CLINICAL TRIAL PROTOCOL

	Document Number:	**c03463451-08**
EudraCT No.:	2015-000732-15	
BI Trial No.:	1199.229	
BI Investigational Product(s):	Nintedanib (Ofev®)	
Title:	Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study)	
Brief Title:	A study to compare the amount of nintedanib and pirfenidone in the blood when nintedanib and pirfenidone are given separately or in combination	
Clinical Phase:	IV	
Trial Clinical Monitor:	[redacted] Phone : [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised Protocol, based on Global Amendments 1, 2 and 3)	
Version and Date:	**Version: 4.0**	**Date: 29 July 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: **Boehringer Ingelheim**			
Name of finished product: Ofev®			
Name of active ingredient: Nintedanib			
Protocol date: 17 July 2015	**Trial number:** 1199.229		**Revision date:** 29 July 2016

Title of trial:	Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study)
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s):	Trial conducted in approximately 9 sites in the UK
Clinical phase:	IV
Objective(s):	The primary objective of this study is to investigate the effect of steady state pirfenidone on the pharmacokinetics of nintedanib and its metabolites following oral administration of 2403 mg/day pirfenidone and to investigate the effect of steady state nintedanib on the pharmacokinetics of pirfenidone at steady state following oral administration of 150 mg bid nintedanib. There will be two cohorts of patients; one group will be patients who are currently not treated with pirfenidone or nintedanib and one group will be patients treated with pirfenidone.

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Name of finished product: Ofev®			
Name of active ingredient: Nintedanib			
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Methodology:	Open-label, multiple dose, two-group PK trial. An optional Named Patient Programme of nintedanib will be discussed with patients at the end of the trial. This Named Patient Programme will not be part of the study.
No. of patients:	
total entered:	Approximately 34 patients
each treatment:	Group 1: 16 patients Group 2: 18 patients
Diagnosis:	Idiopathic Pulmonary Fibrosis (IPF)
Main criteria for inclusion:	Male or female patients aged ≥ 40 years at visit 1; IPF diagnosis based on the ATS/ERS/JRS/ALAT 2011 IPF guidelines; Chest High-Resolution Computed Tomography (HRCT) performed within 18 months of visit 1; FVC ≥ 50% predicted of normal at visit 1.

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PK EVALUATION PERIOD GROUP 1:	
Trial product 1:	Nintedanib soft gelatin capsule
Dose:	Single dose of 150 mg on Day 1 and 23 only
Mode of administration:	Oral administration with food
Trial product 2:	Pirfenidone hard capsule
Dose:	Titrated up to 2403 mg daily according to the following schedule: • Day 2 to 8: one capsule tid (267 mg tid / 801 mg daily) • Day 9 to 15: two capsules tid (534 mg tid / 1602 mg daily) • Day 16 to 23: three capsules tid (801 mg tid / 2403 mg daily)
Mode of administration:	Oral administration with food
Duration of treatment:	23 days
PK EVALUATION PERIOD GROUP 2:	
Trial product 1:	Nintedanib soft gelatine capsule
Dose:	Day 9 – Day 15 300 mg daily (150 mg bid) Day 16 150 mg morning dose only (this is the last dose in the PK period)
Mode of administration:	Oral administration with food
Trial product 2:	Pirfenidone
Dose:	Day1 – Day 15 - three capsules tid (801 mg tid / 2403 mg daily) with possibility to reduce to two capsules tid (534 mg tid / 1602 mg daily) Day 16 three capsules in the morning only (801 mg; this is the last dose

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	in the PK period)
Mode of administration:	Oral administration with food
Duration of treatment:	16 days
Endpoints	Pharmacokinetic Parameters: Group 1: Primary endpoints: $AUC_{0\text{-}tz}$ and C_{max} of nintedanib Secondary endpoints: $AUC_{0\text{-}\infty}$ of nintedanib Group 2: Primary endpoints: $AUC_{\tau,ss}$ and $C_{max,ss}$ of pirfenidone
Safety criteria:	Incidence and intensity of adverse events, physical examination, vital signs, ECG, change from baseline in laboratory parameters
Statistical methods:	Descriptive statistics and analysis of variance (ANOVA) for $AUC_{0\text{-}tz}$, C_{max} and $AUC_{0\text{-}\infty}$ of nintedanib with and without the association with pirfenidone (group 1) and for $AUC_{\tau,ss}$ and $C_{max,ss}$ for pirfenidone with and without the association with nintedanib (group 2).

FLOW CHART - GROUP 1

Trial Periods	**Screening Period[1]**	**PK evaluation Period[10]**			**PK Follow-up Period[18]**
Visit	**1**	**2**	**Phone call[6]**	**3[13]**	**4**
Weeks		**0**	**2**	**3[11]**	**7**
Days	**-28 to -1**	**1-2**	**15**	**23-24**	**52**
Time window for visits			+6 days		+3 days
Informed consent[2]	X				
Demographics	X				
Medical history	X				
Review of in-/exclusion criteria	X	X			
Drug and alcohol testing at site	X	X			
Physical examination	X	X		X	X
Vital signs[3]	X	X		X	X
Laboratory tests	X			X	X
Pregnancy test (urine)[9]	X	X		X	X
PK sample[7]		X[17]		X[17]	
[redacted]		X			
[redacted]		X[14]		X[14]	X
[redacted]		X[14]		X[14]	
12 lead-Electrocardiogram (ECG)	X				X
Spirometry[12]	X	X		X	X
DLCO[19]	X	(X)[19]			
Register screening / start of treatment	X	X			
Dispense trial drugs[4]		X[17]		X	
Collect trial drug & compliance check				X	
Dispense and/or collect & review diary[5]		X[17]		X	
AEs and Concomitant therapy[16]	X	X[17]	X	X[17]	X
Conclusion of PK evaluation period				X	
Conclusion of subject participation					X[15]

FOOTNOTES – GROUP 1

1. The screening period between Visit 1 and 2 should last a maximum of 28 days. Eligible patients can be started on treatment 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. Vital signs to include blood pressure and pulse rate.
4. Patient will be dispensed three wallets of pirfenidone. They will use one wallet to uptitrate for 14 days (Day 2 to Day 15) and then the next wallet for the complete dose of 801 mg tid daily (Day 16 to Day 22). On Day 23 the patient should bring their medication into clinic and will be given the morning and the 14:00 of pirfenidone at the clinic. They will take their evening dose at home and this will be their final dose during the PK period. The patient will also be dispensed a single 150mg dose of nintedanib on Day 1 and Day 23. (See Section 4.1.4).
5. Patients will be supplied with a diary and a dosing card and they will be asked to document the number of capsules they have taken each day and also to record any adverse events during this period.
6. At the end of the 14 day uptitration (Day 15) a call will be made to the patient to check whether there have been any issues with uptitration and when the patient has reached the full dose (the phone call should be documented in the patient notes). The patient will then continue on full dose (801 mg tid) for 7 consecutive days (Day 16 to Day 22) before returning to the clinic for the next PK day (Day 23). The patient would have their final PK sample taken on Day 24.
7. Please see separate PK flowchart Group 1 for details during the PK evaluation period Section 10.2.
8. [redacted]
9. Urine dipstick pregnancy tests will be provided by central lab and should be performed in all women of childbearing potential.
10. If a patient withdraws from the PK evaluation period or does not tolerate uptitration then the patient should be managed according to Figure 4.1.4:1
11. The patient will stop all trial medication on Day 23 and have a washout period from study drug until the PK FU visit.
12. Spirometry should be conducted using local standard equipment.
13. The uptitration phase between Visit 2 and Visit 3 can be extended by a maximum of 6 days if the patient needs longer to uptitrate or to achieve 7 consecutive stable days at full dose.
14. [redacted]
15. At Visit 4 (PK FU) the optional nintedanib Named Patient Programme will be discussed with the patient.
16. AEs and concomitant therapy should be checked at regular intervals during the PK days.
17. At Visit 2 Day 2 and Visit 3 Day 24 only these procedures need to be done see Section 6.2.2.
18. The PK Follow Up visit should occur at least 28 days after last drug intake.
19. DLCO testing will be performed once at visit 1 or 2, or during the screening period (visit 1 to visit 2). The results will be corrected for haemoglobin by the site, see section 10.3 for further details.

FLOW CHART - GROUP 2

Trial Periods	**Screening Period[1]**	**PK evaluation period[9]**			**PK Follow-up Period[16]**
Visit	**1**	**2**	**3a**	**3b[12]**	**4**
Weeks		**0**	**1**	**2**	**6**
Days	**-28 to -1**	**1**	**8**	**16[10]**	**44**
Time window for visits			+3 days	+3 days	+3 days
Informed consent [2]	X				
Demographics	X				
Medical history	X				
Review of in-/exclusion criteria	X	X			
Drug and alcohol testing at site	X	X			
Physical examination	X	X	X	X	X
Vital signs[3]	X	X	X	X	X
Laboratory tests	X		X	X	X
Pregnancy test (urine)[8]	X	X	X	X	X
PK sample[6]			X	X	
[redacted]		X			
[redacted]		X	X[13]	X[13]	X
[redacted]		X	X[13]	X[13]	
[redacted]	X				X
Spirometry[11]	X	X	X	X	X
DLCO[17]	X	(X)[17]			
Register screening / start of treatment	X	X			
Dispense trial drugs[4]		X	X	X	
Collect trial drug & compliance check			X	X	
Dispense and/or collect & review diary[5]		X	X		
AEs and Concomitant medication[15]	X	X	X	X	X
Conclusion of PK evaluation period				X	
Conclusion of subject participation					X[14]

FOOTNOTES – GROUP 2

1. The screening period between Visit 1 and 2 should last a maximum of 28 days. Eligible patients can be started on treatment 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. Vital signs to include blood pressure, pulse rate and weight.
4. Patient will be dispensed two wallets of pirfenidone at Visit 2 and take the full dose (801 mg tid) for 7 consecutive days (Day 1 to Day 7) and then return to the clinic for Visit 3a (Day 8). At Visit 3a they will be dispensed one wallet of pirfenidone and one bottle of nintedanib and be given the remaining wallet of pirfenidone that was dispensed at the previous visit. The will take nintedanib 150mg bid and pirfenidone 801mg tid (or 534mg tid) from Day 9 to Day 15 and then come in to the clinic at Day 16 where they will receive only the morning dose of each drug. (See Section 4.1.4).
5. Patients will be supplied with a diary and a dosing card and they will be asked to document the number of capsules they have taken each day and also to record any adverse events during this period.
6. Please see separate PK flowchart Group 2 for details during the PK evaluation period Section 10.2.
7. [redacted]
8. Urine dipstick pregnancy tests will be provided by central lab and should be performed in all women of childbearing potential.
9. If a patient withdraws from the PK evaluation period then the patient should be managed according to Figure 4.1.4:1.
10. The patient will stop all trial medication on Day 16 (except for the doses given at clinic) and have a washout period from study drug until the PK FU visit.
11. Spirometry should be conducted using local standard equipment.
12. During the PK evaluation period the patient must have seven consecutive days of both nintedanib 150mg bid and pirfenidone 801mg tid (or 534mg tid) before they should have the PK day on Visit 3b.
13. [redacted]
14. At Visit 4 (PK FU) optional nintedanib Named Patient Programme will be discussed with the patient
15. AEs and concomitant therapy should be checked at regular intervals during the PK days.
16. The PK Follow Up visit should occur at least 28 days after last drug intake.
17. DLCO testing will be performed once at visit 1 or 2, or during the screening period (visit 1 to visit 2). The results will be corrected for haemoglobin by the site, see section 10.3 for further details..

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	Latin American Thoracic Association
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	ANalysis Of VAriance
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AUC	Area under the Curve
b.i.d.	Bis in die (twice daily dosing)
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CrCl	Creatinine Clearance
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DDI	Drug-drug interaction
DEDP	Drug exposure during pregnancy
DILI	Drug induced liver injury
DLCO	Diffusing capacity of the Lung for Carbon monoxide
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EOT	End of Treatment
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine-tetraacetic acid
EMA	European Medicines Agency
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FC	Flow Chart
FGFR	Fibroblast growth factor/receptor
FVC	Force Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
Hb	Haemoglobin
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
INR	International normalised radio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
JRS	Japanese Respiratory Society
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LTx	Lung Transplant
MedDRA	Medical Dictionary for Drug Regulatory Activities
NAC	N-acetylcysteine
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NICE	National Institute for Health and Care Excellence
nRTKs	Non-receptor tyrosine kinases
PDGFR	Platelet derived growth factor/receptor
PFS	Progression-free survival
P-gp	P-glycoprotein
PKS	PK analysis set
PT	Prothrombin time
PTT	Partial thromboplastin time
RDC	Remote data capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic acid
RTKs	Receptor Tyrosine Kinases
SAE	Serious Adverse Event
s.c.	Subcutaneous
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
t.i.d.	Ter in die (3 times a day)
TMF	Trial Master File
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a rare disease of unknown aetiology that is characterized by progressive fibrotic of the interstitium of the lung, resulting in 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 2011 evidence-based guideline on diagnosis and management of IPF, jointly issued by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) did not give a positive recommendation for any pharmacologic treatment (P11-07084). 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 [P11-07084; 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 (LTx) has been shown to positively impact survival in patients with IPF. Median survival after LTx in IPF patients is approximately 4-5 years, and 5-year survival is estimated at 39-50% (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].

These guidelines have been updated, presented during the 2015 International ATS Conference in Denver and are expected to be published before mid-2015. These guidelines will include, for the first time in IPF, recommendations favouring pharmacological treatment.

The PANTHER trial showed that NAC, commonly used off label, offered no significant benefit with respect to the preservation of forced vital capacity (FVC) as compared with placebo in patients with idiopathic pulmonary fibrosis [P14-07665].

Pirfenidone is a compound, which demonstrated anti-fibrotic activity in non-clinical models and 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 has been licensed since February 2011 for the treatment of mild to moderate IPF in Europe and since October 2014 for the treatment of IPF in US. 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 US in October 2014 and in the EU in January 2015. It has been submitted for marketing authorization in other countries across the world.

With the future introduction of these new drugs in the evidence-based treatment algorithm of IPF, there is an additional need to further characterize their profile, including their use in potential combination treatment regimens.

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 gelatine capsule formulation of nintedanib is used in humans. Nintedanib is absorbed moderately fast, with maximum plasma concentrations occurring between 2 - 4 hours after oral administration. Exposure to nintedanib increases in a dose proportional manner. The terminal half-life is in the range of 7 to 19 h and steady state is reached at the latest within one week of dosing. After food intake, a trend towards an increased systemic exposure (around 15 to 20%) and a delayed absorption was observed compared to administration under fasted conditions. Nintedanib is recommended to be taken with food. Nintedanib is preferentially distributed in plasma, with a blood to plasma ratio of 0.87. The absolute bioavailability of the capsule formulation of nintedanib was slightly below 5%. Nintedanib is mainly eliminated via faeces, with renal elimination playing a very minor role (0.7% of an orally administered radioactive dose).

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 (C_{max}) 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 C_{max} 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.

Based on a multiple-dose study in Japanese IPF patients, exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on C_{max} upon co-administration with pirfenidone compared to administration of nintedanib alone. Further studies are needed to confirm this finding [P14-17347].

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. Weight decrease and decreased appetite have also frequently been reported in studies with nintedanib.

Potential risks of nintedanib treatment also include arterial hypertension, gastrointestinal perforations, thromboembolism and bleeding. Patients treated with full-dose anticoagulation or at known risk for bleeding were excluded from the INPULSIS trials. This has led to recommendations stating that patients at known risk for bleeding should be treated with nintedanib only if the anticipated benefit outweighs the potential risk. Although cardiac disorders adverse events 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. The clinical significance of this finding is unknown, and further observation is needed.
For patients finalizing the 52-week study treatment in the TOMORROW and INPULSIS trials, participation in open label extension trials (1199.35 and 1199.33) was offered. Long term treatment in these still ongoing open label extension trials confirm the safety profile observed in the phase II and III trials.

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 Pirfenidone

The mechanism of action of pirfenidone in the treatment of IPF has not been established. After single oral-dose administration of 801 mg pirfenidone, C_{max} was achieved between 30 minutes and 4 hours (median time of 0.5 hours). Food decreased the rate and extent of absorption. Median t_{max} increased from 0.5 hours to 3 hours with food. Maximum plasma concentrations and $AUC_{0\text{-}inf}$ decreased by approximately 49% and 16% with food, respectively. A reduced incidence of adverse reactions was observed in the fed group when compared to the fasted group. Pirfenidone was taken with food in controlled studies with IPF patients. The absolute bioavailability of pirfenidone has not been determined in humans. The mean terminal half-life is approximately 3 hours in healthy subjects and, as such, steady state accumulation is expected to be minimal. Pirfenidone is excreted predominantly in the urine (approximately 80% of the dose).

Pirfenidone is a substrate of cytochrome P450 1A2. Co-administration with the strong CYP1A2 inhibitor fluvoxamine increased exposure to pirfenidone by approximately 4-fold in non-smokers and 7-fold in smokers. Co-administration with ciprofloxacin (moderate inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP iso-enzymes involved in the metabolism of pirfenidone (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be avoided during treatment with pirfenidone.

The efficacy of pirfenidone 2403 mg/day (3 capsules tid) was evaluated in patients with IPF in three phase III, randomized, double-blind, placebo-controlled, multi-centre trials (CAPACITY and ASCEND trials). The CAPACITY 2 trial showed a positive result on the primary endpoint of change from baseline in FVC % predicted at week 72, as well as on the secondary endpoint of progression-free survival (PFS). In the CAPACITY 1 trial there was no statistically significant difference at Week 72 for the primary endpoint. The ASCEND trial reported a positive result on the primary endpoint of change from baseline in FVC % predicted at week 52, as well as positive results on both key secondary endpoints of PFS and change from baseline in 6-minute walk test distance [R11-4827; R14-2103].

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials. Adverse events included gastrointestinal events (nausea, abdominal pain, diarrhoea, dyspepsia, vomiting, anorexia and weight decrease) and skin disorders (e.g. rash, photosensitivity) that were generally mild or moderate and led to few treatment discontinuations.

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

The prognosis of IPF is devastating, with 50% of patients dying within 3 years of diagnosis. The course of the disease ranges from relative stability for several years to rapid deterioration to death over months, sometimes punctuated by episodes of rapid decline (acute IPF exacerbations) [P12-03241]. Until recently, IPF was essentially an untreatable disease. It appears to be characterized by abnormalities in multiple pathways involved in the fibrotic process. Clinical trials of targeted therapies (e.g. bosentan and etanercept) have shown no benefit, whereas drugs that are pleiotropic in their activity, such as nintedanib and pirfenidone, have proven to be clinically efficacious by reducing the decline in lung function [P15-01243]. However, the disease continues to progress, albeit more slowly, and the scientific community, in search of better outcomes, is now looking for new treatment approaches including combination regimens. This is in line with several other serious chronic diseases including most solid tumours, infection with human immunodeficiency virus and pulmonary arterial hypertension [P14-16496].

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 [P08-08684; P14-02860]. Although the mechanism of action of pirfenidone is not fully understood, it also has been shown to have anti-fibrotic, anti-inflammatory and antioxidant properties in animal models [R12-4811]. Pirfenidone has not been shown to inhibit tyrosine kinases similar to nintedanib and combining these two drugs with different molecular targets might ultimately provide additive efficacy benefits to patients and therefore is an attractive option for treating physicians [U12-2505-01; P14-16496].

Although both drugs do not share similar mechanisms of action and metabolism routes, the side effect profile of nintedanib and pirfenidone overlaps (gastrointestinal side effects and liver enzyme elevations) and therefore there is also a potential for additive adverse effects when combining both treatments.

To date, there is only limited evidence for combined treatment, from a double-blind, randomized, placebo-controlled phase II study in Japanese patients in which nintedanib was added to pre-existing treatment with pirfenidone. In this study (1199.31), 13 patients received nintedanib 150 mg bid on top of standard doses of pirfenidone used in Japan, and 11 patients received 150 mg bid nintedanib alone for maximum treatment duration up to 28 days. In the 150 mg bid dose group, exposure to nintedanib decreased by 31.7% based on mean AUC and by 40.8% based on mean C_{max} upon co-administration with pirfenidone compared to administration of nintedanib alone. Nintedanib had no effect on the PK of pirfenidone. Due to the short duration of concomitant exposure and low number of patients, no conclusion on the safety and efficacy of the combination can be drawn [P14-17347].

This study is conducted at the request of the European Medicines Agency (EMA) as a post-approval commitment and will examine the relative bioavailability for nintedanib and

pirfenidone when administered together versus when administered alone. [redacted]

2.2 TRIAL OBJECTIVES

The primary objective of this study is to investigate the effect of steady state pirfenidone on the pharmacokinetics of nintedanib and its metabolites following oral administration of 2403 mg/day pirfenidone and to investigate the effect of steady state nintedanib on the pharmacokinetics of pirfenidone at steady state following oral administration of 150 mg bid nintedanib. There will be two cohorts of patients; the first one will consist of patients not treated with pirfenidone or nintedanib, while the second one will consist of patients on pirfenidone treatment.

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 first acute exacerbation in 2 out of 3 clinical trials [P11-11216, P14-07514].

All patients in this trial will also be treated with pirfenidone for a limited period in addition to nintedanib. Pirfenidone has shown a similar effect on slowing the decline of lung function in 2 out of 3 large phase III clinical trials [R11-4827; R14-2103]. As this period of combination treatment during the PK part of the trial is short, there is expected to be no additional benefit to the patient. An optional nintedanib Named Patient Programme to allow patients to continue on nintedanib will be discussed at the end of the trial. Patients participating in this PK trial will help to elucidate the pharmacokinetic characteristics of the combination of pirfenidone and nintedanib. The risks of the treatments with nintedanib and pirfenidone are described in section 1.2. The side effect profile of both drugs partially overlaps, especially in terms of gastrointestinal events (diarrhoea, nausea, vomiting, abdominal pain), as well as liver enzyme elevations.

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 elevations.

In case of lack of tolerability, symptomatic treatment, dose adjustments and/or interruptions of one or both trial drugs (at the discretion of the investigator) will have to be considered to allow for resolution of the symptoms (Section 4.2.1).

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.

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

Overall, the clinical safety profile of both nintedanib and pirfenidone as established during the development programs 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, single country, open-label, multiple-dose, two-group trial to investigate the relative bioavailability of nintedanib and pirfenidone when administered alone and after co-administration in patients with IPF. The study will be performed in approximately nine centres in the United Kingdom.

Patients with IPF will sign informed consent before or at Visit 1 (screening visit). After a screening visit, if the patient complies with all inclusion and exclusion criteria, they will start treatment at Visit 2. The trial will not be randomised. Patients who are currently not being treated with either nintedanib or pirfenidone will enter Group 1, and patients who are chronic pirfenidone users will enter Group 2. Within each group, a fixed sequence design will be followed. At the end of the PK evaluation period there will be a 4-week period where the patient will take no study drugs. After the end of the trial an optional Named Patient Programme of nintedanib will be discussed with patients.. See Figure 3.1:1 below, Section 6 and the flowchart 1 and flowchart 2 for details of each study visit.

Group 1 – 16 patients

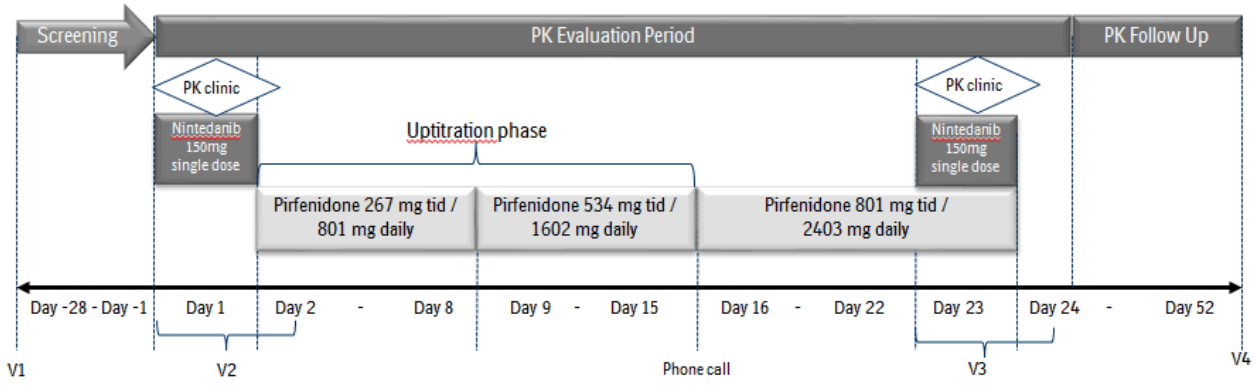


Figure 3.1:1 Trial design diagram for each group for PK evaluation period

Group 2 – 18 patients

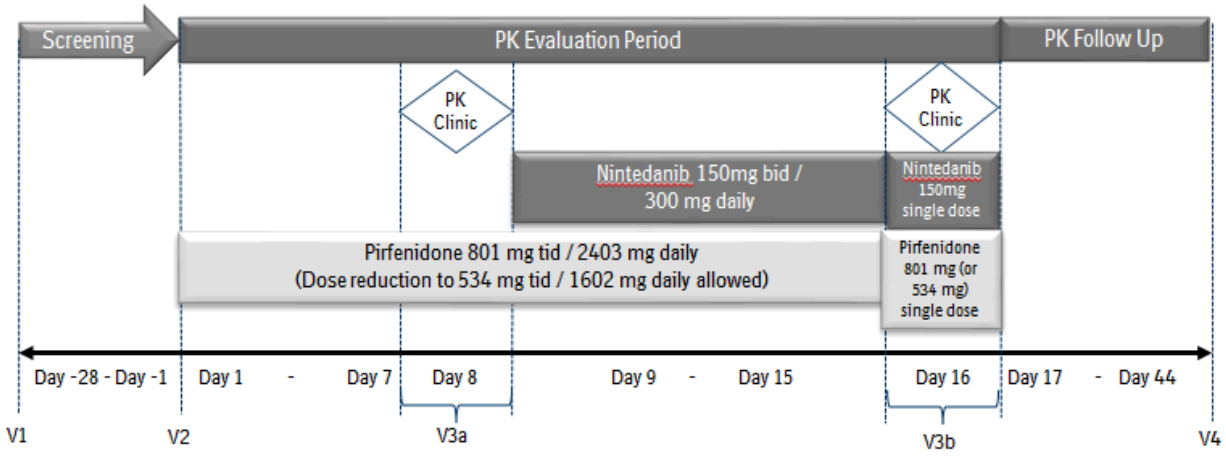


Figure 3.1:1 Trial design diagram for each group for PK evaluation period continued

3.2 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,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

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

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

A Coordinating Investigator 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 ISF.

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

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

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

For relative bioavailability studies the intra-individual comparison design is viewed favorably due to its efficiency: since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between treatments (cf. R94-1529). The design is expected to deliver valid results on the PK of a single oral dose of nintedanib with and without co-administration of pirfenidone at steady state (Group 1), as well as steady state pirfenidone with and without co-administration of nintedanib at steady state (Group 2). The current study design for Group 1 allows the perpetrator drug, pirfenidone, to reach a stable therapeutic dose, while minimizing the potential impact on nintedanib, the victim drug, which has previously shown a decrease in exposure upon co-administration with pirfenidone. Furthermore, as it is unknown whether there may be additive AEs when administering nintedanib and pirfenidone together, increasing the duration of concomitant administration of nintedanib and pirfenidone may elevate the potential for AEs unnecessarily. Therefore, the current study design for Group 1 minimizes both the risk of intolerability due to increasing AEs, as well as the risk of dropouts due to reduced drug efficacy, during co-administration of pirfenidone and nintedanib.

For Group 2, it is expected that there will already be patients stable on pirfenidone, as this drug is currently available for IPF in the UK. As such, using a steady state design for both the perpetrator (nintedanib) and the victim drug (pirfenidone) allows patients to remain at a stable therapeutic dose of pirfenidone, while reducing the likelihood of intolerability during an up-titration phase and, at the same time, reducing the likelihood of patients dropping out.

3.4 SELECTION OF TRIAL POPULATION

A total of approximately 34 patients with an IPF diagnosis will be treated. Each group will have a different number of patients. Approximately 16 patients who are not currently treated with pirfenidone or nintedanib will go into Group 1 and 18 patients who are currently treated with pirfenidone will go into Group 2.

Each group requires at least 12 evaluable patients to complete each arm. Once 12 evaluable patients in a group have completed treatment, recruitment into that group will stop. The other group may continue to recruit until 12 evaluable patients in that group also complete treatment.

Any patient still in the PK evaluation period when their group closes to recruitment may complete the PK evaluation period.

Approximately 9 sites are each expected to include a minimum of 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.

Patients who have screen failed may be permitted to be re-screened following agreement by the Sponsor. Screening procedures may not need to be repeated if they are within 28 days of visit 2. The decision on what screening procedures do not need to be repeated will be made by the Sponsor.

3.5 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.

3.6 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. IPF diagnosis, based upon the ATS/ERS/JRS/ALAT 2011 guideline (P11-07084) and chest high-resolution computed tomography (HRCT) scan.

4. FVC ≥ 50% of predicted normal (refer to Section 10.3) at visit 1.

5. DLCO (corrected for Hb [visit 1]): 30%-79% predicted of normal (refer to Section 10.3) at visit 2 (test can be performed at visits 1 or 2, or during the screening period).

6. Currently treated with pirfenidone at full dose (this is only for patients going into Group 2).

3.7 EXCLUSION CRITERIA

1. ALT, AST >1.5 fold upper limit of normal (ULN) at visit 1[1].

2. Total bilirubin >1.5 fold ULN at visit 1[1].

3. Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment[1, 6])

4. Relevant airways obstruction (i.e. pre-bronchodilator FEV_1/FVC <0.7 at visit 1).

5. History of myocardial infarction within 6 months of visit 1 or unstable angina within 1 month of visit 1.

6. Bleeding Risk:
    - Known genetic predisposition to bleeding

- Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, 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.

- Prothrombin time (PT) and partial thromboplastin time (PTT) >150% of institutional ULN at visit 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. Severe renal impairment (Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula at visit 1) or end-stage renal disease requiring dialysis.

10. Treatment with n-acetylcysteine, prednisone >15 mg daily or >30 mg every 2 days OR equivalent dose of other oral corticosteroids or fluvoxamine within 2 weeks of visit 2.

11. Treatment with azathioprine, cyclophosphamide, cyclosporine as well as any other investigational drug within 8 weeks of visit 2.

12. Previous treatment with pirfenidone in the past three months prior to Visit 2 (Group 1 only).

13. Previous treatment with nintedanib in the past 14 days prior to Visit 2.

14. Permanent discontinuation of nintedanib or pirfenidone in the past due to adverse events considered drug-related.

15. Known hypersensitivity to nintedanib, pirfenidone or their excipients; or to peanut or soya.

16. 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.

17. Alcohol or drug abuse, which in the opinion of the treating physician would interfere with treatment.

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

19. Women of childbearing potential[4] not using highly effective methods of birth control per ICH M3 [R09-1400], note 3, highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate of less than 1% per year when used consistently and correctly[5] such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomised partner. Barrier contraceptives (e.g. male condom or diaphragm) are acceptable if used in combination with spermicides (e.g. foam, gel). Contraception must be used for 28 days prior to and 3 months after nintedanib and pirfenidone administration.

20. Patients not able to understand and follow study procedures including completion of diaries without help.

21. Current smoker (vaping and e-cigarettes are acceptable)

[1]Laboratory parameter 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 s.c. per day) and prophylactic use of antiplatelet therapy (e.g., acetyl salicylic acid up to 325 mg/d, or clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy).

[3]Definition of major is per investigator judgement.

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

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

[6]Child Pugh classification does not need to be performed at screening.

3.8 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENTS

3.8.1 Removal of individual patients

An individual patient is to be withdrawn from all trial drugs (nintedanib and pirfenidone) if:

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take restricted therapy that may interfere with the investigational product (section 4.2.2).

- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

- The patient experiences liver function impairment as follows:
  - ALT and/or AST ≥5 fold ULN
  - ALT and/or AST ≥3 fold ULN with signs or symptoms of severe liver damage (section 4.2.1.4) (including total bilirubin >2 fold ULN).

    For potential drug induced liver injury (DILI) follow up requirements please see section 5.3.7.1.
- In the opinion of the investigator, the patient experiences unacceptable toxicity despite dose adjustments and supportive care.
- CrCl <30mL/min during the course of the trial. Study medication should be stopped and a repeat test performed as soon as feasible. If this second measurement confirms a CrCl <30mL, the patient should be permanently discontinued.

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

- Gastrointestinal perforation
- Major surgery including abdominal or intestinal surgery
- Signs or symptoms of acute myocardial ischemia, stroke, deep vein thrombosis and pulmonary embolism

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

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

In such cases as above, continuation of nintedanib should be discussed with the patient and the decision documented in the source data.

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

- ALT and/or AST ≥ 5 fold ULN
- Patient develops signs or symptoms of angioedema

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the FC and section 6.2.3.

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

3.8.2 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 GCP, the 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(s) and comparator product(s)

Table 4.1.1: 1 Nintedanib (investigational drug)

Substance:	Nintedanib
Pharmaceutical formulation:	Soft gelatine capsule
Source:	BI Pharma GmBH & Co. KG
Unit Strength:	150 mg
Posology:	Group 1: Day 1 and Day 23: one 150 mg capsule in the morning Group 2: Days 9-15: one 150 mg capsule in the morning and one in the evening Day 16: one 150 mg capsule in the morning
Route of administration:	Oral (swallowed) administration with food

Table 4.1.1: 2 Pirfenidone (investigational drug)

Substance:	Pirfenidone
Pharmaceutical formulation:	Capsule
Source:	Roche Registration Limited (previously InterMune UK Ltd)
Unit Strength:	267 mg
Posology:	Group 1 Days 2-8: one capsule three times a day Days 9-15: two capsules three times a day Days 16-23: three capsules three times a day Group 2 Days 1-15: three capsules three times a day Day 16: three capsules in the morning only
Route of administration:	Oral (swallowed) administration with food

4.1.2 Method of assigning patients to treatment groups

Patients are allocated to either Group 1 or Group 2 based on their current treatment at screening. There will be no randomisation required in this trial. Patients who are not being treated for IPF and fulfil all eligibility criteria will enter Group 1. Patients who are chronic users of pirfenidone and fulfil all eligibility criteria will enter Group 2.

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 the participating country. Dose adjustments are permitted as described in section 4.2.

Pirfenidone: A dose titrated up to 801 mg tid (total daily dose of 2403 mg) was selected for this trial as this is the recommended dose based on prescribing information in the participating country. Dose adjustments permitted as per section 4.2.

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. If the patient is currently not being treated for IPF at screening and they fulfil the inclusion/exclusion criteria, they will be assigned manually by the study site personnel to Group 1 and if they are a chronic pirfenidone user at screening and they fulfil the inclusion/exclusion criteria they will be assigned manually by the site to Group 2. There will be no IRT used in this trial. Sites will be required to inform the Sponsor of each screening and each start of treatment using the form provided in the ISF. The Sponsor will monitor recruitment to each group and inform sites when recruitment is close to complete.

Group 1
Visit 2 will be over two days. The patient is not required to stay in the clinic overnight between Day 1 and Day 2. At Visit 2, Day 1, eligible patients will receive one 150 mg nintedanib capsule in the clinic in the morning (Table 4.1.4:2 see Flowchart for Group 1 patients and Section 10.2 for timings of dosing and PK samples). This will be given to the patient by the site staff from a nintedanib bottle (this bottle should be kept at clinic and be used for patients who are in Group 1 for the first and second PK day). Gloves should be worn by the person giving the capsule to the patient and the capsule should be tipped out into a pot where the patient can then pick it up and take it. The patient should swallow nintedanib, unchewed, with food and a glass of water at the clinic.

At Visit 2, Day 2, the patient will return to clinic for their 24 hour PK sample (see Section 10.2) and they will be dispensed three wallets of pirfenidone. The patient will take the first dose at the clinic in the morning with food and a glass of water, under supervision and then go home and continue dosing at home. A dosing card will be provided to the patient, which will explain how they should uptitrate during the trial.

The patient will use the first wallet for 14 days titrating according to Table 4.1.4:1. Once the patient has completed the uptitration then they would use the second wallet and take 3 capsules 3

times a day for the next 7 days. Once the patient has had 7 consecutive, stable days on 801 mg tid they would then come to the clinic for the next PK day (Visit 3, Day 23; there is a 6 day window during the uptitration phase and Visit 3. This allows for extending the uptitration if required and ensuring that there are 7 consecutive, stable days at 801 mg tid before the patient returns to clinic for the second PK day Visit 3. The third wallet of pirfenidone can be used if required during this period).

The patient will return to the clinic for Visit 3. They should not take their medication at home, but should bring it to the clinic with them. At the clinic, they will be given their morning dose of 801mg pirfenidone and they will also receive one 150 mg capsule of nintedanib at the clinic with food and a glass of water. They will also be given their second dose of pirfenidone at the clinic at 14:00. They will take their final dose of pirfenidone at 20:00 in the evening at home once they have left the clinic. They should be advised to take this with food and a glass of water. The following day (Visit 3, Day 24), the patient will return to the clinic for their 24 hour PK sample (see Section 10.2). The patient will then have a washout of 28 days where no study medication is taken and then they will return to clinic for the PK Follow-Up visit (see Flowchart).

If the patient does not achieve 7 consecutive, stable days prior to Visit 3 plus the 6 day window then the patient would stop medication and attend the clinic for Visit 3, but would not have the PK samples taken (See Figure 4.1.4:1).

Table 4.1.4:1 Schedule for the titration phase of pirfenidone (Group 1)

Titration Period	Administration	Dose	Total daily Dose
Day 2 to Day 8 of titration	1 capsule tid	267 mg tid	801 mg
Day 9 to Day 15 of titration	2 capsules tid	534 mg tid	1602 mg

Table 4.1.4:2 Quantity of medication kits dispensed to the patient

Group 1

Visit	Nintedanib bottle	Pirfenidone wallet
2	0 (1 capsule given in clinic)	3
3	0 (1 capsule given in clinic)	

Table 4.1.4:2 Quantity of medication kits dispensed to patient continued

Group 2

Visit	Nintedanib bottle	Pirfenidone wallet
2	0	2
3a	1	1
3b	0	

Group 2

The patient will come to the clinic for Visit 2 (this is not a PK day). They should take their full dose of commercial supply of pirfenidone the previous day and then stop taking their commercial supply. At the clinic, eligible patients will receive two wallets of pirfenidone. The patient will take the first dose at the clinic in the morning with food and a glass of water, under supervision and then go home and continue dosing at home. A dosing card will be provided to the patient which will explain how they should take their study medication during the trial.

Once the patient has had 7 consecutive, stable days on 801 mg tid (3 capsules 3 times a day; this can be reduced to 534 mg tid) they would then come to the clinic for the next PK visit (Visit 3a, Day 8; see flowchart and section 10.2; there is a 3 day window to ensure that the patient has 7 consecutive days at full dose).

The patient will return to the clinic for Visit 3a. They should not take their medication at home, but should bring it to the clinic with them. At the clinic, they will be given their morning dose of 801mg pirfenidone (or 534mg if they have dose reduced) at the clinic with food and a glass of water. They will also be given their second dose of pirfenidone at the clinic at 14:00. They will take their final dose of pirfenidone at 20:00 in the evening at home once they have left the clinic. They should be advised to take this with food and a glass of water. Before they leave the clinic they will be given another wallet of pirfenidone and a bottle of nintedanib to take home (they should also be given the remaining pirfenidone wallet from the previous visit once compliance has been assessed). They will be advised to start the nintedanib with the morning and evening doses of pirfenidone.

For the next 7 days the patient will continue on pirfenidone 801 mg tid (3 capsules 3 times a day; or 534 mg tid) and take nintedanib 150 mg twice a day. Once the patient has had 7 consecutive stable days on 801 mg (or 534 mg) pirfenidone tid and nintedanib 150 mg twice a day then they would come to the clinic for the next PK day (Visit 3b, Day 16; there is a three day window for this visit to allow for 7 consecutive days if required; see Figure 3.1:1).

The patient will return to the clinic for Visit 3b. They should not take their medication at home, but should bring it to the clinic with them. At the clinic, they will be given their morning dose of 801mg pirfenidone and they will also receive one 150 mg capsule of nintedanib at the clinic with

food and a glass of water. The patient will then have a washout of 28 days where no study medication is taken and then they will return to clinic for the PK Follow-Up visit (see Flowchart).

If the patient does not achieve 7 consecutive, stable days prior to visit 3b plus the 3 day window then the patient would stop medication and attend the clinic for Visit 3b, but would not have the PK samples taken (See Figure 4.1.4:1) .

Group 1 patients

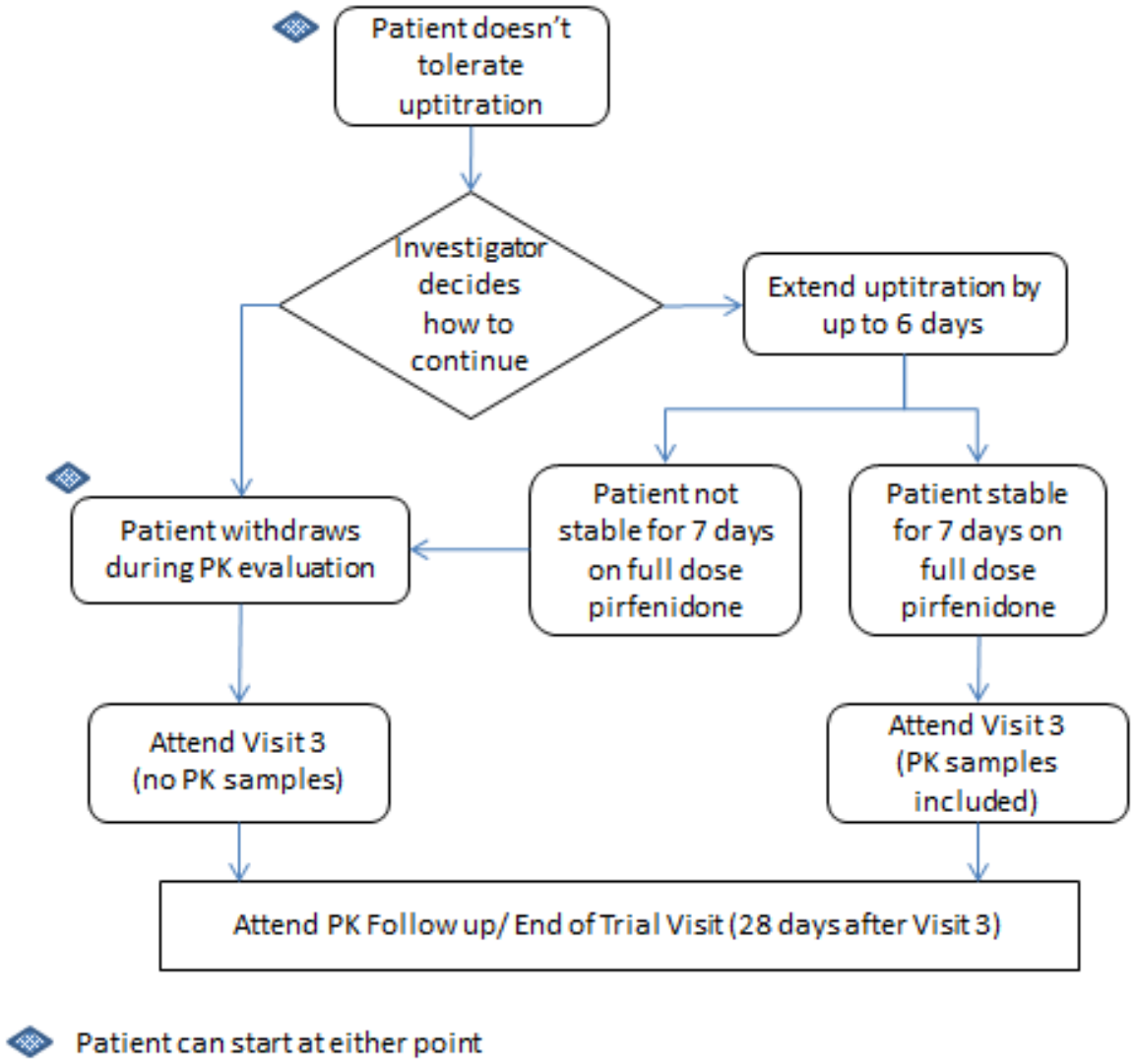


Figure 4.1.4: 1 Guidance for patients who withdraw or do not tolerate uptitration during the PK evaluation period

Group 2 patients Day 1-7

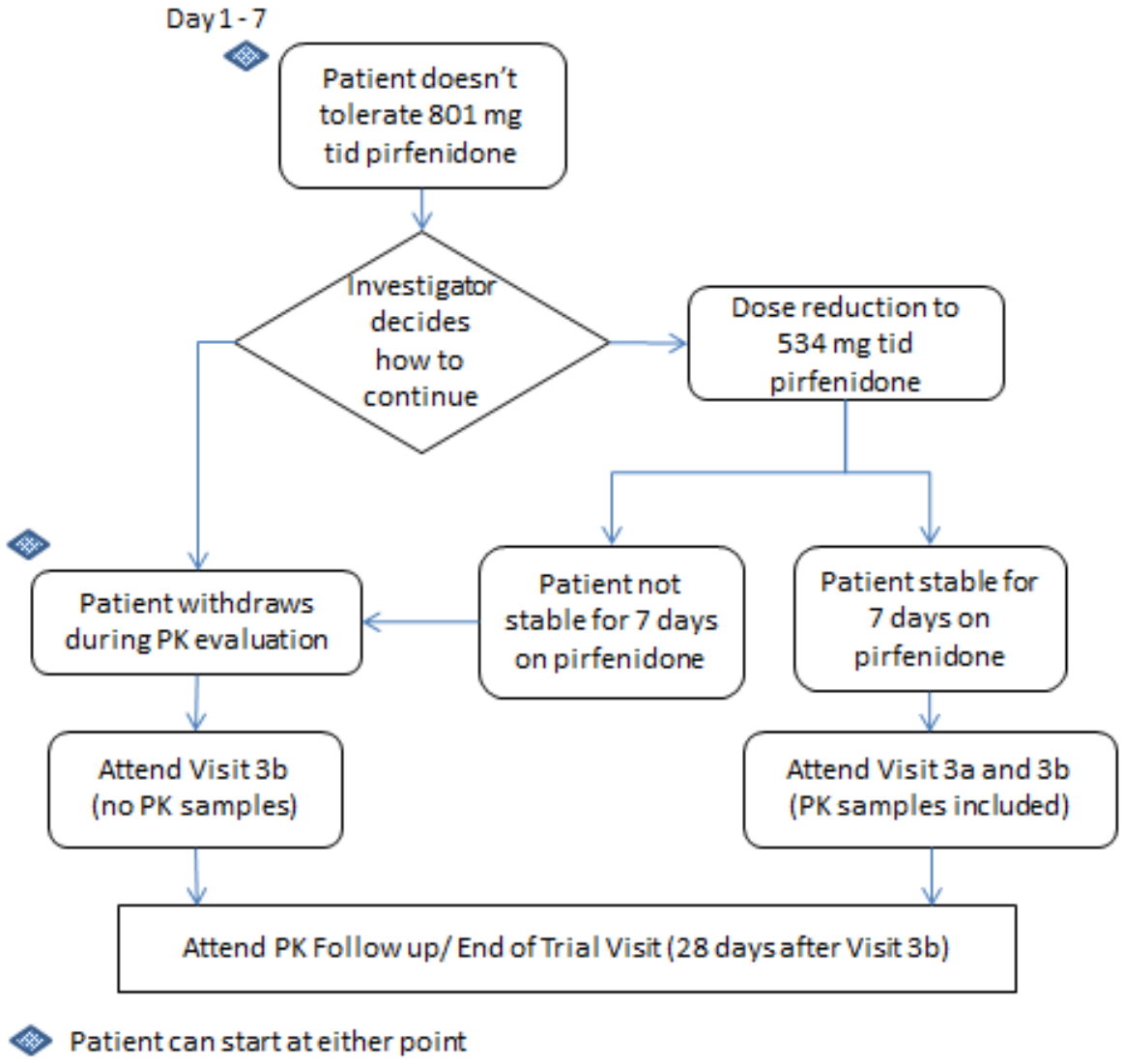


Figure 4.1.4:1 Guidance for patients who withdraw or do not tolerate uptitration during the PK evaluation period continued

Group 2 patients Day 9-15

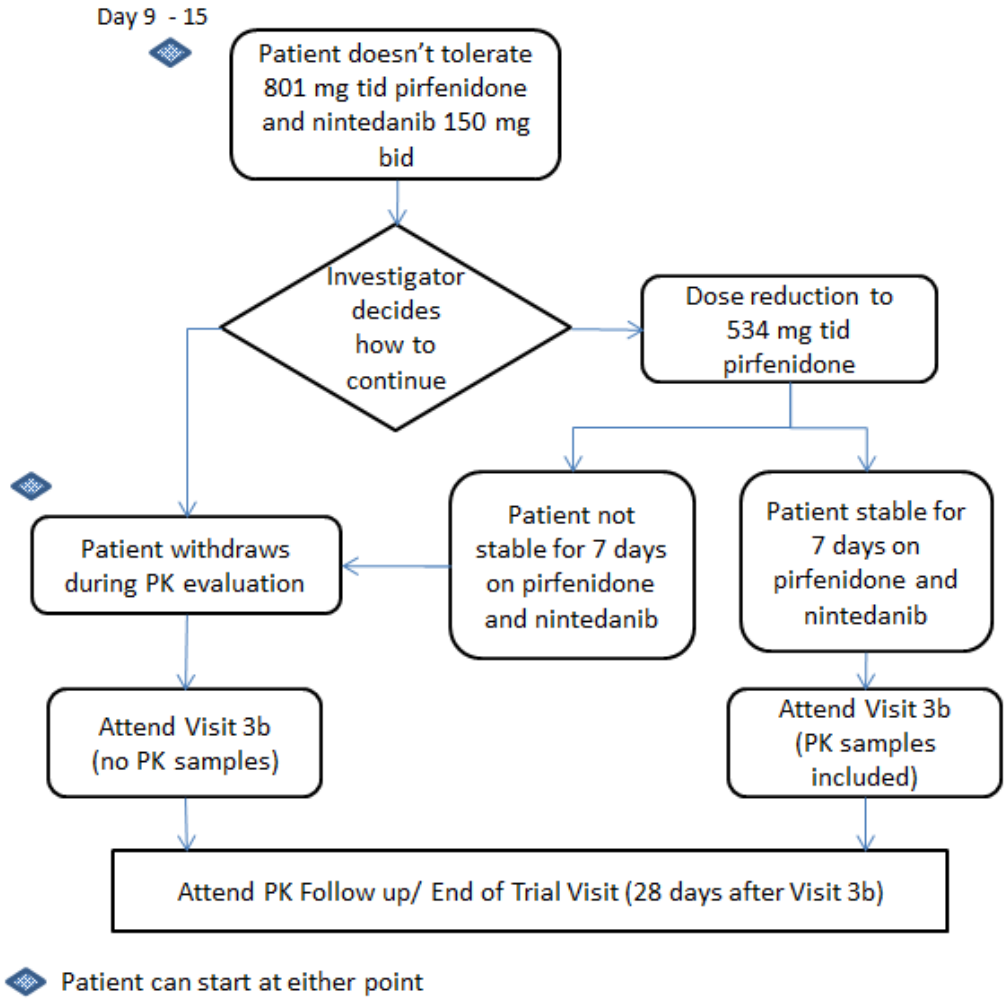


Figure 4.1.4:1 Guidance for patients who withdraw or do not tolerate uptitration during the PK evaluation period continued

4.1.4.1 Nintedanib and pirfenidone

The Investigator should emphasise to the patient the importance of taking all doses of trial medication in order to avoid missed doses throughout the PK period.

Group 1

- If a dose of pirfenidone is missed, administration should resume at the next scheduled time at the recommended dose. Double doses should not be taken to make up for the forgotten capsules.
- It is recommended that pirfenidone is administered at the same time in the morning and evening with food and a glass of water, with the third pirfenidone dose administered at the midpoint with food and a glass of water.

- If a patient withdraws from the PK period or is unable to tolerate uptitration please refer to Figure 4.1.4:1.

Group 2

- The patient should swallow nintedanib unchewed with food and a glass of water twice daily and should observe a dosing interval of approximately 12 hours.
- If a dose of pirfenidone or 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.
- It is recommended that nintedanib and pirfenidone are administered together at the same time in the morning and evening with food and a glass of water, with the third pirfenidone dose administered at the midpoint with food and a glass of water.
- If a patient withdraws from the PK period or is unable to tolerate uptitration please refer to Figure 4.1.4:1.

Patients experiencing adverse events may require drug interruption or reduction of dose. For additional details refer to section 4.2.1.

2403 mg daily (801 mg tid) pirfenidone may be reduced to 1602 mg daily (534 mg tid) to manage adverse events (in Group 2 only). If dose reduction is required for pirfenidone then the patient must have 7 stable days at the reduced dose along with the nintedanib for the second PK day. Further dose reductions for pirfenidone are not permitted within the trial. If the patient has tolerability issues they should contact the Investigator immediately.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on the group to which a patient has been allocated.

4.1.5.2 Unblinding and breaking the code

Not applicable. This is an open label trial.

4.1.6 Packaging, labelling, and re-supply

The medication kit for nintedanib is a 75cc PE bottle and contains 30 capsules. These will be provided by BI.
Medication kits for pirfenidone will comprise of a blister package of 63 capsules in a blister package (wallet). These will be provided by BI.

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

Medication will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

No re-supply is planned.

The nintedanib used in the nintedanib Named Patient Programme does not form part of the study supplies.

4.1.7 Storage conditions

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

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

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

4.1.8 Drug accountability

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

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator

The Investigator and/or Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor< and/or >appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

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

4.2.1.1 Recommendations for adverse events considered drug related (exceptions include diarrhoea and photosensitivity/rash):

If a patient experiences adverse events considered drug related, symptomatic treatment should be initiated (if appropriate).

- If necessary, dose reduction for pirfenidone to 534 mg tid is allowed in Group 2 only. Further dose reduction to 267 mg tid or temporary interruption of pirfenidone should be considered (at the discretion of the investigator) to allow for resolution of the symptoms.[1]
- After resolution of AE, re-introduction and re-escalation of pirfenidone should be considered on a stepwise approach.[1]
- If symptoms persist, then the patient should stop all trial medication during the PK evaluation period and return to clinic for Visit 3 (Group 1) or Visit 3b (Group 2) as per Figure 4.1.4:1.

4.2.1.2 Recommendations for managing diarrhoea

Symptomatic treatment should be initiated at first signs or symptoms of diarrhoea (hydration, antidiarrhoeal treatment e.g. loperamide).

- Interruption of nintedanib should be considered (at the discretion of the investigator; for patients in Group 2) to allow for resolution of symptoms.[1]
- If diarrhoea persists: dose reduction or interruption of pirfenidone should be considered (at the discretion of the physician) to allow for resolution of symptoms.[1]

4.2.1.3 Recommendations for managing phototoxicity and/or rash (PK evaluation period only)

- Symptomatic treatment should be considered at first signs or symptoms of phototoxicity/rash
- Dose reduction or interruption of pirfenidone should be considered (at the discretion of the investigator) to allow for resolution of symptoms.[1]
- After resolution of phototoxicity/rash, re-introduction and re-escalation of pirfenidone should be considered on a stepwise approach.[1]

- If phototoxicity/rash persists despite dose adjustment, permanent discontinuation of pirfenidone should be considered.

Footnote:

[1] If dose reduction, interruption or re-escalation does not allow for 7 consecutive stable days prior to Visit 3 for Group 1 patients or Visit 3a or Visit 3b for Group 2 patients then the patient should stop all trial medication during the PK evaluation period and return to clinic for Visit 3 (Group 1) or visit 3b (Group 2) as per Figure 4.1.4:1.

4.2.1.4 Management of liver enzyme elevations

Patients who experience:

- AST /ALT ≥3 ULN with signs or symptoms of severe liver damage* (including total bilirubin >2 fold ULN)
  or
- ALT and/or AST ≥5 fold ULN

Should interrupt all study drugs and return to clinic for a visit 3 (Group 1) or Visit 3b (Group 2).

* Signs of severe liver damage are defined as:

- ALT/AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
- ALT/AST ≥ 3 x ULN and unexplained INR > 1,5
- ALT/AST ≥ 3 x ULN and unexplained eosinophilia (>5%)
- ALT/AST ≥ 3 x 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 5.3.7.1.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant medications (or therapy) to provide adequate care may be given as assessed by the Investigator to be clinically necessary.

If restricted concomitant therapy is necessary, treatment with study medication should be permanently discontinued, see table 4.2.2.1:1 for details of restricted medications.

Table 4.2.2.1:1 Permitted and Restricted Concomitant therapy

Therapy	**Prior to Study**	**Screening Period**	**PK evaluation period**	**PK Follow-Up period)**
N-acetylcysteine[1] / Prednisone / other oral corticosteroid[2]	Permitted	Not permitted (2w prior to visit 2)	Not permitted	Not permitted
Azathioprine / Cyclophosphamide / Cyclosporine	Not permitted (8w prior to visit 2)	Not permitted	Not permitted	Not permitted
Investigational Medication	Not permitted (8w prior to visit 2)	Not permitted	Not permitted	Not permitted
Potent P-gp Inhibitors (e.g. ketoconazole, erythromycin) or Inducers (e.g. Rifampicin, Phenytoin, St. John's Wort)	Not permitted (8w prior to visit 2)	Not permitted	Not permitted	Not permitted
Potent or moderate CYP1A2 inhibitors (e.g. Fluvoxamine[1], enoxacin, ciprofloxacin, amiodarone) and inducers (e.g. rifampicin, omeprazole).	Permitted	Not permitted (2w prior to visit 2)	Not permitted	Not permitted
Oramorph, dextromethorphan (Opioids for the treatment of diarrhoea e.g. loperamide may be used as per section 4.2.1.2. Other opioids to be discussed with Sponsor beforehand).	Permitted	Permitted	Not Permitted on PK days[6].	Permitted
Anticoagulation at full dose[3] / Antiplatelet therapy at high dose [4] / Fibrinolysis	Permitted	Not permitted	Not permitted	Not permitted
Pirfenidone	Group 1 not permitted 3 months prior to visit 2 Group 2 permitted	Group 1 not permitted Group 2 permitted	Trial drug only	Not permitted
Nintedanib	Permitted	Not permitted (14 days prior to visit 2)	Trial drug only	Not 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. This will need to be recorded in the eCRF.
3. Anticoagulation at full dose (vitamin K antagonists, dabigatran, heparin, hirudin, etc). Exceptions: prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U s.c per day). This will need to be recorded in the eCRF.

4. Antiplatelet therapy at high dose. Exceptions: prophylactic use of antiplatelet therapy (e.g. acetylsalicylic acid up to 325 mg/day or clopidrogrel at 75 mg/day or equivalent doses of other antiplatelet therapy) is allowed. This will need to be recorded in the eCRF.

5. Patients should not receive treatment for IPF during the PK follow-up period unless they have an acute worsening of their disease. Should this occur then the investigator may use any standard of care treatment available to them. The treatments to be administered should be done after due consideration of the SPCs for nintedanib and pirfenidone. It is preferable that nintedanib and pirfenidone are not used during the PK follow-up period so that there is a clear Residual Effect Period. Investigational Medicinal Products must not be used during this period.

6. There should be at least a 2-4 hour gap between the opioid intake and nintedanib/pirfenidone intake prior to the first PK sampling.

4.2.2.2 Restrictions on diet and life style

Patients, when taking pirfenidone, should not smoke and should avoid exposure to direct and indirect sunlight, use an effective sunblock (at least SPF 50 against UVA and UVB) and wear protective clothing. Grapefruit juice is an inhibitor of CYP1A2 and, thus, consummation should be avoided while taking pirfenidone.

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 for each treatment, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. A compliance worksheet will be provided in the ISF.

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

If the number of doses taken is not between 80-120% without identified cause like AE or consent withdrawal, site staff will explain to the patient the importance of treatment compliance. In addition, the compliance calculation should be cross checked with the patient diary and discrepancies documented in the eCRF accordingly (Section 5.3.6).

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 Endpoints

Primary endpoints are pharmacokinetic endpoints defined as:

- Group 1:
  - $AUC_{0\text{-}tz}$ area under the concentration-time curve of **nintedanib** in plasma over the time interval from 0 to the last measured time point
  - C_{max} maximum measured concentration of **nintedanib** in plasma after single dose administration
- Group 2:
  - $AUC_{\tau,ss}$ area under the concentration-time curve of **pirfenidone** in plasma over a dosing interval
  - $C_{max,ss}$ maximum measured concentration of **pirfenidone** in plasma at steady state

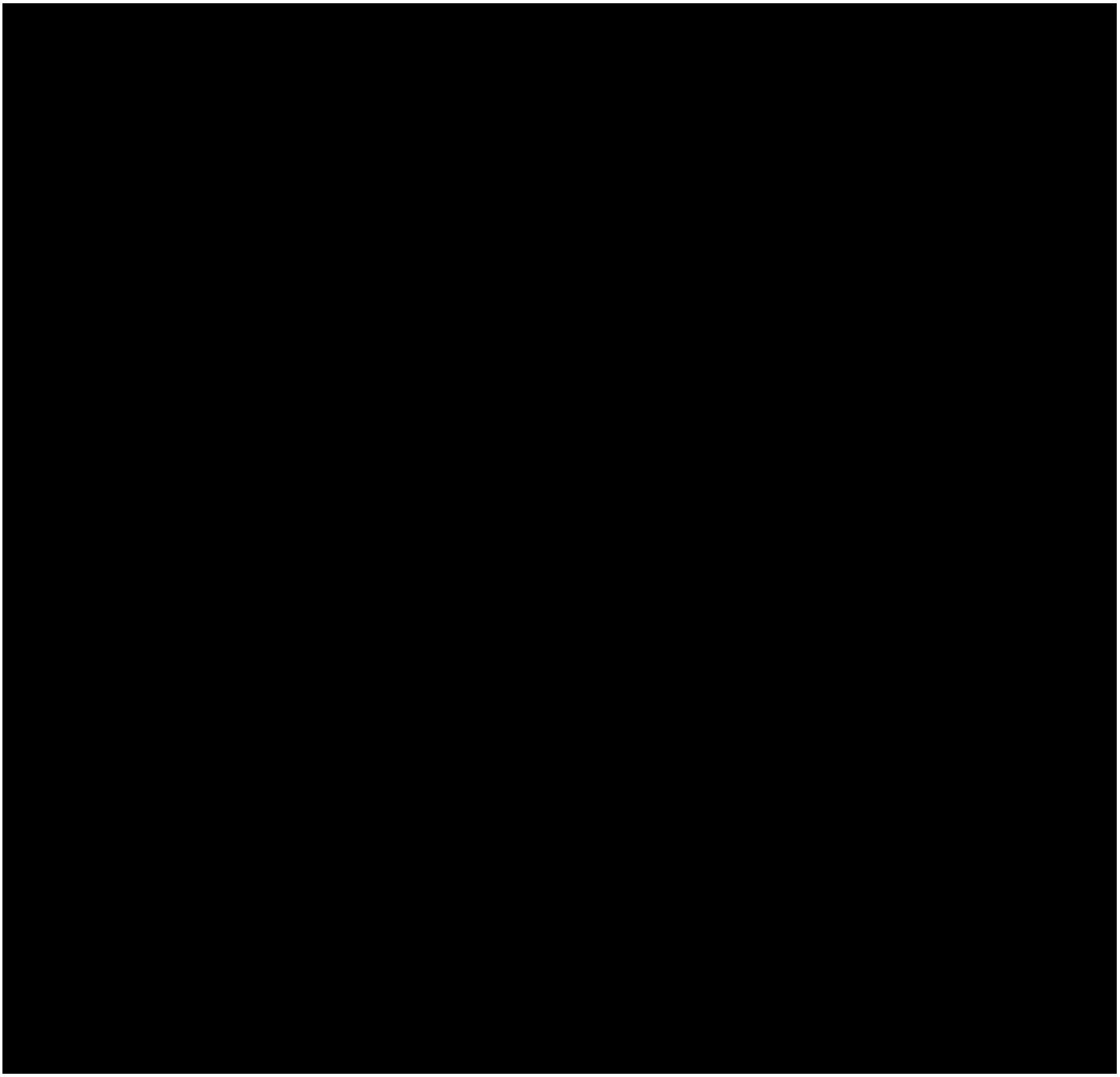
5.1.2 Secondary Endpoints

Secondary endpoints are pharmacokinetic endpoints defined as:

Group 1:
$AUC_{0\text{-}\infty}$ area under the concentration-time curve of **nintedanib** in plasma over the time interval from 0 extrapolated to infinity

5.1.3 Further Endpoints

[redacted]



5.2 ASSESSMENT OF EFFICACY

Not applicable, there are no efficacy endpoints.

5.3 ASSESSMENT OF SAFETY

These assessments are applicable throughout the trial.

5.3.1 Physical examination

Physical examination includes assessment of heart, lung, abdomen and measurement of weight. Height will be measured at Visit 1. Abnormal finding at the time of screening will be recorded as baseline conditions on the appropriate eCRF page. New abnormal findings or worsening of baseline conditions detected at 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, with platelet count, haemoglobin 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 and thyroid stimulating hormone (TSH), serum albumin (if required for liver assessment), Creatinine Clearance (according to Cockcroft-Gault formula)
- Coagulation: International normalised ratio (INR) and partial thromboplastin time (PTT), Prothrombin Time.
- Urine: pregnancy testing.

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

Laboratory analysis during main visits will be done using central laboratory services. Venous whole blood will be collected in appropriate syringes provided by the sponsor through the assigned central laboratory. 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 elevation, close monitoring must be ensured by the Investigator (section 4.2.1.3).

Renal Function Measurements
CrCl will be calculated using the Cockcroft-Gault formula, as follows:

- For creatinine in µMol/L:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \times 1.23 \ (\times 0.85 \text{ if female})}{\text{serum creatinine [µMol/L]}}$$

- For creatinine in mg/dL:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$$

Please refer to Section 3.8.1 for guidance if a patient has started IMP and their CrCl is <30mL/min.

5.3.4 Electrocardiogram

ECGs are to be conducted with site equipment as specified in flowchart 1 and flowchart 2. Changes should be examined, compared to previous test, and assessed for clinical relevance. Clinically relevant findings at Visit 1 will be recorded as baseline conditions, new abnormal findings thereafter will be recorded as adverse events.

5.3.5 Spirometry

Spirometry (FVC measurements) is to be conducted with site equipment as specified in flowchart 1 and flowchart 2. Changes should be examined, compared to previous test, and assessed for clinical relevance. Clinically relevant findings at Visit 1 will be recorded as baseline conditions, new abnormal findings thereafter will be recorded as adverse events.

5.3.6 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 whilst they are taking study treatment. The diary will be used to prompt patient recollection during adverse event and medication compliance discussions at clinic visits. A dosing card will also be provided to the patient so they are aware of what dosing they should complete each day (one for each group). A copy of the diary and dosing cards will be provided in the ISF.

5.3.7 Assessment of adverse events

5.3.7.1 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.

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.

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.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

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

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

The following are considered as AESIs:

Adverse events relating to gastrointestinal perforation

and

Hepatic injury

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 via the RDC-system.

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**, **nausea** and **vomiting** AEs should be classified and recorded in the (e)CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R10-4848):

Table 5.3.7:1 CTCAE Categorization (R10-4848)

CTCAE Grade	Diarrhoea	Nausea	Vomiting
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Loss of appetite without alteration in eating habits	1-2 episodes (separated by 5 minutes) in 24 hours
2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Oral intake decreased without significant weight loss, dehydration or malnutrition	3-5 episodes (separated by 5 minutes) in 24 hours
3	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	≥6 episodes (separated by 5 minutes) in 24 hours ; tube feeding, TPN or hospitalization indicated
4	Life-threatening consequences; urgent intervention indicated	Not applicable	Life threatening consequences; urgent intervention indicated
5	Death	Not applicable	Death

Causal relationship of AEs
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.
Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

5.3.8 Adverse event collection and reporting

AE Collection:
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 the end of the REP (for this trial it will be classed as 28 days after the end of the PK evaluation period):
  - all AEs (non-serious and serious) and all 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.

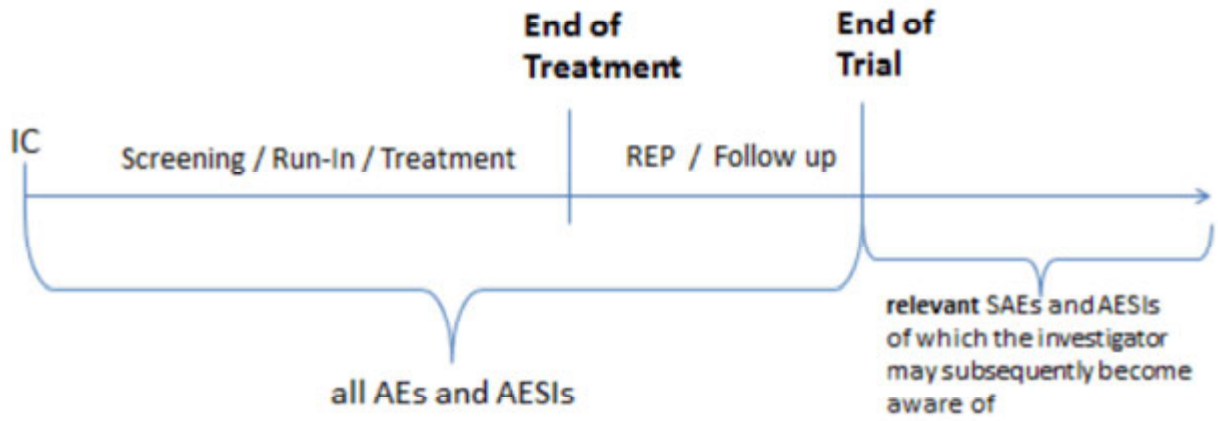


Figure 5.3.8:1 Adverse Event Collection and Reporting

The REP is defined as 28 days after the last trial medication application (for this trial it will be classed as 28 days after the end of the PK evaluation period; this is a general diagram and there will be no run-in period in this trial. Treatment will be classed as the PK evaluation period). 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.

Information required:
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drugs. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drugs.

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 might occur in a study. Once a subject has been enrolled into the clinical trial after having taken trial medication the investigator must report any drug exposure during pregnancy which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form to the Sponsor's unique entry point.

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If

there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Plasma concentration monitoring of pirfenidone, nintedanib, [redacted] will be performed in order to characterize any potential drug-drug interaction between pirfenidone and nintedanib (see Section 10.2).

Date and exact time points of plasma sampling and drug intake at the clinical site will be documented in the eCRFs by the medical personnel.

5.4.2 Methods of sample collection

A detailed description of sample collection and handling is provided in the Lab Manual in the ISF. For quantification of drug plasma concentrations of pirfenidone, nintedanib (BIBF 1120) and its metabolites [redacted], 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 3 vials (nintedanib, pirfenidone and one back-up sample).

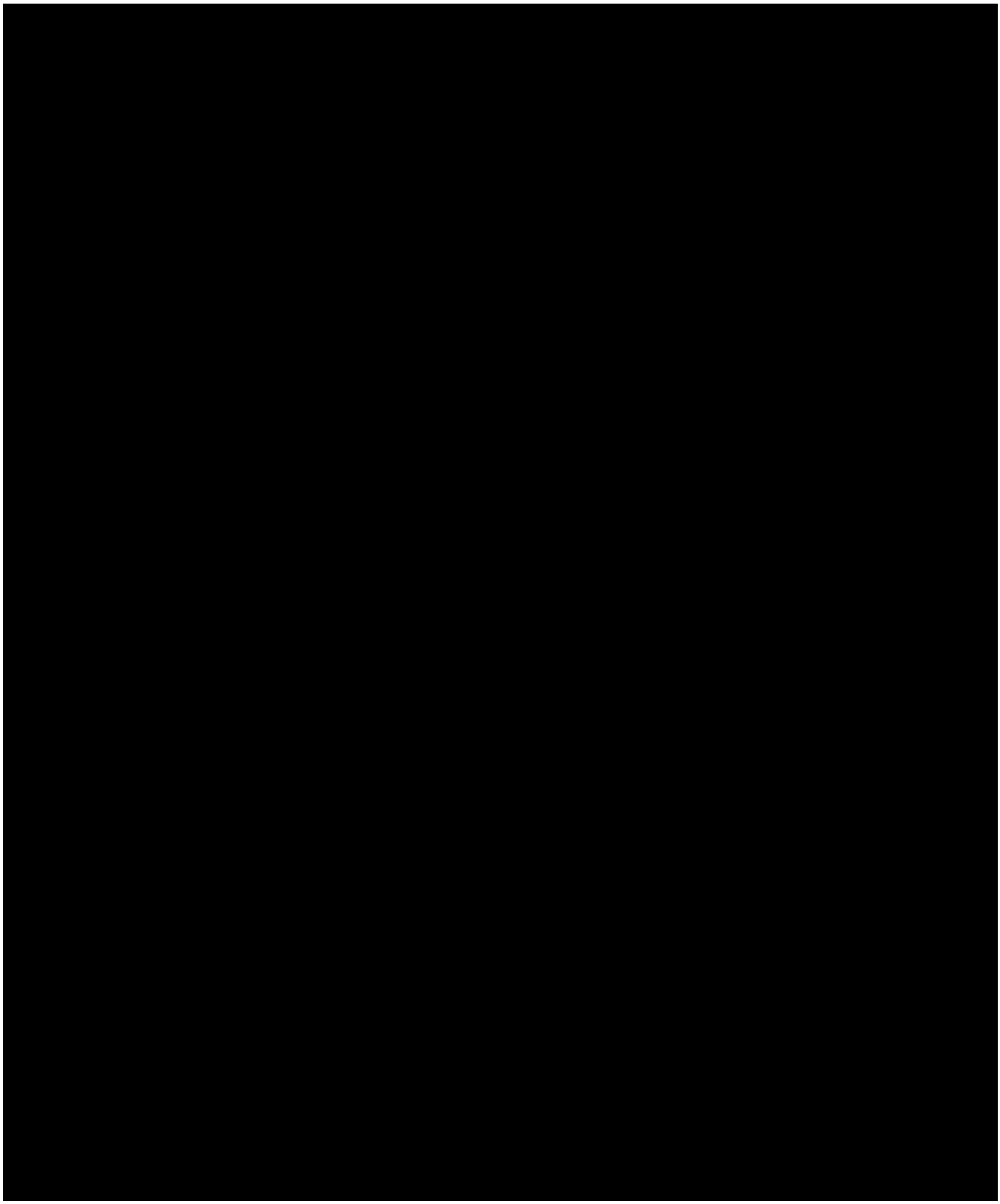
5.4.3 Analytical determinations

Nintedanib (in form of its free base BIBF 1120 BS), its metabolites [redacted]) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem mass spectrometry (LC-MS/MS). Pirfenidone plasma concentrations will be determined by a validated HRCT-MS/MS assay.

The procedures and specifications of the analytical method are available at the bioanalytical site [redacted])

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

[redacted]



5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted in the trial are using standard methods.

The pharmacokinetic parameters and measurements outlined in section 5.4 are generally used as measurements to assess drug exposure.

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 washout of restricted medications.

The study will consist of three sequential periods; a screening period, a PK evaluation period, and the follow-up period.

Screening will be up to 4 weeks (28 days) in duration. The PK evaluation period will be 24 days in Group 1 and 16 days in Group 2 plus a follow up period of 28 days.
All patients are to adhere to the visit schedule as outlined in flowchart 1 and flowchart 2. Some flexibility is allowed in scheduling the visits according to the visit time windows specified. The trial medication dispensed allows for these time windows. All deviations from the planned schedule will be documented. If any visit is to be rescheduled, subsequent visits should follow the previous visit date schedule. 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 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.

Visit 1

- Informed consent

After informed consent is obtained, the following procedures will be performed:

- Patient demographics
- Medical history, including pre-existing conditions
- Assessment of inclusion/exclusion criteria
- Drug and alcohol test performed at site
- Physical examination including height and weight
- Vital signs
- Blood sample for laboratory tests (Section 5.3.3)
- Urine sample for pregnancy test as required for women of childbearing potential
- 12 Lead ECG using standard site equipment
- Spirometry using standard site equipment
- Register screening by emailing the form provided in the ISF to the Sponsor.
- Assess adverse events since informed consent (if obtained on a previous date)

- Review of concomitant therapy including previous medication taken within the last three months. Dose of all medication to be recorded.
- Schedule next visit to occur within 28 days.

6.2.2 Treatment period(s)

Group 1
The PK evaluation period for Group 1 is a minimum of 24 days plus 28 days follow-up and begins at Visit 2.

Visit 2 Day 1
The patient should attend the clinic at approximately 07:00 so that the following assessments can be started before breakfast is given:

- Review concomitant therapy and any adverse events since screening and throughout the day at regular intervals.
- A drug and alcohol test will be done at the clinic.
- Physical examination and vital signs.
- Urine pregnancy test for women of childbearing potential.
- Spirometry
- Reassessment of inclusion/exclusion criteria.
- Pre-dose PK samples should be taken according to PK Flowchart (Group 1; this should be taken prior to the other blood samples).
- [redacted]
- Registration of treatment start by emailing the form provided in the ISF to the sponsor.
- One 150 mg nintedanib capsule should be given to the patient at 08:00 during breakfast (See PK Flowchart - Group 1).
- PK samples should be taken according to PK Flowchart (Group 1).
- The patient should be given lunch at 12:00 and a snack at 16:00.
- After the 10-hour PK time point PK collection, the patient can leave the clinic and return to the clinic the next day.

Visit 2 Day 2

- The patient must return to the clinic the next morning (Visit 2 Day 2) for the 24 hour time point at 07:55 (See PK Flowchart – Group 1).
- AEs and concomitant medications should also be assessed.
- Dispense two wallets of pirfenidone and instruct the patient to begin the uptitration of pirfenidone, the first dose should be given at the clinic with a snack.
- Provide dosing instructions regarding uptitration to the patient.
- Dispense patient diary.
- Schedule Visit 3 for Day 23.
- Other assessments listed for Visit 2 in the PK Flowchart are conducted at Day 1.

Phone call Day 15
At the end of the planned uptitration, there will be a phone call made to the patient, the following assessments should be covered:

- Assessment of adverse events.
- Review concomitant therapy including dose.
- Remind patient to uptitrate to the full dose of three capsules three times a day from the second wallet of pirfenidone. If the patient is not tolerating the full dose then the patient has a six-day time window to reach full dose for 7 consecutive days. If the patient is not tolerating the uptitration then refer to Figure 4.1.4:1 for instructions.
- Remind patient of Visit 3 scheduled for Day 23.
- Remind patient not to take morning dose of study medication on the day of Visit 3 and to bring their study medication with them to the clinic and also the diary card.

Visit 3 Day 23
Once the patient has been on stable, full dose pirfenidone for 7 days (a 6 day window is allowed to ensure 7 consecutive days) they will return to clinic for the next PK day.

The patient should attend the clinic at approximately 07:00 so that the following assessments can be started before breakfast is given:

- Physical examination and vital signs.
- Urine pregnancy test for women of childbearing potential.
- Blood sample for laboratory tests (Section 5.3.3)
- Pre-dose PK samples should be taken according to PK Flowchart (Group 1, this should be taken prior to the other blood samples).
- [redacted]
- Spirometry.
- Review concomitant therapy and any adverse events since previous visit and throughout the day at regular intervals.
- Patients will return all unused medication. Medication compliance will be assessed by counting returned (unused) capsules.
- The patient will return the diary card and this will be reviewed to check that the patient has received seven consecutive, stable days of treatment.
- One 150mg nintedanib capsule and three 267 mg pirfenidone capsules should be given to the patient at should be given to the patient at 08:00 during breakfast (See PK Flowchart – Group 1).
- PK samples should be taken according to PK Flowchart (Group 1).
- The patient should be given lunch at 12:00.
- Three 267 mg pirfenidone capsules will be given to the patient at 14:00 along with a snack.
- A snack will also be given to the patient at 16:00.
- After the PK time point at 18:00, the patient can leave the clinic.
- The patient should take the final dose of three 267 mg pirfenidone capsules at home at approximately 20:00 with food and a glass of water.

Visit 3 Day 24

- The patient must return the next morning (Visit 3 Day 24) for the 24 hour PK time point at 07:55 the next day.
- AEs and concomitant medications should also be assessed.
- Other assessments listed for Visit 3 in the PK Flowchart are conducted at Day 23
- No study drugs are given.
- Remind patient of PK FU visit scheduled for 28 days after this visit.

PK Follow-up/ End of Trial

The patient should return to the clinic 28 days or more after Visit 3 Day 24 for their PK Follow-up/ End of Trial Visit as detailed in section 6.2.3.

Group 2

The PK evaluation period for this group is for a minimum of 16 days plus 28 days follow-up and begins at Visit 2.

Visit 2 Day 1

- Review concomitant therapy and any adverse events since screening.
- A drug and alcohol test will be done at the clinic.
- Physical examination and vital signs.
- Urine pregnancy test for women of childbearing potential.
- Spirometry
- Reassessment of inclusion/exclusion criteria.
- [redacted]
- Registration of treatment start by emailing the form provided in the ISF to the sponsor.
- No PK samples are taken on this day.
- Dispense two wallets of pirfenidone and instruct the patient to take 801mg tid, the first dose should be given at the clinic with food and a glass of water.
- Provide patient with dosing instructions.
- Dispense diary.
- Remind patient of Visit 3a scheduled for Day 8.

Visit 3a Day 8

Once the patient has been on stable, full dose pirfenidone for 7 days (a 3 day window is allowed to ensure 7 consecutive days) they will return to clinic for the first PK day.

The patient should attend the clinic at approximately 07:00 so that the following assessments can be started before breakfast is given:

- Physical examination and vital signs.
- Urine pregnancy test for women of childbearing potential.
- Blood sample for laboratory tests (Section 5.3.3)

- Pre-dose PK samples should be taken according to PK Flowchart (Group 2, this should be taken prior to the other blood samples).
- [redacted]
- Spirometry.
- Review concomitant therapy and any adverse events since previous visit and throughout the day at regular intervals.
- Patients will return all unused medication. Medication compliance will be assessed by counting returned (unused) capsules.
- The patient will return the diary card and this will be reviewed to check that the patient has received seven consecutive, stable days of treatment.
- Three 267 mg pirfenidone capsules should be given to the patient at 08:00 during breakfast (See PK Flowchart – Group 2).
- PK samples should be taken according to PK Flowchart (Group 2).
- The patient should be given lunch at 12:00.
- Three 267 mg pirfenidone capsules will be given to the patient at 14:00 with a snack.
- After the PK time point at 14:00, the patient can leave the clinic.
- The patient should be given the remaining pirfenidone from the previous visit and also one new wallet of pirfenidone and one bottle of nintedanib to take home.
- The patient should take the final dose of three 267 mg pirfenidone capsules at home at approximately 20:00 with food and a glass of water.
- The patient should be reminded to take pirfenidone and nintedanib from Day 9 at home for seven consecutive days.
- Remind patient of Visit 3b scheduled for Day 16.

Once the patient has received nintedanib and pirfenidone for 7 consecutive days, they will return to clinic for Visit 3b for the next PK day. If the patient needs to dose reduce the pirfenidone then this is allowed see Section 4.1.4.

Visit 3b Day 16
Once the patient has been on stable, pirfenidone and nintedanib for 7 days (a 3 day window is allowed to ensure 7 consecutive days) they will return to clinic for the next PK day.

The patient should attend the clinic at approximately 07:00 so that the following assessments can be started before breakfast is given:

- Physical examination and vital signs.
- Urine pregnancy test for women of childbearing potential.
- Blood sample for laboratory tests (Section 5.3.3)
- Predose PK samples should be taken according to PK Flowchart (Group 2, this should be taken prior to the other blood samples).
- [redacted].
- Spirometry.
- Review concomitant therapy and any adverse events since previous visit and throughout the day at regular intervals.

- Patients will return all unused medication. Medication compliance will be assessed by counting returned (unused) capsules.
- The patient will return the diary card and this will be reviewed to check that the patient has received seven consecutive, stable days of treatment.
- One 150mg nintedanib capsule and three 267 mg pirfenidone capsules should be given to the patient at 08:00 during breakfast (See section 10.2; this will be the last study medication that the patient will receive in the PK evaluation period of the trial).
- PK samples should be taken according to PK Flowchart (Group 2).
- The patient should be given lunch at 12:00.
- After the PK time point at 14:00, the patient can leave the clinic.
- No study drugs are given.
- Remind patient of PK FU visit scheduled for 28 days after this visit.

PK Follow-up/ End of Trial
The patient should return to the clinic 28 days or more after Visit 3b Day 16 for their PK Follow-up/ End of Trial Visit as detailed in section 6.2.3.

6.2.3 Follow Up Period and Trial Completion

A minimum of 28 days after the end of treatment all patients who started treatment are asked to come for a final follow up visit.

Follow up visit:
Assessments at this visit include:

- Physical examination and vital signs.
- [redacted]
- Urine sample for pregnancy test for women of childbearing potential.
- ECG.
- Review concomitant therapy and any adverse events.
- Spirometry.
- At the end of this visit the patient will have concluded their time in the trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The objectives of the current study are to investigate the effect of steady state pirfenidone on the pharmacokinetics of nintedanib and its metabolites following oral administration of 2403 mg/day pirfenidone and to investigate the effect of steady state nintedanib on the pharmacokinetics of pirfenidone at steady state following oral administration of 150 mg bid nintedanib.

This open-label, multiple-dose study consists of two groups. In total, 34 patients will participate in the trial, 16 patients in group 1 and 18 patients in group 2. Within each group, there will be a fixed sequence design: in group 1, a single oral dose of nintedanib of 150mg will be administered alone (reference treatment, R1) and in combination with 801mg tid pirfenidone (test treatment, T1; cf. Section 3.1) and in group 2, 7 days of 801mg tid pirfenidone will be administered alone (reference treatment, R2) and in combination with 7 days 150mg bid of nintedanib (test treatment, T2).

For each comparison between test and reference treatment, the statistical model used will be an ANOVA (analysis of variance) model on the logarithmic scale (see Section 7.3.1)

7.2 NULL AND ALTERNATIVE HYPOTHESES

For the comparisons described in Section 7.1, there is no hypothesis to be tested in a confirmatory sense. Instead, the ratios of adjusted geometric means (test/reference) for the primary PK endpoints and their two-sided 90% confidence intervals (CIs) will be provided.

7.3 PLANNED ANALYSES

The statistical analysis will be based on the following populations:

Treated Set:

The treated set consists of patients who receive at least one dose of study medication.

PK analysis set:

PK concentrations and parameters of a subject will be included in the analysis if they are not flagged for exclusion, e.g. due to PK non-evaluability or a protocol violation relevant to the evaluation of PK endpoints, which will be decided no later than in the Report Planning Meeting.

A PK concentration or parameter will be considered non-evaluable, if for example

- the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment for this treatment period (median t_{max} is to be determined excluding the subjects experiencing emesis),
- a pre-dose concentration is > 5% of the C_{max} value of that subject.

Relevant protocol violations may be for example

- Administered dose (amount of drug) is not in compliance with the protocol, i.e. is too low or too high
- Restricted medication use

Criteria for important protocol violations may be updated and more details will be provided in the TSAP.

The PK analysis set (PKS) includes all subjects in the treated set who provide at least one primary or secondary PK endpoint value not excluded according to the description above. Thus, a subject will be included in the PKS, even if he/she contributes only one PK endpoint value for one of the two PK days to the statistical assessment. The PKS will be used for the primary and secondary endpoint analyses.

7.3.1 Primary endpoint analyses

For each comparison between test and reference treatment, the statistical model used will be an ANOVA (analysis of variance) model on the logarithmic scale. Thus, prior to fitting the ANOVA model, the PK parameters described in section 5.1.1 will be log transformed (natural logarithm). The difference between the expected means for log (T)-log(R) will be estimated by the difference in the corresponding Least Squares Means (point estimate).

Furthermore, the two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test treatment and response under reference treatment.
The above mentioned ANOVA model will include effects accounting for the following sources of variation: 'subject' and 'treatment'. The effect 'subject' will be considered random, whereas the 'treatment' effect will be considered fixed. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where
y_{km} = logarithm of response ($AUC_{0\text{-}tz}$ / C_{max} for group 1 and $AUC_{0\text{-}tau}$ / $C_{max,ss}$ for group 2) measured on subject m receiving treatment k
μ = the overall mean,
s_m = the effect associated with the m^{th} subject
τ_k = the k^{th} treatment effect, k = 1, 2,
e_{mk} = the random error associated with the m^{th} subject who received treatment k.

All patients from the PKS will be included in the analysis of relative bioavailability (see Section 7.3).

As a sensitivity analysis, the model above will be fitted with the "subject" as a fixed effect.

7.3.2 Secondary endpoint analyses

The secondary PK parameters described in Section 5.1.2 will be analysed as described for the primary PK endpoints.

7.3.3 Further endpoint analyses

[redacted]

7.3.4 Safety analyses

All treated patients will be included in the safety analysis.

All adverse events with an onset between start 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 and displayed by group (group 1 and group 2).

AEs recorded prior to intake of trial medication will be assigned to 'screening', those between first intake until the last intake of trial medication plus 28 days will be assigned to the 'on-treatment' period. Events occurring after the on-treatment period will be summarized as 'follow-up' period and those after the end of trial visit will be assigned to 'post-study' period.

Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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 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. Laboratory data will be described with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Sections 5.1.1, 5.1.2 and 5.1.3 will be calculated according to the relevant BI internal procedures.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

The PKS will be used for the primary and secondary endpoint analyses.

The following descriptive statistics will be calculated for plasma concentrations and PK parameters: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The exception to this is [redacted] where only median, minimum and maximum will be calculated. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. Thereafter, the individual values, as well as the descriptive statistics, will be reported with three significant digits in the clinical trial report.

For handling of missing data, please refer to Section 7.5.

Analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software, version 9.4 (or later).

7.3.6 Biomarker analyses

[redacted]

7.4 INTERIM ANALYSES

Interim analysis will be performed if required by the regulatory agencies.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

For partial or missing AE onset and/or end dates, BI internal rules will be followed for imputation (see Reference Document 001-MCG-156_RD01 “Handling of missing and incomplete AE dates”).

7.5.2 Plasma concentration - time profiles

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analyzed), and BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase). 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, NOA are included).

7.5.3 Pharmacokinetic parameters

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored. Every effort will be made to include all concentration data in an analysis. If not possible, a case-to-case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are 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. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

Not applicable.

7.7 DETERMINATION OF SAMPLE SIZE

The primary endpoints for this study upon which sample size calculations have been based are AUC0-tz and Cmax of nintedanib for group 1 and AUCτ,ss and Cmax,ss of pirfenidone for group 2.

It is planned to have at least a total of 12 patients with both evaluable PK assessments (see Section 7.3) per group in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference; T/R) can be expected with 95% probability. Precision is defined as the ratio of upper confidence interval limit to the relative BA estimate for both groups. Note that the precision is independent of the actual ratio of geometric means.

In the case that less than 12 patients have both PK assessments, the Trial Clinical Monitor together with the Trial Pharmacokineticist and the Trial Statistician will decide if and how many patients will be additionally included.

The observed intra-individual geometric coefficient of variation (gCV) for nintedanib in previous trials in healthy volunteers (U13-1925-01; U13-1478-01) was roughly 30% for C_{max} and 20% for $AUC_{0\text{-}tz}$.

For three assumptions on the intra-individual gCV of nintedanib (taking into account that the variability will be higher in patients than in healthy volunteers), Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (T/R) for nintedanib. For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of the ratios T/R of geometric means.

Table 7.7:1 Precision and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different intra-individual gCVs and ratios (T/R) in a fixed design trial (N=12)

Intra-individual gCV [%]	Ratio[1] [%]	Precision upper CL/Ratio	90% CI [%]
30	100	1.33	75 – 133
	110	1.33	82 – 147
35	100	1.40	72 – 140
	110	1.40	79 – 153
40	100	1.42	69 – 146
	110	1.42	75 – 161

1) Ratio of the geometric means (test/reference) for a PK endpoint defined by exp(μT)/exp(μR)

The expected 90% confidence interval limits in the table were derived by
$CI\ limit_{upper,lower} = \exp(\ln(\theta) \pm \omega)$,
with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale.

Accounting for up to 4 dropouts (around 25%), a total of 16 patients (12 + 4) will be entered in the trial.

The observed total gCV in a previous parallel group trial in patients (c01787180-03) was roughly up to 40% for $C_{max,ss}$ and 40% for $AUC_{\tau,ss}$ for pirfenidone, whereby the most relevant scenarios in this trial yielded total gCVs of up to 31% for both parameters. The corresponding intra-individual gCVs can be estimated based on an assumption on the correlation between two responses of the same subject.

For three assumptions on the total gCV of pirfenidone, and assuming a ratio T/R of geometric means of 100%, Table 7.7: 2 provides an overview of the achievable precision for estimating the ratio of geometric means (T/R) for pirfenidone. For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of the correlation between two responses of the same subject.

Table 7.7:2 Precision and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R; assumed to be 100%) for different total gCVs and intro-subject correlations in a fixed sequence design trial (N=12)

Total gCV [%]	Correlation	Intra-individual gCV [%]	Precision upper CL/Ratio[1]	90% CI [%]
30	0.5	21	1.23	82 – 123
	0.7	16	1.17	85 – 117
35	0.5	24	1.27	79 - 127
	0.7	19	1.19	83 – 120
40	0.5	28	1.31	77 – 131
	0.7	21	1.21	81 – 123

1) Ratio of the geometric means (test/reference) for a PK endpoint defined by $\exp(\mu_T)/\exp(\mu_R)$

Accounting for up to 6 dropouts (around 30%), a total of 18 patients (12 + 6) will be entered in the trial.

For these calculations the MOC3 routine from commercial software nQuery Advisor® 7.0 (Statistical Solutions, Ltd., Cork, Ireland (R15-1331) was used.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonized standards for Medical Devices (ISO 14155-01 and ISO 14155-02).

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*.

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.

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."

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

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

8.3.1 Source documents

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

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

8.4 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 metical 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.

8.5 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.6 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 nintedanib this is the IB and pirfenidone this is the SmPC. The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for trial design, or invasive procedures.

8.7 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.

8.8 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.

8.9 END OF TRIAL

The end of the trial is defined as last patient out (see section 6.2.3). The IEC / competent authority in the participating EU member state will be notified about the end or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P08-08684 Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig WJ BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 68 (12), 4774 - 4782 (2008)

P11-00203 Reck M, Kaiser R, Eschbach C, Stefanic M, Love J, Gatzemeier U, Stopfer P, Pawel J von. A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. Ann Oncol 22 (6), 1374 - 1381(2011)

P11-07084 Raghu G, et al, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183 (6), 788 - 824 (2011)

P11-10116 Ledermann JA, Hackshaw A, Kaye S, Jayson G, Gabra H, McNeish I, Earl H, Perren T, Gore M, Persic M, Adams M, James L, Temple G, Merger M, Rustin G. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. 45th Ann Mtg of the American Society of Clinical Oncology (ASCO), Orlando, 29 May - 2 Jun 2009 J Clin Oncol 29 (28), 379838 (2011)

P11-11216 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klueglich M, Bois RM du Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 365 (12), 1079 - 1087 (2011)

P12-03241 King TE, Pardo A, Selman M Idiopathic pulmonary fibrosis.Lancet 378 (9807), 1949 - 1961 (2011)

P12-06085 Idiopathic Pulmonary Fibrosis Clinical Research Network Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 366 (21), 1968 - 1977 (2012)

P13-06268 Eisen T, Shparyk Y, Jones R, MacLeod NJ, Temple G, Finnigan H, Kaiser R, Studeny M, Loembe AB, Bondarenko I Phase II efficacy and safety study of nintedanib versus sunitinib in previously untreated renal cell carcinoma (RCC) patients. 49th Ann Mtg of the American Society of Clinical Oncology. (ASCO), Chicago, 31 May - 4 Jun 2013 J Clin Oncol 31 (Suppl), Abstr 4506 (2013)

P13-12693 Yen CJ, Kim TY, Feng YS, Chao Y, Lin DY, Studeny M, Hocke J, Huang DCL, Ryoo BY, Cheng AL Efficacy and safety of nintedanib versus sorafenib in Asian patients with advanced hepatocellular carcinoma: a randomised phase II trial. 38th Ann Cong of the European Society for Medical Oncology (ESMO), Amsterdam, 27 Sep - 1 Oct 2013 (Poster)

P14-02860 Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B Anti-fibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor, nintedanib, in experimental models of lung fibrosis. J Pharmacol Exp Ther 349, 209 - 220 (2014)

P14-07514 Richeldi L, et al, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 370 (22), 2071 - 2082 (2014)

P14-07665 Idiopathic Pulmonary Fibrosis Clinical Research Network Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis.N Engl J Med 370 (22), 2093 - 2101 (2014)

P14-08020 Scagliotti GV, Leighl NB, Nowak AK, Pavlakis N, Popat S, Sorensen JB, Barrueco J, Kaiser R, Loembe AB, Mueller M, Wangenheim U von, Reck M Nintedanib plus pemetrexed/cisplatin followed by maintenance nintedanib for unresectable malignant pleural mesothelioma (MPM): an international, multicenter, randomized, double-blind, placebo-controlled phase II study. 50th Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 30 May - 3 Jun 2014

P14-16496 Wuyts WA, Antoniou KM, Borensztajn K, Costabel U, Cottin V, Crestani B, Grutters JC, Maher TM, Poletti V, Richeldi L, Vancheri C, Wells AU Combination therapy: the future of management for idiopathic pulmonary fibrosis? Lancet Respir Med 2, 933 - 942 (2014)

P14-17347 Ogura T, Taniguchi H, Azuma A, Inoue Y, Kondoh Y, Hasegawa Y, Bando M, Abe S, Mochizuki Y, Chida K, Klueglich M, Fujimoto T, Okazaki K, Tadayasu Y, Sakamoto W, Sugiyama Y. Safety and pharmacokinetics of nintedanib and irfenidone in idiopathic pulmonary fibrosis. Eur Respir J, (2014)

P15-01243 Spagnolo P, Wells AU, Collard HR. Pharmacological treatment of idiopathic pulmonary fibrosis: an update. Drug Discov Today, (2015)

R06-2002 Macintyre N, Crapo RO, Viegi G, Johnson DC, Grinten CPM van der, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26 (4) :720 -735

R06-2070 Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, Sato A, Kudoh S, Research Group for Diffuse Lung Diseases in Japan, Raghu G Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis.Am J Respir Crit Care Med 171, 1040 – 1047 (2005)

R09-1400 European Medicines Agency (EMEA) ICH topic M3 (R2) non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals: step 4: note for guidance on non-clinical safety studies for the conduct of human clinical trials

and marketing authorization for pharmaceuticals (June 2009, CPMP/ICH/286/95). http://www.emea.europa.eu (2009)

R10-4316 Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nukiwa T, Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 35 (4), 821 - 829 (2010)

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

R11-4827 Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, Bois RM du, CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 377, 1760 - 1769 (2011)

R11-5086 Thabut G, Christie JD, Ravaud P, Castier Y, Dauriat G, Jebrak G, Fournier M, Leseche G, Porcher R, Mal HSurvival after bilateral versus single-lung transplantation for idiopathic pulmonary fibrosis. Ann Intern Med 151 (11), 767 - 774 (2009)

R12-2785 Keating D, Levvey B, Kotsimbos T, Whitford H, Westall G, Williams T, Snell G. Lung transplanation in pulmonary fibrosis: challenging early outcomes counterbalanced by surprisingly good outcomes beyond 15 years. Transplant Proc 41, 289 - 291 (2009)

R12-2786 Kim DS, Collard HR, King TE Classification and natural history of the idiopathic interstitial pneumonias. Proc Am Thorac Soc 3, 285 - 292 (2006)

R12-3474 Kotloff RM, Thabut G Lung transplantation. Am J Respir Crit Care Med 184, 159 - 171 (2011)

R12-3676 McCurry KR, Shearon TH, Edwards LB, Chan KM, Sweet SC, Valapour M, Yusen R, Murray S, Lung transplantation in the United States, 1998 - 2007. Am J Transplant 9, 942 - 958 (2009)

R12-4811 Schaefer CJ, Ruhrmund DW, Pan L, Seiwert SD, Kossen K. Antifibrotic activities of pirfenidone in animal models. Eur Respir Rev 20 (120), 85 - 97 (2011)

R14-2103 King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, ASCEND Study Group A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 370 (22), 2083 - 2092 (2014)

R15-1331 Elashoff JD. nQuery Advisor version 7.0 user's guide. http://www.statsols.com/wp-content/uploads/2013/10/nQ70_version2_manual.pdf (access date: 20 March 2015) ; Los Angeles: Statistical Solutions 2007

R94-1408 Quanjer PH et al, Lung volumes and forced ventilatory flows.Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal.Official Statement of the European Respiratory Society, Eur Respir J 1993; 6 (Suppl 16), 5-40

R94-1529 Chow SC, Liu JP, Design and Analysis of Bioavailability and Bioequivalence Studies. New York: Marcel Dekker Inc (1992)

R99-1243 Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R, Transsection of the oesophagus for bleeding oesophageal varices. Br J Surg 60 (8), 646 - 649 (1973)

R99-1244 Trey C, Burns DG, Saunders SJ, Treatment of hepatic coma by exchange blood transfusion, Postgraduate Medical Sem, 15 Sep 1965, N Engl J Med 274 (9), 473 - 481 (1966)

9.2 UNPUBLISHED REFERENCES

U07-1248 [redacted] Investigator's brochure: BIBF 1120, Indication:Idiopathic Pulmonary Fibrosis. 1199.P3.

U12-2505-01 [redacted], Ph.D. The effect of pirfenidone on selective in vitro tyrosine kinase activity assays. 07 December 2011

U13-1478-01 [redacted]. Relative bioavailability of a single oral dose of nintedanib given alone and in combination with multiple oral doses of rifampicin in healthy male volunteers (an open-label, two-period, fixed-sequence Phase I trial). 08-Aug-2013

U13-1925-01 [redacted]: Relative bioavailability of nintedanib given alone and in combination with ketoconazole at steady state in healthy male volunteers (an open-label, randomised, two-way cross-over clinical Phase I study). Study 1199.161. 4 July 2013

c01787180-03 [redacted] double-blind, randomised, placebo-controlled (within a dose group) study to evaluate safety and pharmacokinetics of multiple rising doses of BIBF 1120 at 50 mg b.i.d. (14 days), 100 mg b.i.d. (14 days), and 150 mg b.i.d. (28 days) po, on top of standard medical care with stratification according to pirfenidone use, in Japanese patients with idiopathic pulmonary fibrosis. Study no 1199.31. Clinical Report 5 Feb 2015

001-MCG-156_RD01 Handling of missing and incomplete AE dates

10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

For the calculation of pharmacokinetic parameters, only concentrations within the validated concentration range will be used. The actual sampling times will be used. For predose samples, the actual sampling time will be set to zero.

Noncompartmental pharmacokinetic parameters will be determined using WinNonlin or another validated program.

AUC_{t1-t2}: The areas under the curve spanning various time intervals will be calculated using the linear up/log down algorithm. If a drug concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the drug concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_2 \geq C_1$):
The area of the trapezoid between the two data points (t_1, C_1) and (t_2, C_2) will be computed by:

$$AUC_{t1-t2} = 0.5 \times (t_2 - t_1) \times (C_1 + C_2)$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_2 < C_1$):
The area of the trapezoid between the two data points (t_1, C_1) and (t_2, C_2) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_2 - C_1)}{\ln(C_2 / C_1)}$$

C_{max} and t_{max}: Individual C_{max} and t_{max} values will be directly determined from the plasma concentration time profiles of each subject. If the same C_{max} concentration occurs at different time points, t_{max} is assigned to the first occurrence of C_{max}.

Estimation of λ_z: The apparent terminal rate constant λ_z will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles. The log-linear profiles, which include the regression line through the terminal points, will be checked via visual inspection, and it will be determined whether the regression appropriately represents the terminal slope. Only data points that describe the terminal log-linear decline will be included in the regression. A minimum of three points will be used in the determination of λ_z. If the last concentration-time point increases, this time point may be included if the $t_{1/2}$ estimate is reasonable. If λ_z is not determinable then consequently only parameters not requiring λ_z will be reported. In addition, the lower ($t_{\lambda z, start}$) and upper ($t_{\lambda z, end}$) limit on time for values to be included in the calculation of λ_z will be listed.

$t_{1/2}$: The terminal half-life will be calculated from the terminal rate constant using the equation:

$$t_{1/2} = \frac{\ln 2}{\lambda_z}$$

%$AUC_{tz-\infty}$: The percentage of the $AUC_{0-\infty}$ will be obtained by extrapolation according to the following equation:

$$\%\,AUC_{tz-\infty} = \frac{AUC_{0-\infty} - AUC_{0-tz}}{AUC_{0-\infty}} \times 100$$

The parameter $\%AUC_{tz-\infty}$ is used to judge the reliability of the estimate for the parameter $AUC_{0-\infty}$.

MRT_{po}: The mean residence time after extravascular administration (MRT_{po}) will be calculated as follows:

$$MRT_{po} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

The area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) is calculated according to:

$$AUMC_{0-\infty} = AUMC_{0-tz} + \frac{C'_{tz} \times t_z}{\lambda_z} + \frac{C'_{tz}}{\lambda_z^2}$$

CL/F: The apparent clearance after extravascular administration will be determined according to the following equation:

$$CL/F = \frac{Dose}{AUC_{0-\infty}}$$

(F = absolute bioavailability factor)

V_z/F: The apparent volume of distribution during the terminal phase after extravascular administration (at steady state) will be determined according to the following equation:

$$V_z/F = \frac{CL/F}{\lambda_z}$$

The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$gMean = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$gCV(\%) = 100 \cdot \sqrt{\exp\left[Var(\ln(x_i))\right] - 1}$$

where

$$Var(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2$$

10.2 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

GROUP 1 – PK time points

Visit	Day	Window	Planned Time [h:min]	Approximate clock time of actual day [h:min]	Event and comment	PK_{blood} for nintedanib	PK_{blood} for pirfenidone
2	1		-1:00	7:00	Predose[1]	X	X
			0:00	8:00	Breakfast[2], Drug administration nintedanib[3]		
			0:30	8:30		X	
			1:00	9:00		X	
			2:00	10:00	Glass of water	X	
			3:00	11:00		X	
			4:00	12:00	Glass of water, Lunch	X	
			6:00	14:00		X	
			8:00	16:00	Snack	X	
			10:00	18:00		X	
	2		23:55	7:55		X	
			24:00	8:00	Snack, Drug administration of pirfenidone and begin uptitration[6]		
3	23	+6	527:00	7:00	Predose	X	X
			528:00	8:00	Breakfast[2], Drug administration nintedanib and pirfenidone		
			528:30	8:30		X	X
			529:00	9:00		X	X
			530:00	10:00	Glass of water	X	X
			531:00	11:00		X	X
			532:00	12:00	Glass of water, Lunch	X	X
			534:00	14:00	Snack, Drug administration pirfenidone[4,5]	X	X
			536:00	16:00		X	X
			538:00	18:00		X	X
	24		551:55	7:55		X	X

Footnotes Group 1

1. Predose PK sample can be taken prior to breakfast and administration of trial drugs.
2. Breakfast should consist of a continental breakfast and drug should be administered with the meal.
3. Single 150 mg dose of nintedanib given to the patient at the clinic with a glass of water.
4. On PK day 23, it is requested that the patient take their midday pirfenidone dose at 2pm so that there will be a 6 hour profile.
5. On Day 23, the evening dose of pirfenidone will be taken at home at approximately 20:00. This will be the last dose of pirfenidone taken.
6. The midday and evening doses of pirfenidone will be taken at home.

GROUP 2 – PK time points

Visit	Day	Window	Planned Time [h:min]	Approximate clock time of actual day [h:min]	Event and comment	PK_{blood} for nintedanib	PK_{blood} for pirfenidone
3a	8	+3	-1:00	7:00	Predose[1]	X	X
			0:00	8:00	Breakfast[2], Drug administration pirfenidone		
			0:30	8:30			X
			1:00	9:00			X
			2:00	10:00	Glass of water		X
			3:00	11:00			X
			4:00	12:00	Glass of water, Lunch		X
			5:55	13:55			X
			6:00	14:00	Snack, Drug administration pirfenidone[3] and dispense nintedanib[5]		
3b	16	+3	191:00	7:00		X	X
			192:00	8:00	Breakfast, Drug administration nintedanib and pirfenidone[4]		
			192:30	8:30		X	X
			193:00	9:00		X	X
			194:00	10:00	Glass of water	X	X
			195:00	11:00		X	X
			196:00	12:00	Glass of water, Lunch	X	X
			198:00	14:00		X	X

Footnotes Group 2

1. Predose PK sample can be taken prior to breakfast and administration of trial drugs.
2. Breakfast should consist of a continental breakfast and drug should be administered with breakfast.
3. On PK day 8, it is requested that the patient take their midday dose at 14:00 so that there will be a 6 hour profile. On PK day 16, this is not applicable, as the last pirfenidone dose is taken in the morning.
4. The last dose of pirfenidone and nintedanib during the PK evaluation period will be in the morning at 08:00.
5. The evening dose of pirfenidone will be taken at home. Dosing with nintedanib and pirfenidone will start on Day 9.

10.3 LUNG FUNCTION CRITERIA

At visit 1, FVC must fulfil the following criteria:

- 50% predicted of normal ≤ FVC of predicted normal

Predicted normal values will be calculated according to ESCS (R94-1408):

- Males: FVC predicted (L) = 5.76 x height (meters)- 0.026 x age (years) -4.34
- Females: FVC predicted (L) = 4.43 x height (meters)- 0.026 x age (years) -2.89

At visit 2, DLCO must fulfil the following criteria:

- 30% predicted of normal ≤ DLCO corrected for Hb < 80% predicted of normal

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.

DLCO corrected for haemoglobin (R06-2002):

- Males: DLCO corrected for Hb = DLCO measured x (10.22+Hb) /1.7Hb
- Females: DLCO corrected for Hb = DLCO measured x (9.38+Hb)/ 1.7Hb

where Hb is expressed in g·dL-1.

For decision on inclusion/ exclusion, DLCO results taken from the tests at visits 1 or 2, or during the screening period (visit 1 to visit 2) will be corrected for haemoglobin by the site. The haemoglobin sample does not need to be taken on the same day that the DLCO is performed. The haemoglobin value used can be from the central laboratory results or from a local result,

10.4 CHILD-PUGH CLASSIFICATION (R99-1243)

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1 point	**2 points**	**3 points**
Total bilirubin, µmol/l *(mg/dl)*	<34 *(<2)*	34-50 *(2-3)*	>50 *(>3)*
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	Absent	Slight	Moderate
Encephalopathy (grade)*	None	1 – 2	3 – 4

*According to Trey, Burns and Saunders (1966) R99-1244

Total Score:
Child-Pugh A: 5 or 6 points;
Child-Pugh B: 7–9 points;
Child-Pugh C: >9 points

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		29 October 2015
EudraCT number		2015-000732-15
BI Trial number		1199.229
BI Investigational Product(s)		Nintedanib
Title of protocol		Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study followed by nintedanib open label treatment)
To be implemented only after approval of the IRB / IEC / Competent Authority		✓
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Cover Page – BI Investigational Product(s) and Clinical Trial Protocol Synopsis – BI Investigational Product(s)
Description of change		Addition of Ofev® to identify the BI Investigational Product and finished product
Rationale for change		To ensure full identification of nintedanib (Ofev®)

Section to be changed		Cover Page – Trial Clinical Monitor
Description of change		[redacted] Phone : [redacted] Fax: [redacted] Has been changed to [redacted]

		[redacted] Phone : + Fax: + [redacted]
Rationale for change		Change in Trial Clinical Monitor

Section to be changed		Cover Page – Coordinating Investigator and Clinical Trial Protocol Synopsis – Coordinating Investigator
Description of change		[redacted] Phone: Fax: ([redacted] Has been changed to [redacted] Phone: Fax: [redacted]
Rationale for change		To provide the correct dialing format

Section to be changed		3.6 – Inclusion Criteria
Description of change		5. DLCO (corrected for Hb [visit 1]): 30%-79% predicted of normal (refer to Section 10.3) at visit 2 Has been changed to 5. DLCO (corrected for Hb [visit 1]): 30%-79% predicted of normal (refer to Section 10.3) at visit 2 (test can be performed at visits 1 or 2, or during the screening period).
Rationale for change		To clarify that the DLCO test can be performed either

		at visit 1 or visit 2, or at any point during the screening period (visit 1 to visit 2), rather than having to be done at visit 2. This change has been made to allow flexibility to the site and to the patient as the test results should be available prior to the patient receiving IMP. This is particularly important for the patients in Group 1 who are dosed early in the morning.

Section to be changed		3.7 – Exclusion Criteria
Description of change		14. Known hypersensitivity to nintedanib, pirfenidone or their excipients. Has been changed to 14. Known hypersensitivity to nintedanib, pirfenidone or their excipients; or to peanut or soya.
Rationale for change		To bring the exclusion criteria in line with the SPC for nintedanib, which states that nintedanib is contraindicated in patients with *"Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients listed in section 6.1."*

Section to be changed		3.8.1 – Removal of individual patients
Description of change		For potential drug induced liver injury (DILI) follow up requirements please see section 5.3.6.1. Has been changed to For potential drug induced liver injury (DILI) follow up requirements please see section 5.3.7.1
Rationale for change		Typo – incorrect section reference

Section to be changed		5.3.8 – Adverse Event Collection and Reporting
Description of change		Addition of a title and numbering for Figure 5.3.8:1 Adverse Event Collection and Reporting
Rationale for change		The figure did not previously have a number or title for the figure

Section to be changed		6.2.1 – Screening period

Description of change		• Blood sample for laboratory tests (Section 5.1.3) Has been changed to • Blood sample for laboratory tests (Section 5.3.3)
Rationale for change		To correct a typographical error with the link

Section to be changed		6.2.2 – Treatment Periods
Description of change		<u>Group 1</u> The PK evaluation period for Group 1 is a minimum of 24 days plus 28 days follow-up and begins at Visit 2. **Visit 2 Day 1** The patient should attend the clinic at approximately 07:00 so that the following assessments can be started before breakfast is given: • Reassessment of inclusion/exclusion criteria. • A drug and alcohol test will be done at the clinic. • Physical examination and vital signs. • Urine pregnancy test for women of childbearing potential. • Pre-dose PK samples should be taken according to PK Flowchart (Group 1; this should be taken prior to the other blood samples). • [redacted] • Registration of treatment start by emailing the form provided in the ISF to the sponsor. • One 150 mg nintedanib capsule should be given to the patient at 08:00 during breakfast (See PK Flowchart - Group 1). • PK samples should be taken according to PK Flowchart (Group 1). • Spirometry. • Review concomitant therapy and any adverse events since screening and throughout the day at regular intervals. • The patient should be given lunch at 12:00 and a snack at 16:00. • After the 10-hour PK time point PK collection,

		the patient can leave the clinic and return to the clinic the next day. Has been changed to <u>Group 1</u> The PK evaluation period for Group 1 is a minimum of 24 days plus 28 days follow-up and begins at Visit 2. **Visit 2 Day 1** The patient should attend the clinic at approximately 07:00 so that the following assessments can be started before breakfast is given: • Review concomitant therapy and any adverse events since screening and throughout the day at regular intervals. • A drug and alcohol test will be done at the clinic. • Physical examination and vital signs. • Urine pregnancy test for women of childbearing potential. • Spirometry • Reassessment of inclusion/exclusion criteria. • Pre-dose PK samples should be taken according to PK Flowchart (Group 1; this should be taken prior to the other blood samples). • [redacted] • Registration of treatment start by emailing the form provided in the ISF to the sponsor. • One 150 mg nintedanib capsule should be given to the patient at 08:00 during breakfast (See PK Flowchart - Group 1). • PK samples should be taken according to PK Flowchart (Group 1). • The patient should be given lunch at 12:00 and a snack at 16:00. • After the 10-hour PK time point PK collection, the patient can leave the clinic and return to the clinic the next day.
Rationale for change		The assessments have been re-ordered to ensure that the activities that need to be performed to ensure the inclusion & exclusion criteria can be assessed are done prior to IMP being given.

Section to be changed		6.2.2 – Treatment Periods
Description of change		Group 2 The PK evaluation period for this group is for a minimum of 16 days plus 28 days follow-up and begins at Visit 2. **Visit 2 Day 1** • Reassessment of inclusion/exclusion criteria. • A drug and alcohol test will be done at the clinic. • Physical examination and vital signs. • Urine pregnancy test for women of childbearing potential. • [redacted] • Registration of treatment start by emailing the form provided in the ISF to the sponsor. • No PK samples are taken on this day. • Spirometry. • Review concomitant therapy and any adverse events since screening. • Dispense two wallets of pirfenidone and instruct the patient to take 801mg tid, the first dose should be given at the clinic with food and a glass of water. • Provide patient with dosing instructions. • Dispense diary. • Remind patient of Visit 3a scheduled for Day 8. Has been changed to Group 2 The PK evaluation period for this group is for a minimum of 16 days plus 28 days follow-up and begins at Visit 2. **Visit 2 Day 1** • Review concomitant therapy and any adverse events since screening. • A drug and alcohol test will be done at the clinic. • Physical examination and vital signs. • Urine pregnancy test for women of childbearing

		potential. • Spirometry • Reassessment of inclusion/exclusion criteria. • [redacted] • Registration of treatment start by emailing the form provided in the ISF to the sponsor. • No PK samples are taken on this day. • Dispense two wallets of pirfenidone and instruct the patient to take 801mg tid, the first dose should be given at the clinic with food and a glass of water. • Provide patient with dosing instructions. • Dispense diary. • Remind patient of Visit 3a scheduled for Day 8.
Rationale for change		The assessments have been re-ordered to ensure that the activities that need to be performed so inclusion & exclusion criteria can be assessed are done prior to IMP being given.

