of 90% with a treatment allocation ratio of 1:2 (Nintedanib:Placebo).

However, the key secondary endpoint requires more patients for two reasons: firstly, only patients initially treated with Placebo are analysed in the first step (reducing the actual sample size for this analysis to 2/3 of the total sample size) and secondly, some loss of information is associated with the planned analysis due to the binary state of the endpoint. To be more precise, with n=350 randomised patients, n=233 patients will be initially treated with Placebo and based on the INPULSIS results [P14-07514], we expect to observe a total of about 40% of disease progression as defined by FVC decline ≥10% or death over week 52 for that treatment group. Using available data from the observational PROFILE study [R15-1220], we further expect roughly half of the patients to have rising biomarker values (slope greater than zero) and the remaining patients having stable biomarker values (slope less or equal to zero) resulting in about equally sized groups if the rate of change (slope) in blood CRPM from baseline to week 12 is dichotomized. With the stated sample size, an absolute difference in rates of at least 20% (i.e. 30% vs 50% of patients with disease progression) can be detected with a power of 88%.

For these reasons, a sample size of n=350 patients (117 on nintedanib and 233 on placebo) is planned for this study.

Calculations were performed using nQuery Advisor® 6.1.1 statistical package by Statistical Solutions Ltd.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonized 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 Tripartite 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.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

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.

For Japan only: The rights of the investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND 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 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.

For Japan only: The Investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator 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 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.

8.2 DATA QUALITY ASSURANCE

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.

To ensure good quality data, investigators and study site personnel will be familiarized with the study protocol, procedures and principles of GCP during the investigator meeting and/or trial initiation visit. An ISF with all necessary trial related documentation and handling procedures will be provided.

A central laboratory will be used for analysis of all blood samples.

To ensure standardization in FVC measurement, a central spirometry review will be in place. Spirometry devices will be supplied to all participating sites/patients.

Data will be captured using an RDC system. Training will be provided to all investigators, coordinators and CRAs to ensure consistency and accuracy of the data. The data will be source verified by the CRA during regular onsite monitoring.

Data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan which is available in the TMF.
Coding of concomitant medications is according to the World Health Organisation drug dictionary and coding of AEs is according to the MedDRA dictionary.

8.3 RECORDS

Electronic Case Report Forms (eCRF) for individual patients will be provided by the Sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

8.3.2 Direct access to source data and documents

The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA / on site monitor and auditor may review all CRF / eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

For Japan only:
Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to national or local requirements (whatever is longer) valid at the time of the end of the trial.
Sponsor:
The Sponsor must retain the essential documents according to the Sponsor's SOPs.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular AE is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For nintedanib this is the current version of the IB (c01805141-17).

The current versions of these reference documents are provided in the ISF. No AE are classified as listed for trial design, or invasive procedures.

8.4.2 Expedited reporting

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. 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 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 END OF TRIAL

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").
The IEC / competent authority in each participating EU member state will be notified about the end or early termination of the trial.
For Japan only:
When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

For Japan only: The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan only: In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

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10. APPENDICES

10.1 CRITERIA FOR HRCT/BIOPSY CENTRAL

All chest HRCTs, and histopathology slides of surgical lung biopsies (the latter if available) will be centrally reviewed.

In the absence of a surgical lung biopsy, chest HRCT must qualify as “consistent with UIP”.

This will be defined as meeting either criteria A, B and C, or criteria A and C, or criteria B and C below.

A) Definite honeycomb lung destruction with basal and peripheral predominance.

B) Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance.

C) Atypical features are ABSENT, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.

Appearances of a fibrosing lung disease with no definite HRCT features of a specific etiology will be considered “possible IPF”. Convincing HRCT appearances of a diffuse lung disease other than IPF will be considered “definitely not IPF”. “Possible IPF” and “definitely not IPF” will not be allowed for inclusion in the trial.

In the presence of a surgical lung biopsy, the histology will be reviewed based on the ATS/ERS/JRS/ALAT guidelines [P11-07084]. In such case, there will be a multi-disciplinary team approach (radiologist and pathologist) to confirm or exclude the diagnosis of IPF. An HRCT "possible IPF" coupled with a surgical biopsy of “definite UIP” or "probable UIP", upon multidisciplinary team discussion, could qualify for inclusion as “consistent with IPF”.

10.2 CREATININE CLEARANCE

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

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

10.5 DLCO

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS guideline on DLCO measurements [R06-2002], and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

Predicted DLCO corrected for haemoglobin (Hb) expressed in g x dL^{-1} (R06-2002) can be calculated as:

- Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(10.22+Hb)) for males aged 15 years or above
- Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(9.38+Hb)) for females and children aged less than 15 years

DLCO results from Visit 1 will be corrected for haemoglobin (value obtained at Visit 1) by the site.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		23 February 2016
EudraCT number		2015-003148-38
BI Trial number		1199.227
BI Investigational Product(s)		nintedanib
Title of protocol		A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		No content changes
Description of change		The document number on title page and headers was wrong.
Rationale for change		Not Applicable

Number of global amendment		2
Date of CTP revision		25 February 2016
EudraCT number		2015-003148-38
BI Trial number		1199.227
BI Investigational Product(s)		nintedanib
Title of protocol		A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in

		biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		No content changes
Description of change		Not Applicable
Rationale for change		Technical error during signature workflow

Number of global amendment		3
Date of CTP revision		04 May 2017
EudraCT number		2015-003148-38
BI Trial number		1199.227
BI Investigational Product(s)		nintedanib
Title of protocol		A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without		

IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		1. Flow Chart: Biomarker serum and plasma, RNA, PK and optional serum banking samples collections added 2. Explanatory Note 2 on page 29, Old text "or", new text "and/or" 3. Page 45, fingertip added as a possibility to perform measurement of oxygen saturation 4. Further explanation added regarding visit planning and conduct on pages 56, 58 and 62
Description of change		Change 1: correction of typo, allow consistency in procedures between visit 10 (EOT) and Early EOT Change 2 and 3: correction of typos, maintain consistency within the clinical project Change 4: further clarification of visit planning and visit conduct
Rationale for change		Correction of Typos, additional clarification and explanation of trial related procedures, align procedures within the clinical project

Number of global amendment		4
Date of CTP revision		09 July 2018
EudraCT number		2015-003148-38
BI Trial number		1199.227
BI Investigational Product(s)		nintedanib
Title of protocol		A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent		

Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		5.1.3
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c03495745 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-5

Title: A 12-week, double blind, randomised, placebo controlled, parallel group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		10 Jul 2018 10:32 CEST
Author-Trial Clinical Monitor		10 Jul 2018 10:37 CEST
Approval-Team Member Medical Affairs		10 Jul 2018 10:50 CEST
Author-Trial Statistician		10 Jul 2018 16:25 CEST
Approval-Therapeutic Area		16 Jul 2018 10:42 CEST
Verification-Paper Signature Completion		16 Jul 2018 10:46 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed