Clinical Trial Protocol

	Document Number:	**c03484701-03**
EudraCT No.:	2015-002619-14	
BI Trial No.:	1199.36	
BI Investigational Product:	Nintedanib (Ofev®)	
Title:	INSTAGE™: A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment	
Brief Title:	Efficacy and safety of nintedanib co-administered with sildenafil in IPF patients with advanced lung function impairment	
Clinical Phase:	III b	
Trial Clinical Monitor:	Phone : Fax :	
Coordinating Investigator:	Phone ext (Division), (Clinic) Fax	
Status:	Revised Protocol based on Global Amendment 2	
Version and Date:	**Version:**	**Date:**
	3.0	18 AUG 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Ofev®	
Name of active ingredient:		Nintedanib	
Protocol date: 30 Dec 2015	**Trial number:** 1199.36		**Revision date:** 18 Aug 2016

Title of trial:	INSTAGE™: A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment
Coordinating Investigator:	Phone ext (Division), (Clinic) Fax
Trial sites:	Multi-centre trial
Clinical phase:	III b
Objective(s):	To assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung function impairment.
Methodology:	Double-blind, randomized, parallel design comparison of nintedanib 150 mg bid and sildenafil 20 mg tid to nintedanib 150 mg bid and placebo matching sildenafil tid over 24 weeks
No. of patients:	
total entered:	250 patients
each treatment:	Randomization 1:1 125 patients assigned to each treatment arm.
Diagnosis :	Idiopathic Pulmonary Fibrosis (IPF)
Main criteria for inclusion:	Written informed consent;

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	Male or female patients aged ≥ 40 years at visit 1; IPF diagnosis based upon the ATS/ERS/JRS/ALAT 2011 guideline for < 6 years; confirmation of diagnosis by investigator based on chest HRCT performed within 18 months of visit 1 and surgical lung biopsy (if available); DLCO (corrected for Hb) ≤ 35% predicted of normal at visit 1
Test product(s):	Nintedanib and sildenafil
dose:	Nintedanib: 300 mg daily (150 mg bid) with possibility to reduce to 200 mg daily (100 mg bid) to manage adverse events Sildenafil: 60 mg daily (20 mg tid)
mode of administration:	p.o.
Comparator products:	Nintedanib and placebo matching sildenafil
dose:	Nintedanib: 300 mg daily (150 mg bid) with possibility to reduce to 200 mg daily (100 mg bid) to manage adverse events Placebo matching sildenafil: Not applicable
mode of administration:	p.o.
Duration of treatment:	24 weeks of randomized treatment
Endpoints	Primary Endpoint: Change from baseline in SGRQ total score at week 12 Secondary Endpoints: • Change from baseline in dyspnea using UCSD SOBQ at week 12; • Change from baseline in SGRQ total score at week 24; • Change from baseline in dyspnea using UCSD SOBQ at week 24;

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	• Percentage of patients with on-treatment SAEs from baseline to week 24.
Safety criteria:	Adverse events (especially SAE and other significant AE), physical examination including weight, 12 lead electrocardiogram and vital signs, laboratory evaluations.
Statistical methods:	Mixed Effects Model for Repeated Measures (MMRM) for continuous endpoints and Kaplan-Meier and Cox model for time to event endpoints, Cochran-Mantel-Haenszel test for binary endpoints

FLOW CHART

Trial Periods	**Screening Period**	**Randomized Treatment Period**								**Follow-up period**
Visit	**1**[1]	**2**[14]	**3**	**4**	**5**	**6**	**7**[15]	**Dose Adjustment visit**[16]	**Early EOT**[17]	**FUP**[18]
Weeks		**0**	**4**	**8**	**12**	**18**	**24**			**+4**
Days	**-28 to -1**	**1**	**29**	**57**	**85**	**127**	**169**			**+28**
Time window for visits		none	±3 days	±3 days	±3 days	±7 days	±7 days			+7 days
Informed consent[2]	X									
Demographics	X									
Medical history	X									
SGRQ, UCSD-SOBQ, EQ-5D[3]		X	X		X		X		X	
Physical examination[4]	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	X	X	X	
Pregnancy test (urine)[7]	X	X	X	X	X	X	X		X	X
12 lead-ECG	X		X		X		X		X	
Spirometry	X	X	X	X	X	X	X		X	
DLCO, VA[8]	X				X		X		X	
Resting SpO_2		X	X		X		X		X	
Resting PaO_2 and $PaCO_2$[9]		X			X		X		X	
Echocardiogram	X									
Review of in-/exclusion criteria	X	X								
Randomization		X								
Access IRT	X	X	X	X	X		X	X	X	
Dispense trial drugs		X	X	X	X			X		
Collect trial drugs & compliance check			X	X	X	X[10]	X	X	X	
Dispense or review patient diary[11]		X	X	X	X	X	X	X	X	
Adverse events	X[12]	X	X	X	X	X	X	X	X	X
Acute exacerbations	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Completion of patient participation										X
Vital status collection[13]							X			

1. The period between visit 1 and 2 should last a maximum of 28 days. Eligible patients can be randomized once central lab results have been received and are found to be consistent with eligibility criteria.
2. At site discretion, informed consent may be obtained on one day and the remainder of the screening procedures can follow.
3. SGRQ, UCSD-SOBQ and EQ-5D are to be completed in this order and prior to any other trial related procedures.
4. Physical examination to include weight measurement at all visits. At visit 1, height measurement should be included.

7. Urine dipstick pregnancy tests will be provided by central lab and should be performed in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory.
8. The DLCO/VA assessment should always be performed after the FVC assessment.
9. Arterialised blood gases (PaO_2 and $PaCO_2$) will be measured at selected sites experienced in earlobe blood gas sampling.
10. At visit 6 drug supplies should be collected for accountability and compliance check and re-dispensed to the patient.
11. Patient diary will be issued at visit 2 until visit 7. Diary to be reviewed with patient at every visit. Content to be discussed as it pertains to AEs, concomitant therapy, medication compliance and drug administration preceding PK sampling.
12. Adverse events should only be collected at this visit if occurring after obtaining the informed consent. Medical conditions present at time of the informed consent should be recorded in the medical history.
13. Patients who complete an early End of Treatment visit and don't accept to attend all remaining planned visits will be contacted for vital status collection at week 24. This can be done by phone.
14. Visit 2 is defined as baseline assessment if the respective parameter is planned to be collected at that visit. Otherwise, visit 1 will serve as baseline assessment.
15. Visit 7 is the End of Treatment (EOT) visit for patients who complete the treatment period as planned.
16. In case of dose change of nintedanib (reduction or re-escalation), dose adjustment visit must be conducted to allow dispensing of new medication kit.
17. Early end of treatment visit to be completed for all patients who withdraw or discontinue all study drugs prematurely. These patients will be invited to attend all remaining visits as planned until week 24 (Visit 7). The following procedures are no longer required in the visits to be conducted after the early EOT visit: laboratory tests, biomarker sampling, pharmacokinetic sampling and ECG.
18. A follow up visit needs to be completed 28 days (+7 days) after the last drug administration for all patients. Patients who prematurely discontinue all study drugs but accept to conduct all remaining study visits as planned and the remaining duration in the trial is longer than 28 days after the last drug administration are exempted from this visit.

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ABBREVIATIONS

AC	Adjudication Committee
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
AS	Aortic Stenosis
AST	Aspartate Transaminase
AUC	Area under the Curve
AV	Atrioventricular
BI	Boehringer Ingelheim
bid	bis in die (twice daily dosing)
BNP	Brain Natriuretic Peptide
cGMP	Cyclic Guanosine Monophosphate
CI	Confidence Interval
Cmax	Maximum Plasma Concentration
CML	Local Clinical Monitor
$C_{pre,ss}$	Steady State Pre-dose Plasma Concentrations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic Blood Pressure
DDI	Drug-drug Interaction
DILI	Drug Induced Liver Injury
DLCO	Carbon Monoxide Diffusion Capacity
DMC	Data Monitoring Committee
DNA	Desoxyribose Nucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FEV1	Forced Expiratory Volume in 1 second
FGF(R)	Fibroblast Growth Factor (Receptor)
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HRCT	High-resolution Computed Tomography
IB	Investigator's Brochure
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
IHSS	Idiopathic Hypertrophic Subaortic Stenosis
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IU	International Units
i.v.	Intra venous
Hb	Haemoglobin
Kco	Carbon Monoxide Transfer Coefficient
MACE	Major Adverse Cardiovascular Events
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Effects Model for Repeated Measures
NAC	N-acetylcysteine
nRTK	Non-receptor Tyrosine Kinase
$PaCO_2$	Partial Pressure of Carbon Dioxide
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of Oxygen
PDGF(R)	Platelet Derived Growth Factor (Receptor)
PDE5	Phosphodiesterase Type-5
PK	Pharmacokinetics
p.o.	per os (oral)
PRO	Patient Reported Outcomes
PT	Prothrombin Time
REML	Restricted Maximum Likelihood
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic Acid
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SpO_2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reactions
tid	ter in die (3 times a day)
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
VA	Alveolar Volume
VEGF(R)	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 confirmatory ASCEND Phase III trial met the primary endpoint of change from baseline FVC % predicted [R14-2103]. Pirfenidone is now licensed since February 2011 for the treatment of mild to moderate IPF in the EU and since October 2014 for the treatment of IPF in USA. 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 USA in October 2014, in the EU in January 2015 and in Japan in July 2015. 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, there is an additional need to further characterize their profile, including their use in special populations not previously studied or in potential combination treatment regimens to enhance efficacy.

1.2 DRUG PROFILE

1.2.1 Nintedanib

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 is 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 and the terminal half-life found in healthy volunteers is in the range of 7 to 19 h. The absolute bioavailability of nintedanib is 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 with rifampicin compared to administration of nintedanib alone. Since potent P-gp inducers may decrease exposure to nintedanib, selection of alternate 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 randomized, 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, diarrhoea, 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 diarrhoea 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. Also weight decrease and decreased appetite have frequently been reported in studies with nintedanib.

Risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism, pancreatitis, thrombocytopenia 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 disorders 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 confirms 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 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) [U07-1248] which is included in the Investigator Site File (ISF).

1.2.2 Sildenafil

Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. This can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25–63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations. N-desmethyl metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. After oral administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

Sildenafil metabolism is principally mediated by the CYP3A (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance. Concomitant use of sildenafil with ritonavir and other potent CYP3A inhibitors is not recommended.

Sildenafil is indicated for the treatment of Pulmonary Arterial Hypertension (PAH) in adults to improve exercise ability and delay clinical worsening. The efficacy of sildenafil was evaluated in four phase 3 short term studies (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II–III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%). Based on the identification of different mechanistic pathways involved in the pathogenesis of pulmonary arterial hypertension, i.e. the nitric oxid, endothelin and prostaglandin pathways, increasing evidence suggests a role for sequential or upfront combination treatment in patients with PAH [R15-5447]. However, the effects of combination treatment of sildenafil with endothelin antagonists like macicentan or bosentan on morbidity and mortality are mixed [R15-5445; R15-5446].

Sildenafil (20 mg tid) has also been studied in a 12 week double-blind placebo-controlled randomized trial followed by a 12 week period of open-label treatment which enrolled 180 IPF patients with advanced lung function impairment (STEP-IPF). Although this study met significant differences in some secondary endpoints such as quality of life, it failed to meet its primary outcome of change in 6-minute walk distance of ≥ 20% at week 12 [R12-3686].

Safety data of sildenafil in adults were obtained from a 12-week, placebo-controlled clinical study and an open-label extension study in 277 patients with PAH, WHO Group I. The overall frequency of discontinuation in patients treated with sildenafil on 20 mg three times a day was 3% and was the same for the placebo group. Most common adverse reactions greater than or equal to 3% and more frequent than placebo were epistaxis, headache, dyspepsia,

flushing, insomnia, erythema, dyspnea, and rhinitis. Adverse reactions were generally transient and mild to moderate in nature.

Potential risks of treatment with sildenafil include hypotension, worsening of pulmonary veno-occlusive disease, epistaxis, visual loss, hearing loss, priapism and vaso-occlusive crisis in patients with pulmonary hypertension secondary to sickle cell disease.

In the STEP-IPF study approximately 90% of patients in each group (sildenafil or placebo) had at least one adverse event with the most common being dyspnoea, cough and progression of IPF during the double-blind 12 weeks period. The proportion of serious adverse events was also similar between groups (15% in sildenafil vs. 16% in placebo) without significant between-group differences in the occurrence of specific serious adverse events [R12-3686].

Sildenafil is also indicated in adult men with erectile dysfunction with a recommended dose of 50 mg taken as needed approximately one hour before sexual activity. This dose will not be used in this study.

For a more detailed description of the drug profile refer to the current local Prescribing Information or Summary of Product Characteristics 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. Although both drugs are approved for the treatment of all IPF patients (with the exception of pirfenidone in Europe and other countries where it is approved only for "mild to moderate IPF"), patients with advanced lung function impairment have been typically excluded from the most recent clinical trials in IPF.

In contrast to patients with more preserved lung function, abnormalities of the pulmonary vasculature due to continuous destruction of the vasculature by fibrosis and aberrant vascular remodeling, leading to decreased levels of resting and exercise-induced production of nitric oxide, are more common in patients with advanced lung function impairment, specifically in patients with advanced impairment in diffusion capacity. Since nitric oxide is a potent pulmonary vasodilator, reduced levels are associated with pulmonary vasoconstriction and impaired gas exchange.

Nintedanib is an inhibitor of tyrosine kinases (including the PDGF, VEGF and FGF receptors). By inhibiting these receptors, nintedanib regulates cellular proliferation, survival, migration and differentiation, processes which are involved in the profibrotic process of IPF [P08-08684; P14-02860]. The phase II and III clinical studies showed that nintedanib slowed IPF disease progression by reducing the annual lung function decline and potentially the risk for acute exacerbations, however no clinically relevant beneficial effect on health related quality of life or other patient-related outcomes measures was observed [P14-07514; P11-11216].

Sildenafil, a PDE5 inhibitor approved for the treatment of PAH, stabilizes the second messenger of nitric oxide (cGMP) which leads to pulmonary vasodilation. Although the STEP-IPF trial failed to meet its primary outcome of change in 6-minute walk distance of ≥ 20% at week 12, it showed promising results in secondary endpoints with clinically significant differences in the degree of dyspnea and quality of life, as well as in gas exchange parameters [R12-3686].

Combining these two drugs with different molecular targets might ultimately provide additional benefits to patients with IPF and advanced lung function and gas exchange impairment: nintedanib by slowing the disease progression and sildenafil by impacting patient relevant outcomes such as quality of life and dyspnea.

Given the limitations of the STEP-IPF study, including the low number of patients, further data is required in order to confirm the symptomatic benefits of sildenafil. In addition, this trial will allow the collection of safety and tolerability data of the combined treatment of nintedanib and sildenafil as well as of nintedanib alone in a population with advanced disease which has been typically excluded from the most recent clinical trials in IPF.

2.2 TRIAL OBJECTIVES

The primary objective is to assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung function impairment.

A further important objective of the trial is to enlarge the existing nintedanib mono-therapy database with safety and tolerability data in this population.

In addition, the effect of nintedanib and sildenafil on biomarkers related to IPF pathophysiology will be assessed to increase understanding of the mode of action of both compounds.

2.3 BENEFIT - RISK ASSESSMENT

All patients in this trial will be treated with nintedanib. As described in section 1, patients with IPF may benefit from lesser decline in lung function and hence slower disease progression as a result of treatment with nintedanib. In addition, nintedanib significantly reduced the risk of a first acute exacerbation in 2 out of 3 clinical trials [P11-11216, P14-07514].

Half of the patients in this trial will be treated with sildenafil in addition to nintedanib. In the STEP-IPF trial, sildenafil showed promising results in symptomatic or patient-related endpoints such as dyspnea and health-related quality of life [R12-3686].

Although currently unknown, concomitant treatment of both drugs may ultimately be found to add further benefits to patients.

The safety profile of nintedanib and sildenafil is described in section 1.2.

The most common side effects of nintedanib are of gastrointestinal nature (diarrhoea, nausea, vomiting, abdominal pain), as well as liver enzyme elevations. Side effects are generally mild to moderate in nature. In case of side effects, symptomatic treatment, dose adjustments and/or interruptions of nintedanib should be considered to allow for resolution of the symptoms (section 4.2.1).

Risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism, pancreatitis, thrombocytopenia and bleeding. 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.

The most common side effects of sildenafil are epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea and rhinitis. Side effects are generally mild to moderate in nature. In case of side effects, symptomatic treatment and/or interruption of sildenafil should be considered to allow for resolution of the symptoms (section 4.2.1).

Potential risks of treatment with sildenafil include hypotension, worsening of pulmonary veno-occlusive disease, epistaxis, visual loss, hearing loss, priapism and vaso-occlusive crisis

in patients with pulmonary hypertension secondary to sickle cell disease. Patients at higher risk for these conditions are excluded from this trial.

Clinical data on the pharmacokinetics of nintedanib and sildenafil when given in combination is not available. Based on the known metabolic properties of both compounds, the likelihood of a pharmacokinetic drug-drug interaction is considered to be low. Nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in vitro.

It is currently unknown if the co-administration of both drugs will result in additional side effects. To minimize this risk, safety monitoring in this trial will consist of regular visits to the investigational site, blood analyses and specific monitoring procedures to follow-up potential hepatic enzyme elevation. In addition, an independent data-monitoring committee (DMC) will review the safety data at specified intervals during the study conduct (refer to section 3.1.1).

Overall, the clinical safety profile of both nintedanib and sildenafil as established during the previous clinical trials 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, multi-national, prospective, randomised, double-blind, parallel-group clinical trial to investigate the efficacy and safety of nintedanib when co-administered with sildenafil, compared to treatment with nintedanib alone, in patients with IPF and advanced lung function impairment.

A total of approximately 250 patients will be randomised in a blinded fashion to nintedanib 150 mg bid co-administered with sildenafil 20 mg tid or to nintedanib 150 mg bid co-administered with placebo matching sildenafil. Patients will be stratified at randomization by the presence of any echocardiographic signs indicative of right heart dysfunction including right ventricular hypertrophy and right ventricular or atrial dilatation (as described in sections 6.2.1 and 7.6). Randomized treatment will last 24 weeks. During the randomized treatment period, dose reductions and/or temporary interruptions of nintedanib, as well as drug interruption of sildenafil/matching placebo, are allowed to manage adverse events (section 4.2.1). The planned follow-up period for patients after study treatment completion will be four weeks. Patients who prematurely discontinue all study drugs, will be invited to attend all visits as planned until week 24 (visit 7).

Each patient's participation in the trial is estimated to last approximately 32 weeks (from visit 1).

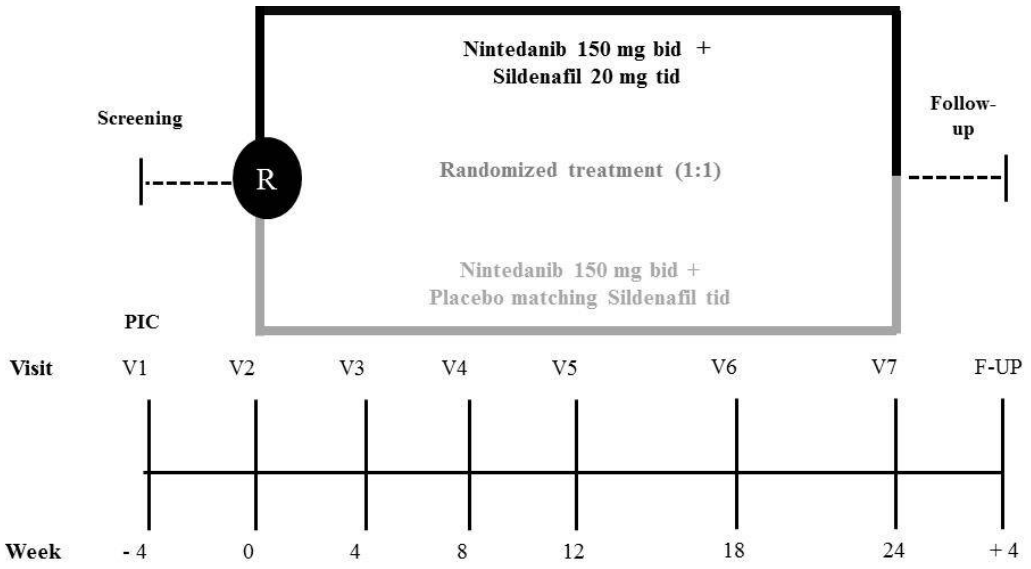

Figure 3.1:1 Trial design scheme

3.1.1 Administrative structure of the trial

The sponsor of this trial is Boehringer Ingelheim (BI).

BI has appointed a 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 of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management, Pharmacokinetic 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.

Additional information for Japan only: A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF.

A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the ISF.

Sites selected for participation will consist of specialized referral centres experienced in the management of IPF.

A DMC, independent of the sponsor, will be established to assess the progress of the clinical trial, including an unblinded safety assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial. Measures are in place to ensure blinding of the sponsor and all other trial participants.

All death cases will be assessed (to evaluate the primary cause of death), as well as all adverse events categorized as major adverse cardiovascular events (MACE) and all acute IPF exacerbations (based on written clinical reports, for diagnostic confirmation) by an independent Adjudication Committee (AC), in a blinded manner before data base lock. The tasks and responsibilities of the DMC and the AC will be specified in a charter.

The DMC and the AC will maintain written records of all its meetings.

A central laboratory will perform all protocol specified blood analysis of the trial.

An IRT will perform randomization of patients and ensure appropriate distribution of trial medication to sites during the trial.

A central vendor will provide spirometers for the complete duration of the trial.

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

In the STEP-IPF trial sildenafil has been shown to improve patient-relevant outcomes such as dyspnea and quality of life in patients with advanced lung function impairment at 12 weeks [R12-3686]. In order to confirm these findings and a potential added benefit of sildenafil when added to current standard of care, a double-blind, parallel group trial design was selected where half of the patients will be treated with sildenafil and half of the patients will be treated with placebo matching sildenafil. All patients will be treated with nintedanib as background therapy considered usual care in patients with IPF.

The randomized treatment period duration of 24 weeks is thought to be adequate to evaluate if the efficacy is maintained after the primary endpoint assessment at 12 weeks. In addition it is considered an appropriate treatment duration to allow the collection of safety and tolerability data of concomitant treatment of nintedanib and sildenafil, as well as collection of additional safety data for nintedanib monotherapy in a population with a more advanced lung function impairment in comparison to the population enrolled in the Phase II and III TOMORROW and INPULSIS® trials.

The frequency of visits will allow close monitoring of emergent adverse events as well as control of liver enzyme values consistent with the recommendations of the prescribing information of nintedanib.

To obtain further efficacy and safety information on the concomitant treatment of nintedanib and sildenafil, lung function tests, clinical laboratory tests and electrocardiograms will be performed. Data on discontinuations and death will be recorded.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 250 patients with an IPF diagnosis and advanced lung function impairment will be randomized. Approximately 80 sites are each expected to include approximately 3 patients.

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 diagnosed with 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 any study procedures being performed (including any required washout);
2. Male or female patients aged ≥40 years at visit 1;
3. A clinical diagnosis of IPF within the last 6 years before visit 1, based upon the ATS/ERS/JRS/ALAT 2011 guideline [P11-07084];
4. Combination of high-resolution computed tomography (HRCT) pattern, and if available, surgical lung biopsy pattern consistent with a diagnosis of IPF (see appendix 10.1) as assessed by the investigator based on a HRCT scan performed within 18 months of visit 1;
5. DLCO (corrected for Hb) ≤ 35% predicted of normal at visit 1[1].

3.3.3 Exclusion criteria

1. Previous enrolment in this trial;
2. ALT, AST > 1.5 fold upper limit of normal (ULN) at visit 1[1];
3. Total bilirubin > 1.5 fold ULN at visit 1[1];
4. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC <0.7 at visit 1[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 activated partial thromboplastin time (aPTT) > 150% of institutional 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 (appendix 10.2) at visit 1[1];
10. Presence of aortic stenosis (AS) per investigator judgement at visit 1;
11. Severe chronic heart failure: defined by left ventricular ejection fraction (EF) < 25% per investigator judgement at visit 1;
12. Presence of idiopathic hypertrophic subaortic stenosis (IHSS) per investigator judgement at visit 1;
13. Second-degree or third-degree atrioventricular (AV) block on electrocardiogram (ECG) per investigator judgement at visit 1;
14. Hypotension (systolic blood pressure [SBP] < 100 mm Hg or diastolic blood pressure [DBP] < 50 mm Hg) (symptomatic orthostatic hypotension) at visit 1;
15. Uncontrolled systemic hypertension (SBP > 180 mmHg or DBP > 100 mmHg) at visit 1[1];
16. Known penile deformities or conditions (e.g., sickle cell anemia, multiple myeloma, leukemia) that may predispose to priapism;
17. Retinitis pigmentosa;
18. History of vision loss;
19. History of nonarteritic ischemic optic neuropathy;
20. Veno-occlusive disease;
21. History of acute IPF exacerbation or respiratory infection within 8 weeks of visit 2.
22. Treatment with nitrates, n-acetylcysteine, pirfenidone, azathioprine, cyclophosphamide, cyclosporine, prednisone >15 mg daily or >30 mg every 2 days OR equivalent dose of other oral corticosteroids as well as any investigational drug within 4 weeks of visit 2;
23. Treatment with prostaglandins (e.g., epoprostenol, treprostinil), endothelin-1 antagonists (e.g., bosentan, sitaxsentan, ambrisentan), phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, vardenafil) or a stimulator of guanylatcyclase (e.g., riociguat) within 4 weeks of visit 2;
24. Treatment with potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir within 4 weeks of visit 2;
25. Supplementation with L-arginine and concurrent use of grapefruit juice or St John's wort within 4 weeks of visit 2;
26. Treatment with the reduced dose of nintedanib (100 mg bid) within 4 weeks of visit 2[4];
27. Permanent discontinuation of nintedanib in the past due to adverse events considered drug-related;
28. Known hypersensitivity or intolerance to nintedanib, sildenafil, galactose, peanut or soya or any other components of the study medication;

29. 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;
30. Alcohol or drug abuse which in the opinion of the treating physician would interfere with treatment;
31. Women who are pregnant, nursing, or who plan to become pregnant while in the trial;
32. Women of childbearing potential[5] 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[6];
33. Patients not able to understand and follow study procedures including completion of self-administered questionnaires without help.
34. Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment)

[1] Laboratory parameters, blood pressure and lung function tests may be re-tested within the permitted timeframe, if found abnormal at Visit 1 and thought to be a measurement error or was the result of a temporary and reversible medical condition.

[2] Exceptions: prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g., enoxaparin 4000 IU subcutaneous (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] Patients on treatment with nintedanib 150 mg bid during the screening period are eligible. However if an interruption or reduction of dose is required during the screening period or at time of randomization, the patient will no longer be eligible.

[5] 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 sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

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

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 participation if the patient withdraws consent for trial participation, without the need to justify the decision.

An individual patient is to be withdrawn from all trial drugs (nintedanib and sildenafil/matching placebo) if:

- The patient withdraws consent for study treatment, without the need to justify the decision;
- The patient needs to take concomitant drugs that interfere with the investigational products (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 study treatment and will be followed up until birth or otherwise termination of pregnancy, please see section 5.3.7.
- The patient experiences signs or symptoms of acute myocardial ischemia or stroke;
- The patient experiences signs of hepatic injury, defined as one of the following:
  - 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 sections 4.2.1.3 and 5.3.6.1.

Treatment with nintedanib must be permanently discontinued in the following situations:

- In the opinion of the investigator, the patient experiences unacceptable toxicity due to nintedanib despite dose adjustments and supportive care;
- Gastrointestinal perforation;
- Major surgery including abdominal or intestinal surgery;
- Signs or symptoms of deep vein thrombosis or pulmonary embolism;
- Treatment interruption longer than 4 weeks (continuous).

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

- Patient who requires 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.

Treatment with sildenafil/matching placebo must be permanently discontinued in the following situations:

- In the opinion of the investigator, the patient experiences unacceptable toxicity due to sildenafil despite supportive care;
- Hypotension (SBP < 100 mmHg or DBP < 50 mmHg) accompanied by symptoms;
- In the event of any sudden visual defect;
- Prolonged erections and priapism;
- Treatment interruption longer than 4 weeks (continuous).

If a patient discontinues all study drugs (nintedanib and sildenafil/matching placebo), he/she will undergo the procedures for early treatment discontinuation and will be invited to attend all planned study visits until week 24 as outlined in the flow chart.

For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the electronic case report form (eCRF). 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

4.1.1 Identity of BI investigational product and comparator product

Table 4.1.1:1 Nintedanib

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

Table 4.1.1:2 Sildenafil and placebo matching sildenafil

Substance:	Sildenafil	Placebo
Pharmaceutical formulation:	Capsules	Capsules
Source:	BI Pharma GmbH & Co.KG tablets for overencapsulation sourced from Pfizer	BI Pharma GmbH & Co.KG
Unit strength:	20 mg	Not applicable
Posology	1 capsule, tid	1 capsule, tid
Route of administration:	Oral (swallowed)	Oral (swallowed)

4.1.2 Method of assigning patients to treatment groups

Patient randomization to treatment groups will be determined by an IRT system. Access to the randomization code will be controlled and documented. All necessary instructions for

using the IRT system will be described in a user guide/manual, a copy of which will be available in the ISF.

At visit 2, eligible patients will be randomised via IRT to one of the two treatment groups. Patients will have an equal chance of being randomised to nintedanib co-administered with sildenafil or to nintedanib co-administered with placebo matching sildenafil.

4.1.3 Selection of doses in the trial

Nintedanib: A dose of 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. Dose adjustments are permitted as per section 4.1.4.1 and section 4.2.1.

Sildenafil: A dose of 20 mg tid (total daily dose of 60 mg) was selected for this trial as this is the recommended dose for the approved indication of PAH based on the prescribing information in participating countries. This was also the dose studied in IPF patients in the STEP-IPF study [R12-3686]. No dose adjustment is allowed during this study.

4.1.4 Drug assignment and administration of doses for each patient

Drug is dispensed by the investigator, study coordinator or pharmacist, depending on the site structure. IRT will be used to assign appropriate treatment kits to each patient.

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

Table 4.1.4:1 Quantity of medication kits dispensed:

Visit	Nintedanib Kit	Sildenafil / Matching Placebo Kit
2	1	1
3	1	1
4	1	1
5	3	3

4.1.4.1 Nintedanib

- Treatment with nintedanib will consist of 1 capsule twice daily (bid).
- The first administration of nintedanib will be taken in the clinic at visit 2.
- The patients should swallow nintedanib unchewed with a glass of water (250mL) and should observe a dosing interval of 12 hours.
- Nintedanib should be taken at the same time every day between 06:00 and 11:00 in the morning and between 18:00 and 23:00 in the evening.

- Because nintedanib may cause stomach discomfort, it is recommended to be taken at the end of a meal.
- If a dose of nintedanib is missed, administration should resume at the next scheduled time at the recommended dose. Double doses should not be taken to make up for forgotten capsules.

Dose adjustment of nintedanib is allowed to manage adverse events: 300 mg daily (150 mg bid) may be reduced to 200 mg daily (100 mg bid). For additional details please refer to section 4.2.1.

Dose reductions or re-escalation of nintedanib must be done in the clinic at a dose adjustment visit (refer to the flow chart), as a new medication kit will need to be assigned through IRT. 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 dose adjustment visit and the next planned study visit. IRT will assign only the number of study medication kits needed until the next planned patient visit.

4.1.4.2 Sildenafil and matching placebo

- Treatment with sildenafil (or matching placebo) will consist of 1 capsule three times daily (tid).
- The first administration of sildenafil (or matching placebo) will be taken in the clinic at visit 2.
- Sildenafil capsules should be taken approximately 6 to 8 hours apart.
- It is recommended that nintedanib and sildenafil are administered together at the same time in the morning and evening at the end of a meal, with the third sildenafil dose administered at the midpoint.
- If a dose of sildenafil is missed, administration should resume at the next scheduled time at the recommended dose. Double doses should not be taken to make up for forgotten capsules.
- No dose adjustments are allowed for sildenafil within this study.

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 (apart from the DMC) will remain blinded with regard to the randomized treatment assignments until after database lock.

The randomization code will be kept secret by Clinical Trial Support up to database lock.

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

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / 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.

For Japan only: In this blinded trial, an emergency code break will be available to the Investigator / the sub-Investigators via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the Investigator /the sub-Investigators in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

4.1.6 Packaging, labelling, and re-supply

Nintedanib will be packaged in blisters (containing either nintedanib 100 mg or nintedanib 150 mg). Each blister will contain 10 capsules. Seven blisters will be packaged into one child-resistant tamper-evident wallet (i.e. 70 capsules/wallet).

Sildenafil / matching placebo will be packaged in blisters. Each blister will contain 15 capsules. Seven blisters will be packaged into one child-resistant tamper-evident wallet (i.e. 105 capsules/wallet).

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

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

4.1.7 Storage conditions

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

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

4.1.8 Drug accountability

The Investigator 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
- If applicable, availability of the proof of a medical license for the principal Investigator
- In the USA, availability of Form 1572

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 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

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

4.2.1.1 Recommendations for managing AEs (exceptions include diarrhoea 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 dimenhydrinate, if appropriate).
- Patients experiencing adverse events considered related to nintedanib may require drug interruption (up to a maximum of 4 weeks) 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/or re-escalated to the higher dose (at the discretion of the investigator):
    a. If dose has been reduced, consider re-escalation to 150 mg bid
    b. 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).
- Patients experiencing adverse events considered related to sildenafil may require drug interruption (up to a maximum of 4 weeks) to allow for resolution of symptoms. No dose adjustments are allowed for sildenafil within this study. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance.
- For adverse events not related to the trial medications, treatment interruptions for a maximum of 4 weeks are allowed. Nintedanib and sildenafil 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.

4.2.1.2 Recommendations for managing diarrhoea

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

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption (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.

If diarrhoea is not manageable after dose reduction and/or nintedanib interruption, interruption of sildenafil should also be considered.

Table 4.2.1.2: 1 Recommendations for managing diarrhoea

CTCAE Grade	Description	Symptomatic Treatment	Action with Nintedanib
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 nintedanib dose
2	Increase of 4-6 stools per day over baseline	Initiate/continue anti-diarrheal medicines; If diarrhoea grade 2 persists for ≥48-72 hours assess for dehydration and electrolyte imbalance; In addition, consider i.v. fluids and electrolyte replacement as clinically indicated.	If diarrhoea grade 2 persists for ≥48-72 hours despite optimal symptomatic care: Interrupt nintedanib until recovery[2] Reduce dose to 100 mg bid after recovery 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 i.v. fluid replacement ≥24 hours, hospitalisation as clinically indicated; consider referral to a GI specialist to rule out potential differential diagnoses.	Interrupt nintedanib until recovery[2] Reduce dose to 100 mg bid after recovery Consider re-escalation to 150 mg bid if deemed clinically appropriate In case of recurrence of diarrhoea grades 3 or 4 despite optimal symptomatic treatment and dose reduction, treatment with nintedanib should be permanently discontinued.

[1] Refer to national prescribing information
[2] Treatment interruptions are allowed up to a maximum of 4 weeks.

4.2.1.3 Recommendations for managing liver enzyme elevations

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 [3]</th></tr>
<tr><td colspan="2">Reduce nintedanib to 100 mg bid or interrupt[2] (at the discretion of the investigator)
Lab tests[1] at 48/72 hours, at 1 week and at 2 weeks</td><td colspan="2">Interrupt[2] nintedanib
Lab tests[1] at 48/72 hours, at 1 week and at 2 weeks</td><td>Permanently discontinue all study drugs</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><th></th></tr>
<tr><td>Re-escalate nintedanib to 150 mg bid if reduced; restart at 100 mg bid if interrupted
Lab tests[1] at weeks 2 and 4</td><td>Interrupt[2] both drugs
Lab tests[1] at weeks 1 and 2</td><td>Reintroduce nintedanib at 100 mg bid
Lab tests[1] at weeks 1, 2 and 4</td><td>Interrupt[2] sildenafil
Lab tests[1] at weeks 1 and 2</td><td></td></tr>
<tr><td>If AST / ALT ≥ 3 x ULN permanently discontinue nintedanib</td><td>If AST / ALT < 3 x ULN reintroduce drugs in a stepwise approach; lab tests[1] every week as needed

If AST / ALT ≥ 3 x ULN permanently discontinue all study drugs</td><td>If AST / ALT ≥ 3 x ULN permanently discontinue nintedanib</td><td>If AST / ALT < 3 x ULN reintroduce drugs in a stepwise approach; lab tests[1] every week as needed

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

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

[2] Treatment interruptions are allowed up to a maximum of 4 weeks.

[3] 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.

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 Visit 7 (Follow-up Period)**	**After early EOT[9]**
Nintedanib	Permitted (150 mg bid dose only)	Study medication	Permitted	Not permitted
Sildenafil	Not permitted in the 4 weeks prior to visit 2 [1]	Study medication	Permitted	Not permitted
Pirfenidone, N-acetylcysteine, Azathioprine, Cyclophosphamide, Cyclosporine	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted
Prednisone and other oral corticosteroid[2]	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted

Table 4.2.2.1:1 (continued) Permitted and Restricted Concomitant therapy

Investigational Medication	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted[10]	Not permitted
Nitrates	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted
Prostaglandins[3], endothelin-1 antagonists[4] or phosphodiesterase inhibitors[5] or a stimulator of guanylatcyclase [6]	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Not permitted
Potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted
L-arginine, grapefruit juice or St John's wort	Not permitted in the 4 weeks prior to visit 2 [1]	Not permitted	Not permitted	Permitted
Anticoagulation at full dose[7], antiplatelet therapy at high dose [8], fibrinolysis	Permitted	Not permitted	Not permitted	Permitted

1. Washout should not occur until after patient has signed informed consent
2. Prednisone >15 mg daily or >30 mg every 2 days OR equivalent dose of other oral corticosteroids.
3. e.g., epoprostenol, treprostinil
4. e.g., bosentan, sitaxsentan, ambrisentan
5. e.g., sildenafil, tadalafil, vardenafil
6. e.g., riociguat
7. 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 IU s.c. per day)
8. Antiplatelet therapy at high dose. Exceptions: prophylactic use of antiplatelet therapy (e.g. acetylsalicylic acid up to 325 mg/day and/or clopidogrel at 75 mg/day and/or equivalent doses of other antiplatelet therapy) is allowed

9. For patients who withdrew all study medications before the planned EOT date and decide to attend all remaining study planned visits.
10. Nintedanib as investigational product is allowed during the follow-up period in case the patient transitions to an extension trial or compassionate use program.

Wash-out periods for concomitant therapy which might influence the spirometry results are described in section 5.2.2.

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

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.

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

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

In addition, the compliance calculation should be cross-checked with the patient diary and discrepancies documented accordingly (section 5.3.5).

Compliance will be verified by the on-site monitor authorized by the sponsor.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is the change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 12.

5.1.2 Secondary Endpoints

- Change from baseline in dyspnea using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at week 12;
- Change from baseline in SGRQ total score at week 24;
- Change from baseline in dyspnea using UCSD SOBQ at week 24;
- Percentage of patients with on-treatment Serious Adverse Events (SAE) from baseline to week 24.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Patient Reported Outcomes

Three different PRO questionnaires will be used:

- St George's Respiratory Questionnaire (SGRQ – See Appendix 10.3)
- The UCSD Shortness of Breath Questionnaire (UCSD-SOBQ – See Appendix 10.4)
- EuroQoL-5D (EQ-5D – See Appendix 10.5)

The PRO questionnaires will be assessed at timepoints as indicated in the flow chart. It should be completed at the start of each applicable visit, prior to performing any other trial procedures and in the following order: SGRQ, UCSD-SOBQ, EQ-5D.

5.2.2 Forced Vital Capacity, Carbon Monoxide Diffusion Capacity, Alveolar Volume, Oxygen Saturation and Arterialised Blood Gases

FVC will be assessed using identical spirometry devices which will be supplied to all participating sites at trial initiation and spirometry performance will be centrally reviewed.

Spirometers and usage of spirometers must meet ATS/ERS criteria [P05-12782], including daily calibration of the spirometer, and regular calibration of the calibration pump (according to the instructions provided in the ISF). Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate and the best result selected according to the guidelines. Spirometry results captured by spirometers provided by the sponsor will be electronically transmitted and confirmed by central reading. The best of three efforts will be

defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria, preferably with a maximum of five manoeuvres.

The site will use its own equipment to assess carbon monoxide diffusion capacity (DLCO) and alveolar volume (VA) during the single breath diffusion test and conduct all measurements with the same equipment (e.g. if several devices would be available at the site). Single-breath diffusion test will be carried out according to the ATS / ERS guidelines [R06-2002]. Before beginning the test, the manoeuvres should be demonstrated and the subject carefully instructed. The mean value between at least two acceptable tests should be reported. Please refer to Appendix 10.6 for additional information.

For each patient, pulmonary function testing and single-breath diffusion test will always start at approximately the same time of day. The DLCO/VA assessment should always be performed after the FVC assessment.

On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing.

Smoking should be discouraged throughout the 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 therapies (betamimetic drugs, anticholinergic drugs) has to be observed before spirometry (24 hours for long acting and 8 hours for short acting bronchodilators).

Oxygen saturation (SpO_2) will be measured at rest by standard pulse oximetry (unaffected skin of earlobe or fingertip). Arterialised blood gases (PaO_2 and $PaCO_2$) will be measured in selected sites experienced in earlobe capillary blood gas sampling. Values will be entered in the eCRF.

5.2.3 Acute IPF exacerbations

Acute IPF exacerbations will be collected as adverse events.

Acute IPF exacerbation is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality [P16-06899].

Extra-parenchymal causes (e.g. pneumothorax, pleural effusion, pulmonary embolism) should be excluded and the following 3 diagnostic criteria need to be met:

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

Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet the three diagnostic criteria due to missing computed tomography data will be termed "suspected acute exacerbations" by the Adjudication Committee.

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 findings 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.

5.3.3 Safety laboratory parameters

The laboratory tests will include:

- Haematology: complete blood count including platelet count and automated differential.
- Chemistry: sodium, potassium, creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), total protein, alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), creatine kinase, brain natriuretic peptide (BNP) and thyroid stimulating hormone (TSH).
- Coagulation: International normalized ratio (INR) and partial thromboplastin time (PTT).
- Urine: pregnancy testing (for all women of childbearing potential).

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

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

In case of liver enzyme elevations, close monitoring must be ensured by the investigator (section 4.2.1.3).

5.3.4 Electrocardiogram

ECGs are to be conducted with site equipment as specified in the flow chart. Changes should be examined, compared to the 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

A patient diary will be used by all patients in this trial to record symptoms and number of capsules taken per day. The diary will be used to prompt patient recollection during AE and medication compliance discussions at clinic visits. 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 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 a SAE.

Other significant adverse event (according to ICH E3)

An "other significant adverse event" is defined as any non-serious adverse event which

- represents a marked haematological or other laboratory abnormality;
- led to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

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 SAEs, see section 5.3.7.

The following are considered AESIs:

Adverse events relating to gastrointestinal perforation

and

Hepatic injury

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

- ALT and/or AST ≥ 8 fold ULN
- ALT and /or AST ≥ 3 fold ULN and total bilirubin ≥ 2 fold ULN*
- ALT and /or AST ≥ 3 fold ULN and unexplained INR > 1,5*
- ALT and /or AST ≥ 3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and /or AST ≥ 3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to 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 diarrhoea 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 CTCAE Categorization for diarrhoea

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; an allergic reaction weeks after discontinuation of the drug concerned)

- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the 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 the patient files.

The following must be collected and documented on the appropriate 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.

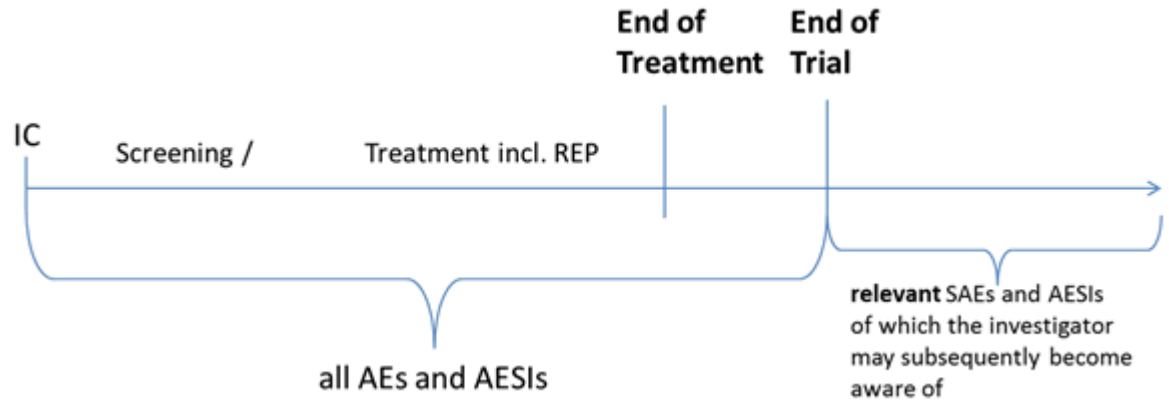

Figure 5.3.7:1 AE Collection

The Residual Effect Period (REP) is defined as 28 days after the last trial medication administration. 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.

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.

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 eCRF 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 eCRF 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.

5.6 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

Informed consent of all study patients will be obtained in compliance with ICH and GCP guidelines and the principles stipulated in the Declaration of Helsinki prior to any study related procedures, including any washout of restricted medications (refer to table 4.2.2.1:1).

The study will consist of a screening period up to 28 days, a randomised treatment period of 24 weeks and a follow up period lasting a minimum of four weeks (28 days).

All patients are to adhere to the visit schedule as outlined in the flow chart. Some flexibility is allowed in scheduling the visits according to the visit time windows as specified. The trial medication kits contain sufficient medication to allow for these time windows. All deviations from the planned visit schedule will be documented. If any visit is to be re-scheduled, subsequent visits should follow the original visit date schedule (calculated from visit 2). No protocol waivers will be given (e.g. sponsor will not grant permission to include a known ineligible patient).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period

No study related procedures will be performed until the patient has signed informed consent. The study will be explained to patients and those who meet entry criteria (section 3.3) will be invited to participate.

Please refer to the flow chart for complete procedures at visit 1.

An echocardiogram will be performed with site equipment at visit 1 to evaluate cardiac function and assess exclusion criteria 10, 11 and 12 (section 3.3.3). In addition, this test will be used for the stratification of patients during randomization (as described in section 7.6). The following questions will be captured in the eCRF based on the investigator's judgement:

- Presence of right ventricular systolic dysfunction (yes/no)
- Presence of right ventricular hypertrophy (yes/no)
- Presence of right ventricular dilatation (yes/no)
- Presence of paradoxical septum motion (yes/no)
- Presence of right atrium enlargement (yes/no)

Clinically relevant findings will be recorded as baseline conditions.

Patients who have a laboratory test, blood pressure or lung function test value outside the range specified by the exclusion criteria and thought to be a measurement error or the result of a temporary and reversible medical condition may have the test repeated once to determine

eligibility; however, the result must be available prior to visit 2. The period between visit 1 and visit 2 should last a maximum of 28 days. If visit 2 could not be performed within this timeframe the patient will be considered as screen failed.

All patients who have signed consent must be entered in the enrolment log and documented in the eCRF. Patients found to be ineligible at or prior to visit 2 and do not initiate treatment will be considered a screen failure.

6.2.2 Treatment period(s)

If the patient has been determined eligible by the investigator to enter the trial (refer to section 3.3), the investigator will assign medication numbers to the patient through the IRT system at visit 2. First dose of trial drugs will be administered at visit 2 in the clinic (day 1).

Additional clinic visits will be scheduled after 4, 8, 12, 18 and 24 weeks of treatment (visits 3-7). For detailed description of the trial procedures at each visit and dispensing schedule, please refer to the flow chart.

Dose Adjustment Visit

The dose of nintedanib can be reduced and increased as described in section 4.2.1. In this case, the patient will be required to return to the clinic for an unscheduled visit where new medication will be assigned via the IRT system. Please refer to the flow chart for complete procedures in this visit.

6.2.3 Follow Up Period and Trial Completion

A follow-up (FUP) visit should be planned for 28 days after last trial drug administration. For detailed description of the trial procedures at the FUP visit, please refer to the flow chart.

Trial completion

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

- At the end of the follow-up visit for patients who have completed the trial on treatment as planned;
- After the early end of treatment (EOT) and follow-up visits, if a patient did not agreed to come to the remaining planned study visits;
- At the end of visit 7 for patients who discontinued drug early but agreed to come to the remaining planned study visits.

Patients who prematurely discontinued trial medication

Patients who prematurely discontinue all study drugs (refer to section 3.3.4) before the planned end of treatment at visit 7, 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 planned visits despite not being under treatment anymore and perform all study procedures except the laboratory tests (optional), biomarker sampling, pharmacokinetic sampling and the ECG. If patients don't accept to attend all remaining study visits, they will be contacted for vital status collection at week 24.

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

Vital status information

In case of early discontinuation of all study drugs, if the patient does not agree to come to future visits as planned, every attempt will be made to get information on vital status at week 24 after his/her randomization.

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 double-blind, randomized, parallel-group study stratified by presence of any echocardiographic signs indicative of right heart dysfunction to evaluate the efficacy and safety of nintedanib when co-administered with sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment.

The primary endpoint is the change from baseline in SGRQ total score at week 12.

The primary endpoint will be analysed using a Mixed Effects Model for Repeated Measures (MMRM). The details are provided in section 7.3.1.

The secondary endpoints related to SGRQ and UCSD SOBQ will be analysed using MMRM. Details are provided in section 7.3.2.

The secondary endpoint percentage of patients with on-treatment SAEs from baseline to week 24 will be analysed using the Cochran-Mantel-Haenszel test exploratorily.

Analysis of further endpoints is described in section 7.3.3.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The objective of this study, demonstrating an additional treatment effect of nintedanib co-administered with sildenafil compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment will be tested using the following null hypothesis:

> H_0: There is no difference in the mean change from baseline in SGRQ total score at week 12 between nintedanib co-administered with sildenafil compared to treatment with nintedanib.

The alternative hypothesis is

> H_a: There is a difference in the mean change from baseline in SGRQ total score at week 12 between nintedanib co-administered with sildenafil compared to treatment with nintedanib.

A hierarchical testing procedure will be applied in order to allow for confirmative testing of the secondary endpoints related to SGRQ and UCSD SOBQ also. This procedure is specified in Table 7.2:1.

Table 7.2:1 Flow of hypothesis testing

Step 1	If H_0 is rejected at 5% level (two-sided test) then go to the next step otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.
Step 2	H_{01}: There is no difference in the mean change from baseline in UCSD SOBQ at week 12 between nintedanib co-administered with sildenafil compared to treatment with nintedanib. H_{a1}: There is a difference in the mean change from baseline in UCSD SOBQ at week 12 between nintedanib co-administered with sildenafil compared to treatment with nintedanib. If H_{01} is rejected at 5% level (two-sided test) then go to the next step otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.
Step 3	H_{02}: There is no difference in the mean change from baseline in SGRQ total score at week 24 between nintedanib co-administered with sildenafil compared to treatment with nintedanib. H_{a2}: There is a difference in the mean change from baseline in SGRQ total score at week 24 between nintedanib co-administered with sildenafil compared to treatment with nintedanib. If H_{02} is rejected at 5% level (two-sided test) then go to the next step otherwise procedure is stopped and subsequent tests will be done only for exploratory purposes.
Step 4	H_{03}: There is no difference in the mean change from baseline in UCSD SOBQ at week 24 between nintedanib co-administered with sildenafil compared to treatment with nintedanib. H_{a3}: There is a difference in the mean change from baseline in UCSD SOBQ at week 24 between nintedanib co-administered with sildenafil compared to treatment with nintedanib.

The hypotheses will be tested using 5% level of significance (two-sided test). Global type I error will be not exceed 5% within this procedure, thus no adjustment for multiplicity is required.

Statistical tests performed for any other endpoints not included in the above defined testing procedure will also be done only for exploratory purposes.

7.3 PLANNED ANALYSES

The statistical analysis will be based on the Treated Set (TS), which consists of patients who are randomised to a treatment group and receive at least one dose of randomised study medication.

Most analyses will be based on the treatment group (nintedanib only or nintedanib co-administered with sildenafil) as randomized. Safety parameters will be analyzed from an as treated perspective.

Although there is no per protocol 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) will be identified at Blinded Review Planning Meetings and listed in the CTR and their impact will be evaluated.

7.3.1 Primary endpoint analyses

Change from baseline in SGRQ total score at week 12 will be analysed using REML based MMRM. The model will include fixed effect for treatment, visit and presence of any echocardiographic signs indicative of right heart dysfunction including right ventricular hypertrophy and right ventricular or atrial dilatation (as described in section 6.2.1), baseline SGRQ total score as a covariate and treatment-by-visit and baseline-by visit as interaction terms. Baseline SGRQ total score will be measured at visit 2. No imputation is planned if this assessment is not available for a patient. An unstructured (co)variance matrix will be used to model the within-patient measurements. In case there is a lack of convergence, a Compound Symmetry (co)variance matrix will be used. The Roger-Kenward approximation will be used to estimate denominator degrees of freedom. Data collected after visit 5 (planned 12 weeks after start of study treatment) will not be used for this analysis. Analyses will be implemented using SAS® Version 9.4 or higher. The primary treatment comparisons will be the contrast between treatments at 12 weeks.

Sensitivity analysis: The effect of missing data will also be investigated using tipping point sensitivity analyses. The technique will be detailed in the TSAP. The effect on the following subgroups will be explored:

- sex (female/male)
- age (<65, ≥65 years)
- race (White, Asian, Other)
- baseline FVC % predicted (<50%, ≥50%)
- baseline St. George's Respiratory Questionnaire (SGRQ) total score (≤40, >40)
- presence of any echocardiographic signs indicative of right heart dysfunction (yes/no)

Within subgroup analyses, subgroup (if not already included in the primary analysis model) and treatment subgroup interaction effect will be added to the primary analysis model. The treatment subgroup interaction effect will be of primary interest for subgroup analyses.

As needed, further details and/or further subgroups will be defined and described in the Trial Statistical Analysis Plan.

7.3.2 Secondary endpoint analyses

Change from baseline in UCSD SOBQ at week 12 will be analysed using the same method as the primary endpoint, but with baseline UCSD SOBQ instead of SGRQ total score as covariate. Data collected after visit 5 (planned 12 weeks after start of study treatment) will not be used for this analysis.

Both changes from baseline in SGRQ and UCSD SOBQ at week 24 will be analysed as in the respective week 12 analysis. For these analyses, data collected from the complete 24 weeks treatment period will be used.

Percentages of patients with on-treatment SAEs from baseline to week 24 will be compared using the Cochran-Mantel-Haenszel test adjusting for the categorical covariate presence of any echocardiographic signs indicative of right heart dysfunction (yes/no). Adjusted Mantel-Haenszel type risk ratios and risk differences with 95% confidence intervals will be used to quantify the treatment effect for the comparison between treatment groups.

7.3.4 Safety analyses

Analysis of key safety endpoints is described in sections 7.3.2 and 7.3.3.

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 but the conduct of the trial will be monitored by a DMC.

7.5 HANDLING OF MISSING DATA

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.

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.

In pharmacokinetic analyses, missing data will not be imputed. Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, and NOA are included). Descriptive statistics of parameters are also calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead.

7.6 RANDOMISATION

Patients will be stratified by the presence of any echocardiographic signs indicative of right heart dysfunction including right ventricular hypertrophy and right ventricular or atrial dilatation (as described in section 6.2.1) and will be randomized in blocks to double-blind treatment. Approximately equal numbers of patients will be randomized to each treatment

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

7.7 DETERMINATION OF SAMPLE SIZE

The hypothesis for expected difference in the change from baseline in SGRQ total score at week 12 is -4.5 units between nintedanib co-administered with sildenafil compared to treatment with nintedanib alone using a two group t-test with a 0.025 one-sided significance level.

The assumed difference is based on observations made in the INPULSIS® trials, where the observed mean change from baseline to week 12 in SGRQ total score when treated with nintedanib alone was 0.75/0.05 units with a standard deviation of 12.93/11.64 (INPULSIS®-1/INPULSIS®-2).

Based on the STEP-IPF trial [R12-3686], the mean change from baseline to week 12 in SGRQ total score when treated with sildenafil alone was -4.08 units with an estimated standard deviation of 11.02 units. It is assumed that the observed treatment effect remains stable when nintedanib is co-administered with sildenafil.

Therefore, power calculations are made based on the assumption of equal standard deviations among groups and an expected difference of -4.5 units.

Table 7.7: 1 presents the different scenarios for the sample size calculation.

Table 7.7: 1 Sample size calculations for difference in the change from baseline in SGRQ total score at week 12 assuming a group difference of -4.5 units for several standard deviations and a 1:1 randomisation ratio using a two group t-test with a 0.025 one-sided significance level.

	Standard deviation	N per group	Total sample size
80% power			
	11	95	190
	12	113	226
	13	132	264
90% power			
	11	127	254
	12	150	300
	13	177	354

So, a sample size of 125 patients in both groups will have about 90% power to detect a difference in means of -4.5 units in change from baseline in SQRG total score assuming that

the common standard deviation is 11 units using a two group t-test with a 0,025 one-sided significance level.

As we use a mixed model, including adjustment for several variable, this sample size based on t-test should provide at least 90% power.

Calculations were performed using nQuery Advisor® 6.1 statistical package by Statistical Solutions Ltd.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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), and relevant regulations and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) only for Japan.

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

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.

8.3 RECORDS

Electronic Case Report Forms (e)CRF 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.
For eCRFs all data must be derived from source documents.

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. CRF/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 Clinical Research Associate (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 documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

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

When it is no longer necessary for the trial site to retain the source documents and essential documents, the sponsor must notify the head of trial site.

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 adverse event 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 the nintedanib this is the current version of the Investigator's Brochure [U07-1248].

For sildenafil the EU SmPC (Revatio®) serves as reference document.

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

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

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 REVIEW

The following criteria should be assessed at screening for all patients based on a HRCT scan performed within 18 months of visit 1:

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

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

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

Patients with HRCT meeting either criteria A, B and C, or criteria A and C, or criteria B and C are eligible for this trial without the need of a surgical lung biopsy.

In the presence of a surgical lung biopsy, the histology should be reviewed based on the ATS/ERS/JRS/ALAT guidelines [P11-07084]. An HRCT pattern "possible UIP" coupled with a surgical biopsy pattern “definite UIP” or "probable UIP", upon multidisciplinary team discussion, could qualify for inclusion as “consistent with a diagnosis of 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)

10.3 ST GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good ☐ Good ☐ Fair ☐ Poor ☐ Very poor ☐

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London SW17 ORE, UK.

Tel.
Fax

continued...

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

		Please check (✓) *one box for each question*: almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1.	Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2.	Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3.	Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4.	Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

	Please check (✓) *one*:
The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

	Please check (✓) *one*:
My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you these days.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog
Doing activities or chores at home or in the garden
Sexual intercourse
Going to a place of worship, or a place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .
. . . . . .
. . . . . .
. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐
It stops me from doing one or two things I would like to do ☐
It stops me from doing most of the things I would like to do ☐
It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

10.4 THE UCSD SHORTNESS OF BREATH QUESTIONNAIRE (UCSD-SOBQ)

UCSD MEDICAL CENTER
PULMONARY REHABILITATION PROGRAM
SHORTNESS-OF-BREATH QUESTIONNAIRE

Please rate the breathlessness you experience when you do, or if you were to do, each of the following tasks. **Do not skip any items.** If you've never performed a task or no longer perform it, give your best estimate of the breathlessness you would experience while doing that activity. Please review the two sample questions below before turning the page to begin the questionnaire.

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

1. Brushing teeth ..... **0 1 2 ③ 4 5**

Harry has felt moderately short of breath during the past week while brushing his teeth and so circles a three for this activity.

2. Mowing the lawn ..... **0 1 2 3 4 ⑤**

Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past week. She circles a five for this activity.

SOBQ - United States/English - Mapi Research Institute.
ID5977 / SOBQ_AU1.0_eng-USori.doc

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

1.	At rest	**0**	**1**	**2**	**3**	**4**	**5**
2.	Walking on a level at your own pace	**0**	**1**	**2**	**3**	**4**	**5**
3.	Walking on a level with others your age	**0**	**1**	**2**	**3**	**4**	**5**
4.	Walking up a hill	**0**	**1**	**2**	**3**	**4**	**5**
5.	Walking up stairs	**0**	**1**	**2**	**3**	**4**	**5**
6.	While eating	**0**	**1**	**2**	**3**	**4**	**5**
7.	Standing up from a chair	**0**	**1**	**2**	**3**	**4**	**5**
8.	Brushing teeth	**0**	**1**	**2**	**3**	**4**	**5**
9.	Shaving and/or brushing hair	**0**	**1**	**2**	**3**	**4**	**5**
10.	Showering/bathing	**0**	**1**	**2**	**3**	**4**	**5**

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ID5977 / SOBQ_AU1.0_eng-USori.doc

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

11.	Dressing	**0**	**1**	**2**	**3**	**4**	**5**
12.	Picking up and straightening	**0**	**1**	**2**	**3**	**4**	**5**
13.	Doing dishes	**0**	**1**	**2**	**3**	**4**	**5**
14.	Sweeping /vacuuming	**0**	**1**	**2**	**3**	**4**	**5**
15.	Making bed	**0**	**1**	**2**	**3**	**4**	**5**
16.	Shopping	**0**	**1**	**2**	**3**	**4**	**5**
17.	Doing laundry	**0**	**1**	**2**	**3**	**4**	**5**
18.	Washing car	**0**	**1**	**2**	**3**	**4**	**5**
19.	Mowing lawn	**0**	**1**	**2**	**3**	**4**	**5**
20.	Watering lawn	**0**	**1**	**2**	**3**	**4**	**5**
21.	Sexual activities	**0**	**1**	**2**	**3**	**4**	**5**

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0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

How much do these limit you in your daily life?

22.	Shortness of breath	**0**	**1**	**2**	**3**	**4**	**5**
23.	Fear of "hurting myself" by overexerting	**0**	**1**	**2**	**3**	**4**	**5**
24.	Fear of shortness of breath	**0**	**1**	**2**	**3**	**4**	**5**

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ID5977 / SOBQ_AU1.0_eng-USori.doc

10.5 EUROQOL-5D (EQ-5D)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

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

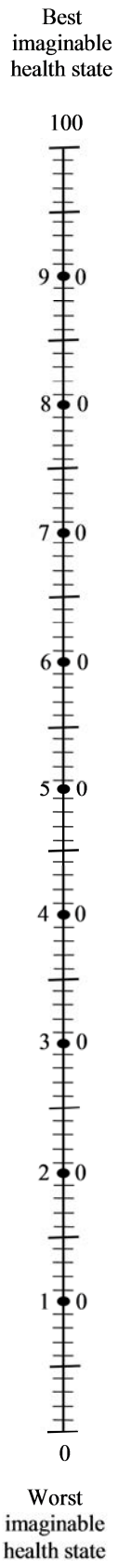
Anxiety/Depression

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

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



10.6 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
- Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(9.38+Hb)) for females

For decision on inclusion / exclusion, DLCO results from Visit 1 will be corrected for haemoglobin (value obtained at visit 1) by the site.

For analysis of the trial data, DLCO results will be corrected for haemoglobin by central data management. This means that the site has to enter the DLCO results without haemoglobin correction in the eCRF, at all visits.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		04 March 2016
EudraCT number		2015-002619-14
BI Trial number		1199.36
BI Investigational Product(s)		nintedanib
Title of protocol		A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒ Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐ No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐ No
Section to be changed		Section 1.2.2 Sildenafil
Description of change		Potential risks of treatment with sildenafil include hypotension, worsening of pulmonary vascular occlusive disease, epistaxis, visual loss, hearing loss, priapism and vaso-occlusive crisis in patients with pulmonary hypertension secondary to sickle cell disease. **Was changed to:**

		Potential risks of treatment with sildenafil include hypotension, worsening of pulmonary veno-occlusive disease, epistaxis, visual loss, hearing loss, priapism and vaso-occlusive crisis in patients with pulmonary hypertension secondary to sickle cell disease.
Rationale for change		Rewording.
Section to be changed		Section 2.3 Benefit – Risk assessment
Description of change		Potential risks of treatment with sildenafil include hypotension, worsening of pulmonary vascular occlusive disease, epistaxis, visual loss, hearing loss, priapism and vaso-occlusive crisis in patients with pulmonary hypertension secondary to sickle cell disease. Patients at higher risk for these conditions are excluded from this trial. **Was changed to:** Potential risks of treatment with sildenafil include hypotension, worsening of pulmonary veno-occlusive disease, epistaxis, visual loss, hearing loss, priapism and vaso-occlusive crisis in patients with pulmonary hypertension secondary to sickle cell disease. Patients at higher risk for these conditions are excluded from this trial.
Rationale for change		Rewording
Section to be changed		Section 3.3 Selection of trial population
Description of change		A total of approximately 250 patients with an IPF diagnosis and advanced lung function impairment will be randomized. Approximately 60 sites are each expected to include approximately 4 patients. **Was changed to:** A total of approximately 250 patients with an IPF diagnosis and advanced lung function impairment will be randomized. Approximately 80 sites are each expected to include approximately 3 patients.
Rationale for change		Number of participating sites (increase) and average number of patients per site (decrease) adjusted following site feasibility.

Section to be changed		Section 3.3.3 Exclusion criterion and abbreviations
Description of change		In exclusion criterion #6 Partial Thromboplastin Time (PTT) was replaced by Activated Partial Thromboplastin Time. The same has been corrected in the Abbreviations section.
Rationale for change		Correction / rewording
Section to be changed		Section 3.3.3 Exclusion criterion
Description of change		Exclusion criterion #34 has been added: Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment)
Rationale for change		Based on interactions with regulatory authorities including the FDA, the recommended dosage of nintedanib for patients with Child Pugh A hepatic impairment is 100 mg bid which has been recently included into the US Prescribing Information. As in the current protocol all patients should initiate treatment with the same starting dose of nintedanib 150 mg bid, patients with Child Pugh A will be excluded. In addition, patients with Child Pugh B and C hepatic impairment will also be excluded to again be in line with the information stated in the US Prescribing Information that treatment with nintedanib in these patients is not recommended.
Section to be changed		Section 5.4.1 Assessment of Pharmacokinetics; Section 5.4.2 Methods of sample collection and Section 5.4.3 Analytical determinations
Description of change		5.4.1 Assessment of Pharmacokinetics

		Pre-dose plasma samples of nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, will be taken according to the flow chart. **Was changed to:** Pre-dose plasma samples of nintedanib will be taken according to the flow chart. 5.4.2 Methods of sample collection A detailed description of sample collection and handling is provided in the ISF/lab manual. For quantification of drug plasma concentrations of nintedanib (BIBF 1120) and its metabolites BIBF 1202 and BIBF 1202- glucuronide, venous blood will be collected using a pre-labeled potassium ethylenediamine-tetraacetic acid (EDTA) containing blood drawing tube. The obtained plasma will be transferred into 1 vial (at least 0.5 mL plasma). After completion of the study, the plasma samples may be used for further methodological investigations, e.g. stability testing. However, only data related to nintedanib and/or its metabolite(s) will be generated by these additional investigations. **Was changed to:** A detailed description of sample collection and handling is provided in the ISF/lab manual. For quantification of drug plasma concentrations of nintedanib, venous blood will be collected using a pre-labeled potassium ethylenediamine-tetraacetic acid (EDTA) containing blood drawing tube. The obtained plasma will be transferred into 1 vial (at least 0.5 mL plasma). After completion of the study, the plasma samples may be used for further methodological investigations, e.g. stability testing. However, only data related to nintedanib will be generated by these additional investigations. 5.4.3 Analytical determinations Nintedanib (in form of its free base BIBF 1120 BS), its metabolites BIBF 1202 (in form of the

		free zwitterion BIBF 1202 ZW) and the acylglucuronid thereof (BIBF 1202 glucuronide) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem mass spectrometry (LC-MS/MS). **Was changed to:** Nintedanib (in form of its free base BIBF 1120 BS) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Rationale for change		As none of the measured metabolites is active, metabolite assessment is not necessary and does not add any important additional information to the study. Following validation of a BIBF 1120 only bioanalytical assay, it is now possible to measure just one analyte. Only pre-dose plasma concentration of nintedanib will be measured.
Section to be changed		Section 5.5.1 Blood, serum and RNA samples for pre-specified biomarker analyses.
Description of change		Overall, approximately 72.5 mL blood will be taken for exploratory biomarker assessment and banking during the course of the trial. **Was changed to:** Overall, approximately 114 mL blood will be taken for exploratory biomarker assessment and banking during the course of the trial.
Rationale for change		Correction of blood volume to be collected for the analysis of biomarkers.

Number of global amendment		2
Date of CTP revision		18 Aug 2016
EudraCT number		2015-002619-14
BI Trial number		1199.36
BI Investigational Product(s)		nintedanib
Title of protocol		A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒ Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐ No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐ No
Section to be changed		Title
Description of change		A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment **Was changed to** : INSTAGE™: A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to

		treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment
Rationale for change		A trade name is now assigned for this study.
Section to be changed		ABBREVIATIONS
Description of change		**Was added**: FEV1 Forced Expiratory Volume in 1 second MACE Major Adverse Cardiovascular Events
Rationale for change		First definition was missing, second one was added.
Section to be changed		Section 1.2.1 Nintedanib
Description of change		Potential risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism and bleeding. **Was changed to :** Risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism, pancreatitis, thrombocytopenia and bleeding.
Rationale for change		Addition of pancreatits and thrombocytopenia as risks of treatment with nintedanib in line with the new information provided in the Investigators Brochure (version 11, dated 21 Jul 2016).
Section to be changed		Section 2.3 Benefit – Risk assessment
Description of change		Potential risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism and bleeding. Therefore, patients requiring full dose concomitant anticoagulation, fibrinolysis or high-dose antiplatelet therapy will be excluded from this trial. **Was changed to** : Risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism, pancreatitis, thrombocytopenia and bleeding. Therefore, patients requiring full dose concomitant anticoagulation, fibrinolysis or high-dose antiplatelet therapy will be excluded from this trial.
Rationale for change		Addition of pancreatitis and thrombocytopenia as risks of treatment with nintedanib in line with the

		new information provided in the Investigators Brochure (version 11, dated 21 Jul 2016).
Section to be changed		Section 3.1.1 Administrative structure of the trial
Description of change		All death cases will be assessed (to evaluate the primary cause of death), as well as all acute IPF exacerbations (based on written clinical reports, for diagnostic confirmation) by an independent Adjudication Committee (AC), in a blinded manner before data base lock. The tasks and responsibilities of the DMC and the AC will be specified in a charter. **Was changed to** : All death cases will be assessed (to evaluate the primary cause of death), as well as all adverse events categorized as major adverse cardiovascular events (MACE) and all acute IPF exacerbations (based on written clinical reports, for diagnostic confirmation) by an independent Adjudication Committee (AC), in a blinded manner before data base lock. The tasks and responsibilities of the DMC and the AC will be specified in a charter.
Rationale for change		MACE events will also be assessed by the Adjudication Committee
Section to be changed		Section 3.3.2 Inclusion criteria Section 3.3.3 Exclusion criteria
Description of change		3.3.2 Inclusion criteria 5. DLCO (corrected for Hb) ≤ 35% predicted of normal at visit 1 **Was changed to** : 5. DLCO (corrected for Hb) ≤ 35% predicted of normal at visit 1[1] 3.3.3 Exclusion criteria 4. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC <0.7 at visit 1); **Was changed to :** 4. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC <0.7 at visit 1)[1]; 3.3.3 Exclusion criteria

		9. Creatinine clearance < 30 mL/min calculated by Cockcroft–Gault formula (appendix 10.2) at visit 1; **Was changed to** : 9. Creatinine clearance < 30 mL/min calculated by Cockcroft–Gault formula (appendix 10.2) at visit 1[1]; 3.3.3 Exclusion criteria 15. Uncontrolled systemic hypertension (SBP > 180 mmHg; DBP > 100 mmHg) at visit 1 **Was changed to :** 15. Uncontrolled systemic hypertension (SBP > 180 mmHg or DBP > 100 mmHg) at visit 1[1] 3.3.3 Exclusion criteria 23. Treatment for pulmonary hypertension with prostaglandins (e.g., epoprostenol, treprostinil), endothelin-1 antagonists (e.g., bosentan, sitaxsentan, ambrisentan), phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, vardenafil) or a stimulator of guanylatcyclase (e.g., riociguat) within 4 weeks of visit 2; **Was changed to :** 23. Treatment with prostaglandins (e.g., epoprostenol, treprostinil), endothelin-1 antagonists (e.g., bosentan, sitaxsentan, ambrisentan), phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, vardenafil) or a stimulator of guanylatcyclase (e.g., riociguat) within 4 weeks of visit 2; [1]Laboratory parameters may be re-tested within the permitted timeframe, if found abnormal at Visit 1 and thought to be a measurement error or was the result of a temporary and reversible medical condition. **Was changed to** : [1]Laboratory parameters, blood pressure and lung

<table>
<tr><td></td><td></td><td>function tests may be re-tested within the permitted timeframe, if found abnormal at Visit 1 and thought to be a measurement error or was the result of a temporary and reversible medical condition.</td></tr>
<tr><td>Rationale for change</td><td></td><td>To allow retest within the screening period of examinations required to assess inclusion criterion #5 and exclusion criteria 4, 9 and 15. Clarification of exclusion criterion #15 and #23.</td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 4.2.2 Restrictions
Table 4.2.2.1:1</td></tr>
<tr><td>Description of change</td><td></td><td>
<table>
<tr><th></th><th>Prior to randomisation</th><th>During treatment period</th><th>After Visit 7 (Follow-up Period)</th><th>After early EOT[9]</th></tr>
<tr><td>Treatment for PAH with prostaglandins[3], endothelin-1 antagonists[4] or phosphodiesterase inhibitors[5] or a stimulator of guanylatcyclase [6]</td><td>Not permitted in the 4 weeks prior to visit 2 [1]</td><td>Not permitted</td><td>Not permitted</td><td>Not permitted</td></tr>
</table>
Was changed to:
<table>
<tr><th></th><th>Prior to randomisation</th><th>During treatment period</th><th>After Visit 7 (Follow-up Period)</th><th>After early EOT[9]</th></tr>
<tr><td>Prostaglandins[3], endothelin-1 antagonists[4] or phosphodiesterase inhibitors[5] or a stimulator of guanylatcyclase [6]</td><td>Not permitted in the 4 weeks prior to visit 2 [1]</td><td>Not permitted</td><td>Not permitted</td><td>Not permitted</td></tr>
</table>
</td></tr>
<tr><td>Rationale for change</td><td></td><td>Clarification of restricted concomitant therapy</td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 5.2.2 Forced Vital Capacity, Carbon Monoxide Diffusion Capacity, Alveolar Volume, Oxygen Saturation and Arterialised Blood Gases</td></tr>
<tr><td>Description of change</td><td></td><td>Oxygen saturation (SpO_2) will be measured at rest by standard pulse oximetry (unaffected skin of earlobe or forehead). Arterialised blood gases</td></tr>
</table>

		(PaO_2 and $PaCO_2$) will be measured in selected sites experienced in earlobe capillary blood gas sampling. Values will be entered in the eCRF. **Was changed to** : Oxygen saturation (SpO_2) will be measured at rest by standard pulse oximetry (unaffected skin of earlobe or fingertip). Arterialised blood gases (PaO_2 and $PaCO_2$) will be measured in selected sites experienced in earlobe capillary blood gas sampling. Values will be entered in the eCRF.
Rationale for change		Correction of the site for measurement of oxygen saturation.
Section to be changed		Section 5.2.3 Acute IPF exacerbations
Description of change		Acute IPF exacerbations are defined as 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 the 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 or any identifiable cause of acute lung injury. **Was changed to** : Acute IPF exacerbation is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality [P16-06899]. Extra-parenchymal causes (e.g. pneumothorax, pleural effusion, pulmonary embolism) should be excluded and the following 3 diagnostic criteria need to be met: • Acute worsening or development of dyspnea typically of less than one month duration; • Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern

		consistent with usual interstitial pneumonia pattern; • Deterioration not fully explained by cardiac failure or fluid overload. Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet the three diagnostic criteria due to missing computed tomography data will be termed "suspected acute exacerbations" by the Adjudication Committee.
Rationale for change		Update of the definition of acute IPF exacerbation in line with new definition recently published by an international working group (Collard et. al. 2016)
Section to be changed		Section 5.5.2 Biobanking (optional)
Description of change		**Was added**: If not authorized by a local IRB / IEC / Competent Authority, biobanking will not be performed for patients of the respective site / country (as applicable).
Rationale for change		Clarification that biobanking is an optional procedure and requires local approval.
Section to be changed		Section 6.2.1 Screening and run-in period(s)
Description of change		Patients who have a laboratory test value that is outside the range specified by the exclusion criteria may have the test repeated once to determine eligibility; however, the result must be available prior to visit 2. **Was changed to :** Patients who have a laboratory test, blood pressure or lung function test value outside the range specified by the exclusion criteria and thought to be a measurement error or the result of a temporary and reversible medical condition may have the test repeated once to determine eligibility; however, the result must be available prior to visit 2.
Rationale for change		To allow retest within the screening period of examinations required to assess inclusion criterion #5 and exclusion criteria 4, 9 and 15.
Section to be changed		
Description of change		

Rationale for change		
Section to be changed		Section 9.1
Description of change		**Was added** : P16-06899 Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. Am J Respir Crit Care Med, (2016)
Rationale for change		Reference added
Section to be changed		Section 10.2
Description of change		In the presence of a surgical lung biopsy, the histology should be reviewed based on the ATS/ERS/JRS/ALAT guidelines [P11-07084]. 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”. **Was changed to :** In the presence of a surgical lung biopsy, the histology should be reviewed based on the ATS/ERS/JRS/ALAT guidelines [P11-07084]. An HRCT pattern "possible UIP" coupled with a surgical biopsy pattern “definite UIP” or "probable UIP", upon multidisciplinary team discussion, could qualify for inclusion as “consistent with a diagnosis of IPF”.
Rationale for change		Correction/rewording according to the guidelines.

APPROVAL / SIGNATURE PAGE

Document Number: c03484701 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: INSTAGE: A 24-week, double-blind, randomized, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		18 Aug 2016 13:15 CEST
Approval-Team Member Medical Affairs		18 Aug 2016 13:28 CEST
Approval-Project Statistician		18 Aug 2016 13:51 CEST
Approval-Team Member Medical Affairs		18 Aug 2016 14:12 CEST
Approval-Therapeutic Area		18 Aug 2016 14:21 CEST
Author-Trial Clinical Pharmacokineticist		22 Aug 2016 08:21 CEST
Verification-Paper Signature Completion		22 Aug 2016 21:01 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**