Section to be changed		10.3 – Lung Function Criteria
Description of change		For decision on inclusion/ exclusion, DLCO results from visit 2 will be corrected for haemoglobin by the site. Has been changed to For decision on inclusion/ exclusion, DLCO results taken from the tests at visits 1 or 2, or during the screening period (visit 1 to visit 2) will be corrected for haemoglobin by the site.
Rationale for change		This is to allow the DLCO assessment to be made at visits 1 or 2, or during the screening period rather than only at visit 2. This change has been made to allow flexibility to the site and to the patient as the test results should be available prior to the patient receiving IMP. This is particularly important for the patients in Group 1 who are dosed early in the morning.

Number of global amendment		2
Date of CTP revision		16 February 2016
EudraCT number		2015-000732-15
BI Trial number		1199.229
BI Investigational Product(s)		Nintedanib
Title of protocol		Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study followed by nintedanib open label treatment)
To be implemented only after approval of the IRB / IEC / Competent Authority		✓
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		

Section to be changed		Cover Page and Synopsis – title:
Description of change		Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study followed by nintedanib open label treatment) Has been changed to: Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study)
Rationale for change		Removal of the Open-label Period

Section to be changed		Cover Page and Synopsis – trial sites:
Description of change		Trial conducted in approximately 7 sites in the UK Has been changed to: Trial conducted in approximately 9 sites in the UK
Rationale for change		Nine sites are already confirmed as participating

Section to be changed		Synopsis - objectives
Description of change		The following text has been removed: The trial will also collect safety information during open label administration of nintedanib.
Rationale for change		Removal of Open-Label Period

Section to be changed		Synopsis – main criteria for inclusion
Description of change		IPF diagnosis based on the ATS/ERS/JRS/ALAT 2011 IPF guidelines; Chest High-Resolution Computed Tomography (HRCT) performed within 12 months of visit 1; Has been changed to: IPF diagnosis based on the ATS/ERS/JRS/ALAT 2011 IPF guidelines; Chest High-Resolution Computed Tomography (HRCT) performed within 18 months of visit 1;
Rationale for change		To allow scans that have been performed within 18 months prior to visit 1 to be used

Section to be changed		Synopsis - Methodology
Description of change		Open-label, multiple dose, two-group study. This study will have two periods; the first will be the PK evaluation period and patients will then move on to the open label nintedanib treatment period. Has been changed to: Open-label, multiple dose, two-group PK study. An optional Named Patient Programme of nintedanib will be discussed with patients at the end of the trial. This Named Patient Programme will not be part of the study.
Rationale for change		Removal of the Open-Label Period

Section to be changed		Synopsis – open-label treatment
Description of change		OPEN LABEL

		<table><tr><td>NINTEDANIB TREATMENT PERIOD:</td><td></td></tr><tr><td>Trial product 1:</td><td>Nintedanib soft gelatine capsule</td></tr><tr><td>Dose:</td><td>3 0 0 m g d a i l y (1 5 0 m g b i d) with possibility to reduce to 200 mg daily (100 mg bid) to manage adverse events (AE)</td></tr><tr><td>Mode of administration:</td><td>Oral administration with food</td></tr><tr><td>Duration of treatment:</td><td>6 months</td></tr></table> This section of the table has been removed.
Rationale for change		Removal of the Open-Label Period.

Section to be changed		Synopsis – safety criteria
Description of change		Proportion of patients with at least one adverse event in the open label nintedanib treatment period. Additional further endpoints may be described in the TSAP. Has been changed to: Incidence and intensity of adverse events, physical examination, vital signs, ECG, change from baseline in laboratory parameters
Rationale for change		Removal of the Open-Label Period and to clarify the safety criteria that will be reviewed

Section to be changed		Flow Chart – Group 1
Description of change		Laboratory tests has been added at visit 3
Rationale for change		To allow safety lab tests to be collected

Section to be changed		Flow Chart – Group 1
Description of change		All of the Open-label treatment Period assessments have been removed. In addition the PK Follow-up period has been separated from the PK Evaluation Period
Rationale for		Removal of the Open-Label Period and clarity of the PK follow-up period

change		

Section to be changed		Flow Chart – Group 1 – footnote 4
Description of change		The following text has been removed: …… At the PK FU visit they will start the nintedanib for the Open label nintedanib treatment period and will be dispensed nintedanib every two months for 6 months….
Rationale for change		Removal of the Open-Label Period

Section to be changed		Flow Chart – Group 1 – footnote 10
Description of change		If a patient withdraws from the PK evaluation period or does not tolerate uptitration then the patient should be managed according to Figure 4.1.4:1. If the patient withdraws during the Open label nintedanib treatment period of the trial then the patient should come in for the Open label nintedanib treatment period End of treatment visit at the time of withdrawal and then a follow-up visit 28 days after this. has been changed to If a patient withdraws from the PK evaluation period or does not tolerate uptitration then the patient should be managed according to Figure 4.1.4:1
Rationale for change		Removal of the Open-Label Period

Section to be changed		Flow Chart – Group 1 – footnote 15
Description of change		At Visit 4 (PK FU) the decision can be made by the Investigator as to whether the patient can start the open label nintedanib treatment period. At this visit the patient will be dispensed nintedanib for the open label nintedanib treatment period see Table 4.1.4: 2 has been changed to: At Visit 4 (PK FU) the optional nintedanib Named Patient Programme will be discussed with the patient.
Rationale for change		Removal of the Open-Label Period

Section to be changed		Flow Chart – Group 1 – Addition of DLCO test and footnote 19
Description of change		DLCO Testing has been added to the flow chart along with footnote 19 – DLCO testing will be performed once at visit 1 or 2, or during the screening

		period (visit 1 to visit 2). The results will be corrected for haemoglobin by the site, see section 10.3 for further details.
Rationale for change		The protocol already states that DLCO testing is to be performed but this had not been specified in the Flow Chart

Section to be changed		Flow Chart – Group 2
Description of change		Laboratory tests has been added at visits 3a and 3b
Rationale for change		To allow safety lab tests to be collected

Section to be changed		Flow Chart – Group 2
Description of change		All of the Open-label treatment Period assessments have been removed. In addition the PK Follow-up period has been separated from the PK Evaluation Period
Rationale for change		Removal of the Open-Label Period and clarity of the PK follow-up period

Section to be changed		Flow Chart – Group 2 – footnote 4
Description of change		The following text has been removed: …… At the PK FU visit they will start the nintedanib for the Open label nintedanib treatment period and will be dispensed nintedanib every two months for 6 months….
Rationale for change		Removal of the Open-Label Period

Section to be changed		Flow Chart – Group 2 – footnote 9
Description of change		If a patient withdraws from the PK evaluation period then the patient should be managed according to Figure 4.1.4:1. If the patient withdraws during the Open label nintedanib treatment period of the trial then the patient should come in for the Open label nintedanib treatment period End of treatment visit at the time of withdrawal and then a follow-up visit 28 days after this. has been changed to If a patient withdraws from the PK evaluation period then the patient should be managed according to Figure 4.1.4:1.
Rationale for change		Removal of the Open-Label Period

Section to be changed		Flow Chart – Group 2 – footnote 14
Description of change		At Visit 4 (PK FU) the decision can be made by the Investigator as to whether the patient can start the open label nintedanib treatment period. At this visit the patient will be dispensed nintedanib for the open label nintedanib treatment period see Table 4.1.4: 2 has been changed to At Visit 4 (PK FU) the optional nintedanib Named Patient Programme will be discussed with the patient.
Rationale for change		Removal of the Open-Label Period

Section to be changed		Flow Chart – Group 2 – Addition of DLCO test and footnote 17
Description of change		DLCO Testing has been added to the flow chart along with footnote 17 – DLCO testing will be performed once at visit 1 or 2, or during the screening period (visit 1 to visit 2). The results will be corrected for haemoglobin by the site, see section 10.3 for further details
Rationale for change		The protocol already states that DLCO testing is to be performed but this had not been specified in the Flow Chart

Section to be changed		Abbreviations
Description of change		The following have been added: CrCl – Creatinine Clearance CTCAE – Common Terminology for Adverse Events NCI – National Cancer Institute PKS – PK analysis set
Rationale for change		CrCl has been added to the protocol CTCAE grading will be performed on AEs of diarrhoea, nausea and vomiting (as per NCI) PKS was missing

Section to be changed		Section 2.1, last paragraph
Description of change		This study is conducted at the request of the European Medicines Agency (EMA) as a post-approval commitment and will examine the relative bioavailability for nintedanib and pirfenidone when administered together versus when administered alone. There will also be an open label nintedanib treatment period to collect additional safety data. [redacted]

		[redacted]. Has been changed to: This study is conducted at the request of the European Medicines Agency (EMA) as a post-approval commitment and will examine the relative bioavailability for nintedanib and pirfenidone when administered together versus when administered alone. [redacted]
Rationale for change		Removal of the open-label period

Section to be changed		2.2 Trial Objectives
Description of change		The last sentence has been removed : This trial will also collect safety information during open label administration of nintedanib and throughout the trial.
Rationale for change		Removal of the open-label period

Section to be changed		2.3 Benefit-risk Assessment
Description of change		The second paragraph …... The patient will be offered to continue on nintedanib at the end of the PK part of the trial and their participation in the PK part will help to elucidate the pharmacokinetic characteristics of the combination of pirfenidone and nintedanib.…. Has been changed to: ….. An optional nintedanib Named Patient Programme to allow patients to continue on nintedanib will be discussed at the end of the trial. Patients participating in this PK trial will help to elucidate the pharmacokinetic characteristics of the combination of pirfenidone and nintedanib.
Rationale for change		To clarify there will be an optional nintedanib Named Patient Programme after the PK Period. This will not be part of the Trial

Section to be changed		3.1 Overall trial and design
Description of change		The study will be performed in approximately seven centres in the United Kingdom. Has been changed to:

		The study will be performed in approximately nine centres in the United Kingdom.
Rationale for change		9 sites are already confirmed as participating

Section to be changed		3.1 Overall trial and design - Paragraph 2
Description of change		There will then be an open label nintedanib treatment period for 6 months after the PK Follow up visit to collect additional safety data. See Figure 3.1:1 below, Section 6 and the flowchart 1 and flowchart 2 for details of each study visit. Has been changed to: After the end of the trial an optional Named Patient Programme of nintedanib will be discussed with patients.
Rationale for change		Removal of the open-label period

Section to be changed		3.3
Description of change		The following text has been removed: Two different designs are being used, as nintedanib is licensed but not currently NICE approved in the UK…… and …….In the open label nintedanib treatment period patients will receive 150mg bid nintedanib with the option of dose reduction to 100 mg bid and/or dose interruption to manage adverse events. Safety and tolerability will be assessed.
Rationale for change		NICE guidance has been published Removal of the open-label period

Section to be changed		3.4 Selection of the Trial Population
Description of change		Addition of: Each group requires at least 12 evaluable patients to complete each arm. Once 12 evaluable patients in a group have completed treatment, recruitment into that group will stop. The other group may continue to recruit until 12 evaluable patients in that group also complete treatment. Any patient still in the PK evaluation period when their group closes to recruitment may complete the PK evaluation period.

Rationale for change		Clarification of the end of recruitment

Section to be changed		3.4 Selection of the Trial Population
Description of change		Approximately 7 sites are each expected to include a minimum of 3 patients. Has been changed to: Approximately 9 sites are each expected to include a minimum of 3 patients.
Rationale for change		9 sites are already confirmed as participating

Section to be changed		Section 3.6 – Inclusion Criteria
Description of change		IPF diagnosis based on the ATS/ERS/JRS/ALAT 2011 IPF guidelines; Chest High-Resolution Computed Tomography (HRCT) performed within 12 months of visit 1; Has been changed to: IPF diagnosis based on the ATS/ERS/JRS/ALAT 2011 IPF guidelines; Chest High-Resolution Computed Tomography (HRCT) performed within 18 months of visit 1;
Rationale for change		To allow scans that have been performed within 18 months prior to visit 1 to be used

Section to be changed		Section 3.7 – Exclusion Criteria
Description of change		The criteria have been re-numbered
Rationale for change		Two new criteria have been added (see below). As there are already criteria relating to liver function it was appropriate to add the chronic liver disease at this point rather than at the end of the list of exclusion criteria

Section to be changed		Section 3.7 – Exclusion Criteria
Description of change		8 – History of end-stage renal disease requiring dialysis. Has been changed to: 9 – Severe renal impairment (Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula at visit 1) or end-stage renal disease requiring

		dialysis.
Rationale for change		Clarification is added to match the SPC of pirfenidone.

Section to be changed		Section 3.7 – Exclusion Criteria
Description of change		The following has been added: 3 – Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment) 21 – Current Smoker
Rationale for change		Patients with underlying chronic liver disease have also been excluded Current smokers have been excluded to match the SPC of pirfenidone. Patients who smoke could affect the bioavailability of pirfenidone.

Section to be changed		3.8.1 Removal of individual patients

Description of change		The patient experiences liver function impairment as follows:
		• ALT and/or AST ≥8 fold ULN
		• ALT and/or AST ≥3 fold ULN with signs or symptoms of severe liver damage (section 4.2.1.3) (including total bilirubin >2 fold ULN).
		For potential drug induced liver injury (DILI) follow up requirements please see section 5.3.7.1.
		
		• In the opinion of the investigator, the patient experiences unacceptable toxicity despite dose adjustments and supportive care.
		
		Has been changed to:
		
		• The patient experiences liver function impairment as follows:
		  • ALT and/or AST ≥5 fold ULN
		  • ALT and/or AST ≥3 fold ULN with signs or symptoms of severe liver damage (section 4.2.1.4) (including total bilirubin >2 fold ULN).
		  For potential drug induced liver injury (DILI) follow up requirements please see section 5.3.7.1.
		• In the opinion of the investigator, the patient experiences unacceptable toxicity despite dose adjustments and supportive care.
		• CrCl <30mL/min during the course of the trial. Study medication should be stopped and a repeat test performed as soon as feasible. If this second measurement confirms a CrCl <30mL, the patient should be permanently discontinued.

Rationale for change		The recommendations for managing liver elevations in section 4.2.1.4 have been updated (see below), this text has been updated accordingly. Severely decreased CrCl can affect PK results. This is also in-line with the pirfenidone SPC

Section to be changed		Section 3.8.1 Removal of individual Patients
Description of change		Treatment with pirfenidone must be permanently discontinued in the following situations: • ALT and/or AST ≥ 5 fold ULN Has been changed to: Treatment with pirfenidone must be permanently discontinued in the following situations: • ALT and/or AST ≥ 5 fold ULN • Patient develops signs or symptoms of angioedema
Rationale for change		Clarification is added to match the SPC of pirfenidone.

Section to be changed		Table 4.1.1: 1 Nintedanib (investigational drug)
Description of change		The following text has been removed: 100mg and Open label nintedanib treatment period: one 150 mg capsule in the morning and one in the evening (can be reduced to 100 mg to manage adverse events)
Rationale for change		Removal of the open-label period

Section to be changed		Table 4.1.4:2 Quantity of medication kits dispensed to the patient (Group 1 and Group 2)
Description of change		The following text has been removed: 4 (PK FU) | 5 | 5 | 5 | 6 | 5 |
Rationale for change		Removal of the open-label period

Section to be changed		4.1.4 Drug assignment and administration of doses for each patient – last paragraph
Description of change		The following text has been removed: <u>Open label nintedanib treatment period</u> The patient will have a washout period from the end of the last PK day (Visit 3, Day 24 for Group 1 and Visit 3b, Day 16 for Group 2) until the PK Follow-Up visit where no study drugs are taken. At the PK Follow-Up visit, if assessed by the Investigator medically indicated, the patient will be supplied with nintedanib for the open label nintedanib treatment period. During this phase the patient will be dosed at 150 mg bid with the possibility to reduce to 100 mg bid for management of adverse events.
Rationale for change		Removal of the open-label period

Section to be changed		Figure 4.1.4:1 (all three flow charts)
Description of change		Have been updated to remove the open-label period
Rationale for change		Removal of the open-label period

Section to be changed		Section 4.1.6 Packaging, labelling, and re-supply
Description of change		The following Test has been removed: There will be one shipment to each site.
Rationale for change		To allow for more than one shipment to site if required

Section to be changed		Section 4.1.6 Packaging, labelling, and re-supply
Description of change		The following text has been added: The nintedanib to be used in the nintedanib Named Patient Programme does not form part of the study supplies
Rationale for change		To clarify that the nintedanib in the Named Patient Programme is not part of the trial supplies

Section to be changed		4.2.1.1 Recommendations for adverse events considered drug related (exceptions include diarrhoea and photosensitivity/rash):
Description of		The following text has been removed:

change		**PK evaluation period** And **Open label nintedanib treatment period** • Dose reduction or interruption of nintedanib should be considered (at the discretion of the investigator) to allow for resolution of symptoms.
Rationale for change		Removal of the open-label period

Section to be changed		4.2.1.2 Recommendations for managing diarrhoea
Description of change		The following text has been removed: **PK evaluation period** And **Open label nintedanib treatment period** • Interruption of nintedanib should be considered (at the discretion of the investigator) to allow for resolution of symptoms.
Rationale for change		Removal of the open-label period

Section to be changed		4.2.1.4 Management of liver enzyme elevations
Description of change		The following text has been removed, as well as Table 4.2.1.4: For a detailed description of recommendations for management of liver enzyme elevations, please refer to table 4.2.1.4:1…… ……NINT: nintedanib * Laboratory tests include ALT, AST, total bilirubin, eosinophils, INR This has been replaced with: Patients who experience: • AST /ALT ≥3 ULN with signs or symptoms of severe liver damage* (including total bilirubin >2 fold ULN) or

		• ALT and/or AST ≥5 fold ULN Should interrupt all study drugs and return to clinic for a visit 3 (Group 1) or Visit 3b (Group 2). * Signs of severe liver damage are defined as: • ALT/AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN • ALT/AST ≥ 3 x ULN and unexplained INR > 1,5 • ALT/AST ≥ 3 x ULN and unexplained eosinophilia (>5%) • ALT/AST ≥ 3 x 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 5.3.7.1.
Rationale for change		The table included recommendations during the open-label period.

Section to be changed		Table 4.2.2.1:1 Permitted and Restricted Concomitant therapy
Description of change		The columns for the open-label period have been removed. In addition the PK evaluation period (incl PK FU period) has been separated to PK evaluation Period and PK Follow-Up Period The PK follow-up period does not permit pirfenidone or nintedanib. Footnote 5 has also been added: [5] Patients should not receive treatment for IPF during the PK follow-up period unless they have an acute worsening of their disease. Should this occur then the investigator may use any standard of care treatment available to them. The treatments to be administered should be done after due consideration of the SPCs for nintedanib and pirfenidone. It is preferable that nintedanib and pirfenidone are not used during the PK follow-up period so that there is a clear Residual Effect Period. Investigational Medicinal Products must not be used during this period.
Rationale for change		To remove the open-label period. To separate the PK Evaluation Period and Follow-up Period and clarify the restricted medications in this period.

Section to be changed		4.2.2.2 Restrictions on diet and life style
Description of change		Patients, when taking pirfenidone should avoid exposure to direct and indirect sunlight, use an effective sunblock (at least SPF 50 against UVA

		and UVB) and wear protective clothing. Grapefruit juice is an inhibitor of CYP1A2 and, thus, consummation should be avoided while taking pirfenidone. Has been changed to Patients, when taking pirfenidone, should not smoke and should avoid exposure to direct and indirect sunlight, use an effective sunblock (at least SPF 50 against UVA and UVB) and wear protective clothing. Grapefruit juice is an inhibitor of CYP1A2 and, thus, consummation should be avoided while taking pirfenidone.
Rationale for change		To align with the pirfenidone SPC

Section to be changed		5.1.3 Further Endpoints
Description of change		The following has been removed: <u>Safety endpoints</u> Proportion of patients with at least one adverse event in the open label nintedanib treatment period.
Rationale for change		This has been removed as it was connected to the open-label period

Section to be changed		5.3.3 Safety laboratory parameters
Description of change		Creatinine Clearance (according to Cockcroft-Gault formula) has been added to chemistry assessments Prothrombin Time has been added to coagulation assessments
Rationale for change		Creatinine Clearance has been added as this now needs to be measured in the protocol Prothrombin time has been added to allow the Child-Pugh Score to be calculated.

Section to be changed		5.3.3 Safety laboratory parameters
Description of change		The following test was added: **Renal Function Measurements** CrCl will be calculated using the Cockcroft-Gault formula, as follows: • For creatinine in µMol/L: $\frac{(140\text{-age [years]}) \times \text{weight [kg]} \times 1.23 \text{ (x 0.85 if female)}}{\text{serum creatinine [µMol/L]}}$

		• For creatinine in mg/dL: (140-age [years]) x weight [kg] (x 0.85 if female) 72 x serum creatinine [mg/dL] Please refer to Section 3.8.1 for guidance if a patient has started IMP and their CrCl is <30mL/min.
Rationale for change		This has been added due to the addition of creatinine clearance testing

Section to be changed		5.3.6 Other safety parameters
Description of change		A patient diary will be used by all patients in this trial to record symptoms and number of capsules taken per day during the PK Period only Has been changed to A patient diary will be used by all patients in this trial to record symptoms and number of capsules taken per day whilst they are taking study treatment.
Rationale for change		Clarification as to when the diary should be completed.

Section to be changed		5.3.7.1 Definitions of AEs
Description of change		The following text has been added: The intensity of diarrhoea, nausea and vomiting AEs should be classified and recorded in the (e)CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R10-4848): Table 5.3.7:1 CTCAE Categorization (R10-4848)

CTCAE Grade	Diarrhoea	Nausea	Vomiting
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Loss of appetite without alteration in eating habits	1-2 episodes (separated by 5 minutes) in 24 hours
2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Oral intake decreased without significant weight loss, dehydration or malnutrition	3-5 episodes (separated by 5 minutes) in 24 hours

		3	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	≥6 episodes (separated by 5 minutes) in 24 hours ; tube feeding, TPN or hospitalization indicated
		4	Life-threatening consequences; urgent intervention indicated	Not applicable	Life threatening consequences; urgent intervention indicated
		5	Death	Not applicable	Death
Rationale for change		CTCAE grading has been added for these AEs as they are AEs of particular note			

Section to be changed		5.3.8 Adverse event collection and reporting
Description of change		From signing the informed consent onwards through the Residual Effect period *(*REP), until the end of the REP (for this trial it will be classed as 28 days after the end of the open label nintedanib treatment period or 28 days after the end of the PK evaluation period) if the patient doesn't go intot he open label nintedanib treatment peiod: Has been changed to: From signing the informed consent onwards through the Residual Effect period *(*REP), until the end of the REP (for this trial it will be classed as 28 days after the end of the PK evaluation period):
Rationale for change		Removal of the open-label period

Section to be changed		5.3.8 Adverse event collection and reporting
Description of change		The REP is defined as 28 days after the last trial medication application (for this trial it will be classed as 28 days after the end of the open label nintedanib treatment period or 28 days after the end of the PK evaluation period if the patient doesn't go into the open label nintedanib treatment period; this is a general diagram and there will be no run-in period in this trial. Treatment will be classed as the PK evaluation period and the open label nintedanib period). Has been changed to:

		The REP is defined as 28 days after the last trial medication application (for this trial it will be classed as 28 days after the end of the PK evaluation period; this is a general diagram and there will be no run-in period in this trial. Treatment will be classed as the PK evaluation period).
Rationale for change		Removal of the open-label period

Section to be changed		6.1 Visit Schedule
Description of change		The study will consist of four sequential periods; a screening period, a PK evaluation period, the open label nintedanib treatment period and the follow-up period. Screening will be up to 4 weeks (28 days) in duration. The PK evaluation period will be 24 days in Group 1 and 16 days in Group 2 plus a follow up period of 28 days. The open label nintedanib treatment period will be for 6 months and this will be completed with a follow up visit 4 weeks after the end of treatment. Has been changed to: The study will consist of three sequential periods; a screening period, a PK evaluation period, and the follow-up period. Screening will be up to 4 weeks (28 days) in duration. The PK evaluation period will be 24 days in Group 1 and 16 days in Group 2 plus a follow up period of 28 days.
Rationale for change		To allow safety samples to be collected during the PK period

Section to be changed		6.2.2 Treatment period(s) – Group 1 (visit 3 day 23)
Description of change		The following text has been added: Blood sample for laboratory test (section 5.3.3)
Rationale for change		To allow safety samples to be collected during the PK period

Section to be changed		6.2.2 Treatment period(s) – Group 1 (PK Follow-up)
		PK Follow-up The patient should return to the clinic 28 days or more after Visit 3 Day 24. Assessments at this visit include:

		• Physical examination and vital signs. • [redacted] • Spirometry. • ECG. • Urine pregnancy test for women of childbearing potential. • Dispense nintedanib (if patient will enter into the open label nintedanib treatment period). • Review concomitant therapy and any adverse events. • At this point the PK evaluation period is complete. Has been changed to: **PK Follow-up/ End of Trial** The patient should return to the clinic 28 days or more after Visit 3 Day 24 for their PK Follow-Up/ End of Trial Visit as detailed in section 6.2.3.
Rationale for change		To combine the PK Follow-up and End of Trial visit

Section to be changed		6.2.2 Treatment period(s) – Group 2 (visit 3a day 8)
Description of change		The following text has been added: Blood sample for laboratory test (section 5.3.3)
Rationale for change		To allow safety samples to be collected during the PK period

Section to be changed		6.2.2 Treatment period(s) – Group 2 (visit 3b day 16)
Description of change		The following text has been added: Blood sample for laboratory test (section 5.3.3)
Rationale for change		To allow safety samples to be collected during the PK period

Section to be changed		6.2.2 Treatment period(s) – Group 2 (PK Follow-up)
Description of change		**PK Follow-up** The patient should return to the clinic 28 days or more after Visit 3b Day 24. Assessments at this visit include: • Physical examination and vital signs. • [redacted]

		• Spirometry. • ECG. • Urine pregnancy test for women of childbearing potential. • Dispense nintedanib (if patient will enter into the open label nintedanib treatment period). • Review concomitant therapy and any adverse events. • At this point the PK evaluation period is complete. Has been changed to: **PK Follow-up/ End of Trial** The patient should return to the clinic 28 days or more after Visit 3 Day 16 for their PK Follow-Up/ End of Trial Visit as detailed in section 6.2.3.
Rationale for change		To combine the PK Follow-up and End of Trial visit

Section to be changed		6.2.2 Treatment period(s) – (Open label nintedanib treatment period for Group 1 and Group 2)
Description of change		The following has been removed: **Open label nintedanib treatment period for Group 1 and Group 2** **Visit 4 to Visit 7 (End of treatment)** During this period the patient will receive an additional six months of open label nintedanib treatment. Patients will be seen in clinic every two months from this point. Assessments at these visits include: • Physical examination and vital signs. • Urine pregnancy test for women of childbearing potential. • [redacted] • Spirometry. • ECG (EOT visit only). • Dispense nintedanib (except at EOT). • Patients will return all unused medication. Medication compliance will be assessed by counting returned (unused) capsules. • Review concomitant therapy and any adverse events. • No diary is required during this period. If the patient requires a dose interruption or dose reduction to manage Adverse Events during this period this should be discussed with the Investigator. Guidance should be followed in Section 4. If the patient withdraws during the open label nintedanib period they should

		come in for Visit 7 (EOT) when they stop the medication and then 28 days later they should attend Visit 8 (FU).
Rationale for change		Removal of the open-label period

Section to be changed		6.2.3 Follow-up Period and Trial Completion
Description of change		A minimum of 28 days after the end of treatment in the open label nintedanib treatment period, all patients who started treatment are asked to come for a final follow up visit. Follow up visit: • Physical examination and vital signs. • Urine sample for pregnancy test for women of childbearing potential. • Review concomitant therapy and any adverse events. • Blood sample for laboratory tests. • Spirometry. • At the end of this visit the patient will have concluded their time in the trial. Has been changed to: A minimum of 28 days after the end of treatment all patients who started treatment are asked to come for a final follow up visit. Follow up visit: Assessments at this visit include: • Physical examination and vital signs. • [redacted] • Urine sample for pregnancy test for women of childbearing potential. • ECG • Review concomitant therapy and any adverse events. • Spirometry. • At the end of this visit the patient will have concluded their time in the trial.
Rationale for change		Due to the removal of the open-label period

Section to be changed		7.1 STATISTICAL DESIGN – MODEL (paragraph 1)
Description of		The following text has been removed:

change		The trial will also collect safety information during open label administration of nintedanib and throughout the trial.
Rationale for change		Due to the removal of the open-label period

Section to be changed		7.3 PLANNED ANALYSES
Description of change		The statistical analysis will be based on the following populations: **Treated Set in PK evaluation period:** The treated set in PK evaluation period consists of patients who receive at least one dose of study medication in the PK evaluation period. **Treated Set in open label nintedanib treatment period:** The treated set in open label nintedanib treatment period consists of patients who receive at least one dose of study medication (nintedanib) in the open label nintedanib treatment period. Has been changed to: The statistical analysis will be based on the following populations: **Treated Set:** The treated set consists of patients who receive at least one dose of study medication.
Rationale for change		Due to the removal of the open-label period

Section to be changed		7.3 PLANNED ANALYSES (PK analysis set:)
Description of change		The PK analysis set (PKS) includes all subjects in the treated set in PK evaluation period who provide at least one primary or secondary PK endpoint value not excluded according to the description above. Has been changed to: The PK analysis set (PKS) includes all subjects in the treated set who provide at least one primary or secondary PK endpoint value not excluded according to the description above.
Rationale for change		Due to the removal of the open-label period

Section to be changed		[redacted]

Description of change		[redacted]
Rationale for change		[redacted]

Section to be changed		**7.3.4 Safety analyses**
Description of change		PK evaluation period All treated patients in the PK evaluation period will be included in the safety analysis. Adverse events with an onset between start and end of treatment plus a period of 28 days after the last dose of trial medication within that period will be assigned to the PK evaluation period for evaluation and displayed by group (group 1 and group 2). AEs recorded prior to intake of trial medication will be assigned to 'screening', those between first intake until the last intake of trial medication plus 28 days will be assigned to the 'ontreatment'period. Events occurring after the on-treatment period until the first intake of treatment in the open label nintedanib treatment period will be assigned to the "PK follow-up"period. Open label nintedanib treatment period All treated patients in the open label nintedanib treatment period will be included in the safety analysis. Adverse events with an onset between start and end of treatment in the open label nintedanib treatment period plus a period of 28 days after the last dose of trial medication within that period will be assigned to the open label nintedanib treatment period for evaluation and displayed overall (all patients treated in the open label nintedanib treatment period). AEs recorded between first intake until the last intake of open label trial

		medication plus 28 days will be assigned to the 'on-treatment' period. Events occurring after the on-treatment period will be summarized as 'follow-up' period and those after the end of trial visit will be assigned to 'post-study' period. Has been changed to: All treated patients will be included in the safety analysis. All adverse events with an onset between start 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 and displayed by group (group 1 and group 2). AEs recorded prior to intake of trial medication will be assigned to 'screening', those between first intake until the last intake of trial medication plus 28 days will be assigned to the 'on-treatment' period. Events occurring after the on-treatment period will be summarized as 'follow-up' period and those after the end of trial visit will be assigned to 'post-study' period.
Rationale for change		Removal of the open-label period

Section to be changed		7.4 INTERIM ANALYSES
Description of change		An interim analysis will be performed after the last patient reaches the PK FU visit. For this purpose an interim database lock will be performed. All analyses related to the PK evaluation period including safety evaluation will be done except for the [redacted] that will be provide for the final analysis. [redacted] Has been changed to: Interim analysis will be performed if required by the regulatory agencies.
Rationale for change		Due to the removal of the open-label period there is no longer a need to do an interim analysis after the PK period

Section to be changed		9.1 Published References
Description of change		The following text has been added: R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Rationale for change		To reference the CTCAE guide

Section to be changed		10.3 Lung Function Criteria
Description of change		The following text has been added: The haemoglobin sample does not need to be taken on the same day that the DLCO is performed. The haemoglobin value used can be from the central laboratory results or from a local result,
Rationale for change		To allow flexibility in performing the DLCO test as this is not being performed as a measure of efficacy.

Section to be changed		10.4 Child-Pugh Classification
Description of change		The following text has been added: **Clinical and Biochemical Measurements** / **Points Scored for Increasing Abnormality** **1 point** / **2 points** / **3 points** Total bilirubin, µmol/l *(mg/dl)*: <34 *(<2)* / 34-50 *(2-3)* / >50 *(>3)* Serum albumin, g/dl: >3.5 / 2.8-3.5 / <2.8 Prothrombin time, prolongation (secs): <4.0 / 4.0-6.0 / > 6.0 Ascites: Absent / Slight / Moderate Encephalopathy (grade)*: None / 1 – 2 / 3 – 4 *According to Trey, Burns and Saunders (1966) R99-1244 **Total Score:** Child-Pugh A: 5 or 6 points; Child-Pugh B: 7–9 points; Child-Pugh C: >9 points
Rationale for change		Due to the addition of Child-Pugh Classification within the protocol

Number of global amendment		3
Date of CTP revision		29 July 2016
EudraCT number		2015-000732-15
BI Trial number		1199.229
BI Investigational Product(s)		Nintedanib
Title of protocol		Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study ~~followed by nintedanib open label treatment~~)
To be implemented only after approval of the IRB / IEC / Competent Authority		✓
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		

Section to be changed		Cover Page and Header
Description of change		Updated from version 3.0 to version 4.0, 27 July 2016
Rationale for change		Documentation of new version

Section to be changed		3.4 Selection of Trial Population
Description of change		The following text was added: Patients who have screen failed may be permitted to be re-screened following agreement by the Sponsor. Screening procedures may not need to be repeated if they are within 28 days of visit 2. The decision on what screening procedures do not need to be repeated will be made by the Sponsor.
Rationale for change		Re-screening will only be permitted following a discussion between the Investigator and Trial Team. To avoid additional burden on the patient screening procedures within 28

		days of visit 2 may not need to be repeated.

Section to be changed		3.6 Inclusion Criteria
Description of change		3. IPF diagnosis, based upon the ATS/ERS/JRS/ALAT 2011 guideline (P11-07084) and chest high-resolution computed tomography (HRCT) scan performed within 18 months of visit 1. 3. IPF diagnosis, based upon the ATS/ERS/JRS/ALAT 2011 guideline (P11-07084) and chest high-resolution computed tomography (HRCT) scan.
Rationale for change		Patients with IPF may not undergo HRCT assessment regular in routine clinical practice. For the group 2 patients in particular their scans may be several years old. Recruitment into group 2 is therefore proving challenging and this change should address this. In this PK study we only need to be reassured that a patient has IPF to avoid them receiving unsuitable treatment with nintedanib/pirfenidone rather than needing to have a scan as a measure of efficacy following treatment.

Section to be changed		3.7 Exclusion Criteria
Description of change		3. Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment1) Was changed to 3. Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment[1])
Rationale for change		To correct a typographical error, the footnote "1" reference should have been written in a superscript font in black rather than in a normal sized font in red

Section to be changed		3.7 Exclusion Criteria
Description of change		3. Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment1) Was changed to

		3. Underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment[1, 6]) Later in the same section the following footnote has been added: [6]Child Pugh classification does not need to be performed at screening.
Rationale for change		This is to clarify that Child Pugh Classification is a historical measure and does not need to be assessed at screening. Child Pugh Classifications are used as a measure of the current status of a patient with liver disease. If the classification is applied to healthy person i.e. without liver disease then these people would score A – we do not wish to exclude these people.

Section to be changed		3.7 Exclusion Criteria
Description of change		21. Current Smoker Was changed to 21. Current smoker (vaping and e-cigarettes are acceptable)
Rationale for change		Additional clarification

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Concomitant medications (or therapy) to provide adequate care may be given as assessed by the Investigator to be clinically necessary. Potent P-gp inhibitors (e.g. ketoconazole, erythromycin) or p-gp inducers (e.g. rifampicin, phenytoin, St. John's Wort) should not be taken concomitantly with nintedanib. Fluvoxamine, as well as other potent or moderate CYP1A2 inhibitors (e.g. enoxacin) and inducers (e.g. rifampicin), are contraindicated when taking pirfenidone. Moderate CYP1A2 inhibitors (e.g. ciprofloxacin, amiodarone) should also be avoided during pirfenidone administration. If restricted concomitant therapy is necessary, treatment with study medication should be permanently discontinued Was Changed to Concomitant medications (or therapy) to provide adequate care may be given as assessed by the Investigator to be clinically necessary. If restricted concomitant therapy is necessary, treatment with study medication should be permanently discontinued, see table 4.2.2.1:1 for

		details of restricted medications.
Rationale for change		The permitted and Restricted Concomitant therapy table (4.2.2.1:1) has been updated to include this information so that all restrictions are in one place

Section to be changed		Table 4.2.2.1:1 Permitted and Restricted Concomitant therapy
Description of change		**N-acetylcysteine[1] / Fluvoxamine[1] / Prednisone / other oral corticosteroid[2]** Was changed to **N-acetylcysteine[1] / Prednisone / other oral corticosteroid[2]** The following has been added to the table.

Potent or moderate CYP1A2 inhibitors (e.g. Fluvoxamine[1], enoxacin, ciprofloxacin, amiodarone) and inducers (e.g. rifampicin, omeprazole).	Permitted	Not permitted (2w prior to visit 2)	Not permitted	Not permitted
Oramorph, dextromethorphan **(Opioids for the treatment of diarrhoea e.g. loperamide may be used as per section 4.2.1.2. Other opioids to be discussed with Sponsor beforehand).**	Permitted	Permitted	Not Permitted on PK days[6].	Permitted

A new footnote was also added

6. There should be at least a 2-4 hour gap between the opioid intake and nintedanib/pirfenidone intake prior to the first PK sampling.

Rationale for change		To move restrictions listed in 4.2.2.1 into the table and to also add additional restrictions.

Section to be changed		5.3.3 Safety laboratory paramters
Description of change		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 and thyroid stimulating hormone (TSH). Creatinine Clearance (according to Cockcroft-Gault formula) Was changed to 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 and thyroid stimulating hormone (TSH), serum albumin (if required for liver assessment), Creatinine Clearance (according to Cockcroft-Gault formula)
Rationale for change		Serum albumin may be tested at the discretion of the Investigator if required for liver assessment.

APPROVAL / SIGNATURE PAGE

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Title: Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open-label, multiple-dose, two group study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Statistician	[redacted]	29 Jul 2016 15:38 CEST
Author-Trial Clinical Pharmacokineticist	[redacted]	29 Jul 2016 15:39 CEST
Approval-Trial Clinical Monitor	[redacted]	29 Jul 2016 15:39 CEST
Approval-Therapeutic Area [redacted]	[redacted]	15 Aug 2016 17:02 CEST
Approval-Team Member Medicine	[redacted]	15 Aug 2016 17:25 CEST
Verification-Paper Signature Completion	[redacted]	15 Aug 2016 17:28 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed