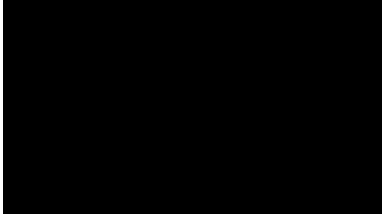
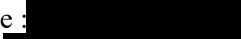


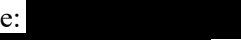



## Clinical Trial Protocol

Doc. No.: c01765254-09

<b>EudraCT No.:</b>	2011-002766-21
<b>BI Trial No.:</b>	1199.33
<b>BI Investigational Product:</b>	BIBF 1120 (nintedanib)
<b>Title:</b>	An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)
<b>Clinical Phase:</b>	III
<b>Trial Clinical Monitor:</b>	 Phone :  Fax : 
<b>Co-ordinating Investigator:</b>	 Phone:  Fax: 
<b>Status:</b>	Final Protocol (Revised Protocol (based on Global Amendment 3))
<b>Version and Date:</b>	Version: 4.0                      Date: 28 Mar 2017
<b>Page 1 of 66</b>	
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## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Name of company:</b> Boehringer Ingelheim		<b>Tabulated Trial Protocol</b>	
<b>Name of finished product:</b> Not applicable			
<b>Name of active ingredient:</b> BIBF 1120 (nintedanib)			
<b>Protocol date:</b> 27 Jan 2012	<b>Trial number:</b> 1199.33		<b>Revision date:</b> 28 Mar 2017
<b>Title of trial:</b> An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)			
<b>Co-ordinating Investigator :</b>			
<b>Trial sites:</b>	Multi-centre, multi-national		
<b>Clinical phase:</b>	III		
<b>Objective:</b>	The primary objective of this study is to assess the long-term safety of BIBF 1120 treatment in patients with Idiopathic Pulmonary Fibrosis who have completed one year treatment and the follow-up period in the phase III trials 1199.32 and 1199.34.		
<b>Methodology:</b>	Open-label, multi-centre, extension trial		
<b>No. of patients:</b>			
<b>total entered:</b>	Approximately 750 patients		
<b>each treatment:</b>	Approximately 600 patients treated with BIBF 1120 150 mg bid Approximately 150 patients treated with BIBF 1120 100 mg bid		
<b>Diagnosis :</b>	Idiopathic Pulmonary Fibrosis (IPF)		
<b>Main criteria for inclusion:</b>	Completion of one year treatment and follow-up period in 1199.32 or 1199.34 trial.		
<b>Test product:</b> Nintedanib			
<b>doses:</b>	300 mg (150 mg bid) 200 mg (100 mg bid)		
<b>mode of admin.:</b>	p.o.		

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<b>Name of company:</b> Boehringer Ingelheim		<b>Tabulated Trial Protocol</b>	
<b>Name of finished product:</b> Not applicable			
<b>Name of active ingredient:</b> BIBF 1120 (nintedanib)			
<b>Protocol date:</b> 27 Jan 2012	<b>Trial number:</b> 1199.33		<b>Revision date:</b> 28 Mar 2017
<b>Comparator products:</b> Not applicable  <b>dose:</b>  <b>mode of admin.:</b>			
<b>Duration of treatment:</b> Treatment duration for each patient will be variable. Treatment will be stopped if a reason for withdrawal is met. The trial is estimated to last a total of approximately 6 ½ years.			
<b>Criteria for efficacy:</b> Not applicable			
<b>Criteria for safety:</b> Adverse events, physical examination including weight, vital signs, laboratory evaluations.			
<b>Statistical methods:</b> Descriptive statistics of adverse events and other safety parameters.			

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## FLOW CHART

Visit	1 <sup>1,2</sup>	2 <sup>1,2</sup>	3	4	5	6	6a	7	7a	8	8a	9	Xa <sup>9</sup>	X <sup>9</sup>	EOT <sup>10</sup>	FU <sup>11</sup>
Week	-6 to 0	0	2	4	6	12	18	24	30	36	42	48	56 + every 16w	64 + every 16w		
Day Time window (days)	-42 to 1	1	15 ±3	29 ±3	43 ±3	85 ±3	127 ±7	169 ±7	211 ±7	253 ±7	295 ±7	337 ±7	±14	±14		+7
Informed consent	X <sup>3</sup>															
Demographics	X															
Baseline Conditions	X															
Physical examination (incl. weight)	X <sup>4</sup>	X	X	X	X	X		X		X		X		X	X	X
Vital signs	X <sup>4</sup>	X	X	X	X	X		X		X		X		X	X	X
12-lead ECG		X						X				X				
Laboratory tests	X <sup>4</sup>	X	X	X	X	X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X	X <sup>8</sup>	X	X	
Pregnancy test <sup>5</sup>		X	X	X	X	X		X		X		X		X	X	X
PFT (FVC)		X	X	X	X	X		X		X		X		X	X	X
Review of in-/exclusion criteria		X														
IVRS/IWRS		X		X		X		X		X		X		X	X	
Dispense trial drug <sup>6</sup>		X		X		X		X		X		X		X		
First drug intake		X														
Collect trial drug				X		X		X		X		X		X	X	
Drug Accountability check				X		X		X		X		X		X	X	
Adverse events, Concomitant Therapy	X <sup>7</sup>	X <sup>7</sup>	X	X	X	X		X		X		X		X	X	X
Exacerbations	X	X	X	X	X	X		X		X		X		X	X	X
Trial medication termination															X	
Conclusion of patient participation																X

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## **FLOW CHART (Cont.)**

1. Visit 1 and Visit 2 may occur on the same date if the period between Visit 9 (End of Treatment) of the previous trial (1199.32 or 1199.34) and the first visit for 1199.33 is  $\leq 6$  weeks. This rule does not apply to patients requiring washout of bronchodilators, as they will need to sign informed consent at Visit 1 in order to be asked to perform washout for PFT at Visit 2.
2. Visit 1 should occur at least one day after the Follow-up Visit of the parent trial and Visit 2 within 12 weeks of Visit 9 (End of Treatment) of the parent trial (1199.32 or 1199.34).
3. The patient is required to sign informed consent prior to any study related activities.
4. For patients performing Visit 1 and Visit 2 on the same day, eligibility assessment will be based on laboratory data from Visit 9 of the parent trial. Laboratory tests, physical examination and vital signs will be performed only once on that day and will be recorded under Visit 2 in the eCRF.
5. Urine dipstick pregnancy tests will be provided by central lab and should be performed in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory.
6. An additional visit must be performed in case of dose reduction or increase. Please refer to [Section 6.2.4](#) for visit procedures.
7. Only medical conditions that are occurring concomitantly at the time of screening will be recorded as baseline conditions on the 1199.33 Remote Data Capture (RDC) system. This also applies to ongoing AEs from the parent trial at the time of screening. See ISF for further instructions.
8. Laboratory test only for liver function monitoring: AST, ALT and bilirubin. Blood may be collected at the investigational site, primary physician (GP or Pulmonologist) or external laboratory with specific study kits and sent to the central laboratory for analysis. Information, agreement and training of the primary physician or local laboratory will be ensured on an individual site basis.
9. Same scheme should be repeated as often as needed: one complete visit every 16 weeks and one intermediate visit for liver function monitoring.
10. End of Treatment Visit to be performed if a reason for withdrawal is met. Please refer to [Section 3.3.4](#).
11. A Follow-up (FU) Visit should be planned for 28 days after last drug intake (+7 days window).

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## FLOW CHART FOR PATIENTS WHO CONTINUE TREATMENT AFTER THE DATABASE LOCK FOR THE FINAL ANALYSIS<sup>1</sup>

Visit	X <sup>3</sup>	EOT <sup>4</sup>	FU <sup>5</sup>
Week	every 16w		EOT +28 days
Day Time window (days)	±14		+7
Informed consent	X <sup>2</sup>		
IVRS/IWRS	X	X	
Dispense trial drug	X		
Collect used and unused trial drug	X	X	
Adverse events	X	X	X
Concomitant therapy	X	X	X
Trial medication termination		X	
Conclusion of patient participation			X

1. Patients who require continuation of treatment within this trial after the database lock for the final analyses will have reduced number of trial visits and reduced trial related procedures as described in this flow chart. The objective of these visits will be to dispense new study drug and collect information regarding adverse events and concomitant medication.
2. Patients continuing treatment after the final analysis (patients who don't have access to nintedanib outside the clinical trial) are required to sign an informed consent explaining the objective and study related procedures of the trial after the final analysis. This should happen prior to any study related activities of this new trial period.
3. Same scheme should be repeated as often as needed: one visit every 16 weeks.
4. End of Treatment Visit to be performed if a reason for withdrawal is met. Please refer to [Section 3.3.4](#).
5. A Follow-up (FU) Visit should be planned for 28 days after last drug intake (+7 days window).

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## ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
BI	Boehringer Ingelheim
bid	bis in die (twice daily)
CA	Competent Authority
CK	Creatinine kinase
CK-MB	Creatine kinase - MB fraction
C <sub>max</sub>	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DL <sub>CO</sub>	Carbon monoxide Diffusion Capacity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e.g.	Exempli gratia (for example)
EOT	End of Treatment
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor/receptor
FU	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
gMean	Generalized Mean
GP	General Practitioner
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HRCT	High Resolution Computerized Tomography
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IPV	Important Protocol Violation
IRB	Institutional Review Board
ISF	Investigator Site File

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IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine system
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Drug Regulatory Activities
NAC	N-acetyl cysteine
OPU	Operative Unit
PA	Alkaline phosphatase
PDGFR	Platelet derived growth factor/receptor
PFT	Pulmonary Function Test
p.o.	Per os (oral)
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
qd	Quoque die (once a day)
RDC	Remote Data Capture
RNA	Ribonucleic acid
SAE	Serious Adverse Event
s.c.	Sub cutaneous
SGRQ	Saint George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half life
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TS	Treated Set
TSAP	Trial Statistical and Analysis Plan
TSH	Thyrotrophin-stimulating hormone
UGT	UDP-glucosyltransferase
ULN	Upper Limit of Normal
VEGFR	Vascular endothelial growth factor/receptor
w	Week
WHO	World Health Organization
6-MWT	6 Minute Walk Test

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## 1. INTRODUCTION

### 1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a chronic disease of unknown aetiology that is characterized by progressive fibrotic destruction of the lung, resulting in disabling dyspnoea and poor gas exchange. The average life expectancy in IPF patients is 2-3 years.

The only drug that has been registered in a number of countries for the treatment of IPF is pirfenidone. It was launched in Japan in 2008 under the brand name Pirespa® and was approved for the treatment of mild-to-moderate IPF in Europe and Canada in 2011 (under the brand name Esbriet®). Following the successful completion of a third Phase III trial (PIPF-016, ASCEND) pirfenidone was recently approved by the US FDA for the treatment of IPF. Other pharmacologic options include corticosteroids, azathioprine, cyclophosphamide, and N-acetyl cysteine, albeit none of these has been proven efficacious in clinical trials compared with placebo, and none is indicated for the treatment of IPF. Thus, despite the availability of pirfenidone and the possibility of lung transplantation, the medical need for efficacious and safe treatment of IPF remains high.

Nintedanib has been developed for the treatment of IPF and for several cancer types in two separate clinical development programmes.

In IPF the clinical proof of concept for nintedanib was established in the 52-week phase II trial 1199.30 ([P11-11216](#)). Based on this trial, it was considered that nintedanib may confer clinical benefit to patients with IPF with acceptable safety.

Two phase III international, double-blind, placebo-controlled trials of identical study design 1199.32 and 1199.34 confirmed the efficacy and safety of nintedanib 150 mg bid versus placebo in patients with IPF ([P14-07514](#)) (refer to [Section 1.2](#)). Based on the overall evidence, nintedanib was approved by the US FDA for the treatment of IPF in October 2014.

The current study 1199.33 is a long-term extension study of the Phase III trials and such it is conducted to evaluate the long-term safety and tolerability of nintedanib in IPF.

### 1.2 DRUG PROFILE

Nintedanib is a small molecule tyrosine kinase inhibitor of the Platelet Derived Growth Factor Receptor (PDGFR)  $\alpha$  and  $\beta$ , Fibroblast Growth Factor Receptor (FGFR) 1- 3, and Vascular Endothelial Growth Factor Receptor (VEGFR). Nintedanib binds competitively to the 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. In addition, nintedanib inhibits Flt-3, Lck, Lyn, and Src kinases ([U07-1248](#)).

Nintedanib is currently in clinical development for several types of cancer. In line with the pre-clinical findings, the clinical development programme has provided data suggesting that

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nintedanib is active against a number of advanced malignancies including lung, ovarian, kidney, liver, and colorectal cancer.

Inhibition of FGFR-1 and PDGFR has been proposed as effective principle for the treatment of IPF ([P07-00109](#)). Furthermore, VEGFR inhibition may also have favourable effects, although the precise role of down-regulation of VEGF-mediated actions in IPF has not yet been fully elucidated ([R07-0002](#)). Oral administration of nintedanib to rats with bleomycin-induced lung fibrosis resulted in nearly complete attenuation of fibrosis histologically not only when started at day 1 after bleomycin administration, but also when administered only from day 10 to 21. In this model, nintedanib thus may be acting directly against the fibrotic processes, rather than solely through inhibition of inflammation.

A soft gelatin capsule formulation of nintedanib is used in humans. After oral administration, nintedanib was absorbed moderately fast. Maximum plasma concentrations ( $C_{max}$ ) occurred 1 to 4 hours after administration. Steady state was reached within 9 days of treatment at the latest. The gMean terminal half-life ( $t_{1/2}$ ) was 18 hours after intravenous administration. The major route of elimination of total [ $^{14}C$ ] radioactivity was via the faeces / biliary excretion, while the contribution of renal excretion was low (0.7% of an orally administered radioactive dose). An absolute bioavailability of slightly below 5% was observed by an intra-individual comparison of dose normalized AUC of 100 mg nintedanib administered orally and 6 mg nintedanib administered intravenously. The total percentage absorbed was estimated to be at least 23% compared to an absolute bioavailability of the parent alone of about 5%, thereby confirming the large amount of metabolite formed during intestinal and/or hepatic first pass metabolism.

The by far most frequent metabolites were BIBF 1202 formed by ester cleavage and the subsequently glucuronidation formed BIBF 1202-glucuronide. The glucuronidation of BIBF 1202 was mainly through UGT1A1 (liver and intestine) and UGT1A7, UGT1A8 and UGT1A10 (intestine). Drug-drug interactions based on cytochrome P450 dependent pathways are not expected for nintedanib.

*In vitro* transporter profiling of BIBF 1120 and BIBF 1202 showed that BIBF 1120 - but not BIBF 1202 - is a P-gp substrate. The effect of xenobiotics interacting with P-gp is currently not known.

In the IPF phase II proof-of-concept trial 1199.30, 432 patients with consistent IPF were randomized, with baseline characteristics comparable across groups. The results of the primary endpoint analyses, annual rate of FVC decline, were: 0.19 L (placebo); 0.17 L (50 mg qd); 0.21 L (50 mg bid); 0.16 L (100 mg bid); and 0.06 L (150 mg bid: -68% reduction in rate of decline vs. placebo,  $p=0.0136$ ; closed-testing multiplicity corrected:  $p=0.0639$ ). At end of study, FVC% pred was better preserved in the 100 mg bid ( $p=0.0314$ ) and 150 mg bid ( $p=0.0002$ ) groups when compared to placebo. FVC signal robustness was supported by results of body plethysmography and oxygen saturation. Compared to placebo, fewer patients had acute exacerbations in the 150 mg bid group ( $p=0.0150$ ), and there were a greater number of SGRQ 4-point scale responders in the 100 mg bid ( $p=0.0069$ ) and 150 mg bid ( $p=0.0341$ ) groups. No effect was observed on  $DL_{CO}$  and 6-MWT. The number of deaths was not

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significantly different between groups. Discontinuations (26.2%; 22.4% due to AE) were more frequent with 150 mg bid (37.6%; 31.8%), but less with 100 mg bid (16.3%; 15.1%), compared to placebo (28.2%; 24.7%).

The adverse events most frequently leading to discontinuation were diarrhoea, nausea, and vomiting (in the group receiving 150 mg twice a day as compared with those receiving placebo, the respective rates were 11.8% vs. 0%, 4.7% vs. 0%, and 2.4% vs. 1.2%). Among the 85 patients in the group receiving 150 mg of the study drug twice a day, 4 (4.7%) had serious gastrointestinal events and 5 (5.9%) had severe gastrointestinal events, especially diarrhoea, as compared with no patients in the placebo group.

Clinically significant elevations in liver enzymes levels (at least three times the upper limit of the normal range for ALT or AST at any time after baseline) were observed in 6 patients in the group receiving 150 mg of nintedanib twice a day (7.1%), 1 in the group receiving 100 mg twice a day and none in the placebo group. All aminotransferase levels normalized or decreased from elevated levels with continued treatment (in 3 patients receiving 150 mg twice a day and 1 patient receiving 100 mg twice a day), with a dose reduction (from 150 mg twice a day to 100 mg twice a day in 1 patient), or with withdrawal of the drug (in 2 patients receiving 150 mg twice a day).

For patients of the Phase II study participation in the open label rollover trial 1199.35 was offered. This study is currently ongoing.

Overall, it was considered that nintedanib may confer clinical benefit to patients with IPF with an acceptable safety profile. The benefit/risk assessment of the Phase II trial results justified initiation of 2 large Phase III trials. Trials 1199.32 ([U13-2381-01](#)) and 1199.34 ([U13-2382-01](#)), which are the parent trials of the current 1199.33 trial, evaluated the safety and efficacy of the 150 mg bid dose versus placebo when given over 52 weeks.

In total 515 patients were randomised in study 1199.32 and 551 patients in study 1199.34. The primary endpoint of the annual rate of decline in FVC was met in both studies. In study 1199.32 the adjusted annual rate of decline in FVC was -239.91 mL/year in the placebo group and -114.65 mL/year in the nintedanib group. The difference between treatment groups was 125.26 mL/year (95% CI: 77.68, 172.84) and was statistically significant ( $p < 0.0001$ ). In study 1199.34 the adjusted annual rate of decline in FVC was -207.32 mL/year in the placebo group and -113.59 mL/year in the nintedanib group. The difference between the treatment groups was 93.73 mL/year (95% CI: 44.78, 142.68) and was statistically significant ( $p = 0.0002$ ).

Change from baseline in SGRQ total score at 52 weeks was a key secondary endpoint in the studies. In study 1199.32 there was a small difference between the treatment groups in favour of nintedanib: -0.05 (95% CI: -2.40, 2.50), which was not statistically significant ( $p = 0.966$ ). In study 1199.34 the difference between the treatment groups was -2.69 (95% CI: -4.95, -0.43) in favour of nintedanib and was statistically significant ( $p = 0.0197$ ).

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Time to first acute IPF exacerbation over 52 weeks was a key secondary endpoint in the studies. In study 1199.32 there was no difference between the treatment groups and the hazard ratio (HR) was 1.15 (95% CI: 0.54, 2.42; p=0.673). In study 1199.34 the risk of having a first acute IPF exacerbation was significantly lower in the nintedanib group than in the placebo group, with a HR of 0.38 (95% CI: 0.19, 0.77; p=0.005).

In both studies, survival endpoints showed a consistent numerical difference in favour of nintedanib. The HR for time to death over 52 weeks in a pre-specified pooled analysis of both studies was 0.70 (95% CI 0.43, 1.12; p = 0.1399).

As expected, the most frequent AEs were gastrointestinal disorders. Diarrhoea was reported in 61.5% of the patients in the nintedanib group in study 1199.32 and in 63.2% of the patients in study 1199.34 compared to 18.6% and 18.3% in the placebo group, respectively. Liver enzyme elevations were more frequent in the nintedanib group than in the placebo group in both studies: aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]  $\geq 3$ xULN was observed in 4.9% of the patients in the nintedanib group versus 0.5% of the patients in the placebo group in study 1199.32 and in 5.2% of the patients in the nintedanib group versus 0.9% of the patients in the placebo group in study 1199.34. There was no Hy's law case in the nintedanib group.

Please refer to the current version of the Investigator's Brochure ([U07-1248](#)) for complete and updated information on nintedanib in IPF.



## 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

### 2.1 RATIONALE FOR PERFORMING THE TRIAL

The aim of this extension trial is to provide nintedanib treatment for all patients who have completed one year treatment and the follow up period in the double-blind phase III placebo controlled parent trials (1199.32 and 1199.34), who may have experienced benefit from the study medication and wish to receive treatment.

Moreover it is designed to determine the tolerability and safety of nintedanib and to follow up on survival in IPF patients treated for a long period.

Throughout this protocol, each time “parent trial” is quoted it refers to the 1199.32 and 1199.34 trials (EudraCT no. 2010-024251-87 and no. 2010-024252-29).

### 2.2 TRIAL OBJECTIVES

The primary objective is to assess long term safety of treatment with oral nintedanib in patients with Idiopathic Pulmonary Fibrosis (IPF).

Please refer to [Section 5](#) for a detailed description of the trial endpoints.

### 2.3 BENEFIT - RISK ASSESSMENT

Nintedanib has shown robust, reproducible, statistically significant, and clinically meaningful effects on the decline in lung function as measured by FVC. In two large, international, placebo-controlled phase III trials of identical design, nintedanib 150 mg bid statistically and clinically significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo indicating a relative difference of approximately 50% between nintedanib and placebo. This effect of nintedanib is considered consistent with slowing disease progression as measured by FVC.

The risks of treatment with nintedanib are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain) and to increases in liver enzymes (AST, ALT, ALKP, gamma-GT) and bilirubin. Also weight decrease and decreased appetite have frequently been reported in studies with nintedanib. Moreover, based on experience with other tyrosine kinase inhibitors, impairment of immune and of kidney function, intestinal perforations, increases in blood pressure as well as potential bleeding and thrombotic events should be carefully monitored and evaluated in clinical trials. In patients who develop severe symptoms of gastrointestinal toxicity not amenable to symptomatic treatment with standard measures, severe liver enzyme elevations, severe drug-related infections, or uncontrolled hypertension, treatment with nintedanib must be discontinued and appropriate therapeutic measures taken (refer to [Section 4.2.1.1](#)). Liver enzymes must be followed closely during treatment with nintedanib.

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The dose of nintedanib must be reduced to 100mg bid, or nintedanib must be discontinued in the event of hepatic toxicity and further treatment withheld until recovery of the abnormal laboratory parameters (refer to [Section 4.2.1.2](#)).

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 may reduce the risk of acute IPF exacerbations and worsening of patient's quality of life. Finally, nintedanib may ultimately be found to reduce mortality. Overall, the benefit/risk profile of nintedanib, as established during the phase II and III trials is interpreted as favourable for the treatment of IPF.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients' safety.

Patients who are offered to enter this open label extension trial must have participated in a phase III parent trial (1199.32 or 1199.34) for one year. All patients will be treated with active drug. Patients who have not tolerated the blinded study drug or discontinued for any reason are not eligible for the extension trial. Patients who were randomized to placebo in the parent trial will be receiving the active drug for the first time. Similar safety monitoring procedures as in the phase III trials will be applied.

The routine safety monitoring established in the parent study is considered appropriate for the long term follow-up of the patients. It consists of regular visits to the investigational site, blood analyses and specific monitoring procedures to follow-up potential hepatic enzyme elevation. In case it is considered adequate by the investigator, the dose of nintedanib may be reduced to 100 mg bid or dosing may be interrupted.

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### 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

#### 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, prospective, open label extension clinical trial. It is planned to include approximately 750 patients with IPF who have completed 52 weeks of treatment and the follow up period of the phase III parent trials. Only patients enrolled in the parent trials (1199.32 and 1199.34) will be eligible.

After signing Informed Consent and if all eligibility criteria are met, patients will initiate treatment with nintedanib (Visit 2). Please refer to [Section 4.1.2](#) for the method of assigning patients to treatment groups.

Overall, the trial is estimated to last a total of approximately 6 ½ years. Treatment will be stopped if a reason for withdrawal is met (refer to [Section 3.3.4](#)).

Patients' participation starts once they have signed the Informed Consent form and it is concluded when they have undergone the Follow-up Visit (unless the patient is lost to follow up or informed consent is withdrawn). Adverse events are collected during all the trial period and are considered under treatment until 28 days after drug discontinuation.

##### 3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, ordering the materials as needed for the trial, ensuring appropriate training and information of Clinical Monitors Local (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

Data Management and Statistical evaluation will be performed by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician have been appointed.

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 will be given in the Clinical Trial Master File (CTMF) document.

The organisation of the trial in the participating countries will be done by the respective local BI organisation (Operating Unit (OPU)) or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. In each OPU participating in this study, a CML was appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

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A Co-ordinating Investigator was nominated to coordinate investigators at different sites participating in this multicentre trial. ■■■ will review the trial protocol, any subsequent amendments to the protocol and the (draft) Clinical Trial Report (CTR). ■■■ will provide ■■■ signature on the final protocol signature page and amendments and will provide ■■■ signature on the (draft) Clinical Trial Report (CTR) indicating that, to the best of Co-ordinator's knowledge, the final CTR accurately describes the conduct and results of the Trial.

Trial sites consist of specialised referral centres experienced in the management of IPF. Documents on participating (Principal) investigators and other important participants, especially their curricula vitae, will be filed in the CTMF.

Details of the trial supplies including responsible institutions are given in [Section 4](#) of this protocol.

Central laboratory facilities will handle all laboratory analyses of the trial. In addition liver enzymes intermediate measurements may be performed in a local laboratory or at a local doctor's office using specific laboratory kits supplied for the study that will be analysed centrally.

To assure the standardisation of PFTs, the lung function equipment for spirometry will be provided by the sponsor (refer to [Section 5.2](#)).

The ISF will be maintained at the sites as required by local regulation and BI SOP. A copy of the ISF documents will be kept as an electronic CTMF document according to BI SOPs.

### **3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP**

The trial will be conducted as a prospective, open-label design with the objective to collect long term safety data on nintedanib in patients with IPF. The observation period will extend until either every patient is discontinued or a reason for stopping the trial is met (refer to [Section 3.3.4](#)). Patients who have completed one year treatment plus follow-up period in a parent trial are eligible for participation.

The purpose of this trial is to offer the option to all patients who completed the randomized phase III trial 1199.32 or 1199.34 to receive nintedanib treatment if they perceive an individual benefit. The decision to continue treatment will be made by the patient following a discussion with the investigator. The aim of the study is to allow treatment continuation to individual patients; therefore, randomization, blinding and use of placebo would not be appropriate.

To obtain information on the long term safety and tolerability of nintedanib, adverse events and acute IPF exacerbations will be reported, and clinical laboratory tests, electrocardiograms and lung function tests will be performed. FVC derived endpoints will be assessed and data on discontinuations and death will be recorded.

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The chosen endpoints are a subset of the endpoints used in the parent trial; no new endpoint is introduced in this trial.

### 3.3 SELECTION OF TRIAL POPULATION

It is anticipated that approximately 750 patients will complete 52 weeks of treatment with nintedanib or placebo and the follow up period in the phase III trials 1199.32 and 1199.34 (assuming a similar drop-out rate as in the phase II). These patients will be allowed to participate in this extension trial. Patients previously on active treatment will continue; patients who received placebo in the parent trial will initiate treatment with nintedanib for the first time at Visit 2.

A log of all patients included in the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug (i.e. open label nintedanib) or not.

#### 3.3.1 Main diagnosis for study entry

Patients with IPF are eligible for inclusion if they fulfil all the inclusion criteria ([Section 3.3.2](#)) and do not present any of the exclusion criteria ([Section 3.3.3](#)).

In general patients who have completed the parent trial are eligible. However treatment interruption between the parent trial and the extension open label study should not be > 12 weeks. Patients who had experienced adverse events in the parent trial but were allowed to continue receiving blinded study medication either at 150 mg bid dose or at the reduced dose level 100 mg bid, will be offered participation in the extension trial.

#### 3.3.2 Inclusion criteria

1. Signed Informed Consent consistent with ICH-GCP and local laws prior to trial participation.
2. Patients from trials 1199.32 or 1199.34 who completed the 52 weeks treatment period and performed the follow-up visit.

#### 3.3.3 Exclusion criteria

1. AST, ALT > 1.5 fold ULN

Patients who completed the parent trial with transaminase values > 1.5 fold ULN but < 3 fold ULN are considered eligible.

2. Bilirubin > 1.5 fold ULN
3. Bleeding risk:

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- a. Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, heparin, hirudin), or high dose antiplatelet therapy. 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);
  - b. Hemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or ulcers after completion of the parent trial;
  - c. Coagulation parameters: International normalised ratio (INR) > 2, prothrombin time (PT) and partial thromboplastin time (PTT) > 150% of institutional ULN.
4. Planned major surgery within the next 3 months, including lung transplantation, major abdominal or major intestinal surgery.
  5. New major thrombo-embolic events developed after completion of the parent trial:
    - a. Stroke;
    - b. Deep vein thrombosis;
    - c. Pulmonary embolism;
    - d. Myocardial infarction.
  6. Time period > 12 weeks between Visit 9 of the parent trial and Visit 2 of this study.
  7. Usage of any investigational drug after completion of the parent trial or planned usage of a specific investigational drug during the course of this trial.
  8. A disease or condition which in the opinion of investigator may put the patient at risk because of participation in this trial or limit the patient's ability to participate in this trial.
  9. Alcohol or drug abuse which in the opinion of the investigator would interfere with trial participation.
  10. Pregnant women or women who are breast feeding or of child bearing potential not using two effective methods of birth control (one barrier and one highly effective non-barrier) for at least 1 month prior to Visit 2 and/or not committing to using it until 3 months after end of treatment.

Women will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation, or postmenopausal for at least two years. Highly effective methods of birth control include established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device

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(IUD) or intrauterine system (IUS). A barrier method of contraception includes condom or occlusive cap with spermicidal (foam, gel, film, cream, suppository) or male sterilization (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

### 3.3.4 Removal of patients from therapy or assessments

#### 3.3.4.1 Removal of individual patients

The treatment with nintedanib has to be permanently discontinued in the following circumstances:

- Liver function impairment (refer to [Section 10.1](#)):
  - ALT or AST  $\geq$  8 fold ULN.
  - ALT or AST  $\geq$  3 fold ULN for more than 2 weeks despite dose reduction.
  - ALT or AST  $\geq$  3 fold ULN and total bilirubin  $>$  1.5 fold ULN.
  - ALT or AST  $\geq$  3 fold ULN and INR  $>$  1.5.
  - ALT or AST  $\geq$  3 fold ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $>$  5%).
- Diarrhoea: reoccurrence of diarrhoea ( $>$  4 stools/day) for 8 or more consecutive days despite dose reduction and supportive care as described in [Section 4.2.1.1](#).
- Pregnancy (refer to [Section 5.3.7](#)).
- Planned usage of a specific investigational drug (refer to [Section 4.2.2.1](#)).
- Treatment interruption. Treatment interruption is acceptable in certain cases and for a defined period which are described in [Section 4.2.1](#).

Similar to the parent study, in the following cases withdrawal of study drug is highly recommended. Only in special circumstances, the investigator, upon thorough assessment of all available clinical data, and taking into consideration the potential risks associated with administration of nintedanib, may decide not to withdraw the patient, even though one or more of the below mentioned criteria are fulfilled. However, in such a case, continuation of study treatment should be discussed with the patient, and the decision documented in the source data.

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- Planned major surgery, including any major abdominal or intestinal surgery.
- Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, heparin, hirudin), or high-dose antiplatelet therapy.
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
- Increased risk of bleeding e.g. haemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or ulcers.
- Deterioration of the disease. A  $\geq 10$  % decrease in the absolute value of FVC% predicted within 12 months is considered deterioration (progression of disease).

Patients have the right to withdraw from the study at any time without the need to justify the decision. The investigator has the right to remove patients from the study for non-compliance, administrative or other reasons.

Data of patients who discontinue or withdraw prior to medication assignment will be recorded in the eCRF. Data of patients who discontinue or withdraw after medication assignment must be documented and the reason for withdrawal must be recorded in the eCRF. The data must be included in the trial database and must be reported.

Refer to [Section 6.2.2](#) and [Section 6.2.3](#) for procedures to be followed for patients terminating the trial.

Patients who are discontinued from this trial are not allowed to be re-enrolled.

#### 3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Emergence of any efficacy/safety information that could significantly affect continuation of the trial,
2. Marketing authorization, availability for compassionate use or early access program offered by the sponsor (depending on local laws),
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

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## 4. TREATMENTS

### 4.1 TREATMENTS TO BE ADMINISTERED

Nintedanib will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG.

#### 4.1.1 Identity of BI investigational product and comparator product

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

Substance:	nintedanib
Pharmaceutical form:	Soft gelatin capsule
Source:	BI Pharma GmbH & Co. KG
Unit strengths:	150 mg , 100 mg
Posology:	Twice daily (bid)
Route of administration:	Oral (swallowed)

#### 4.1.2 Method of assigning patients to treatment groups

In the parent blind phase III trials (1199.32 and 1199.34) patients are assigned either active drug (nintedanib 150 mg bid) or placebo. In case patients experience adverse events related to drug tolerability, a dose reduction to 100 mg bid is allowed (both in active or placebo group).

At the end of treatment (Visit 9) in the parent trials, patients will be taking either 150 mg bid blinded study medication (active drug or placebo) or 100 mg bid blinded study medication (active drug or placebo) if their dose was permanently reduced during the trial.

Patients taking 150 mg bid blinded study medication (active drug or placebo) in the parent trial will be treated with nintedanib 150 mg bid in the current extension trial.

Patients who had the dose reduced to 100 mg bid (active drug or placebo) in the parent trial will be allowed to be treated with nintedanib 100 mg bid or 150 mg bid. This will ensure that patients who were on reduced dose placebo in the parent trial will have a chance to get the full dose in the extension trial.

The daily dose of nintedanib will be decided at Visit 2 based on discussion between the patient and the investigator.

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An Interactive Voice Response System (IVRS) will be used to assign medication numbers to eligible patients. Distribution of nintedanib to sites will be triggered by IVRS/IWRS.

Details on the IVRS/IWRS system are provided in the ISF.

After conclusion and unblinding of the parent trials, patients who received 100 mg bid (active drug or placebo) will also be allowed to increase their nintedanib dose to 150 mg bid, if this was not already performed at the beginning of the extension trial and if it is medically justified. In this situation, dose increase will need to be assigned through IVRS/IWRS during an additional visit (refer to [Section 6.2.4](#)).

#### 4.1.3 Selection of doses in the trial

Based on the phase II safety and dose-finding trial 1199.30, a dose of 150 mg bid was selected for confirmatory phase III trials (1199.32/.34) ([U07-1248](#)). With 150 mg bid, the limit of tolerability in IPF patients is considered to be reached. Lower doses may not ensure full efficacy benefit. However, in case of lack of tolerability, the dose may be reduced temporarily or permanently to 100 mg bid.

#### 4.1.4 Drug assignment and administration of doses for each patient

At Visit 2 patients who meet all eligibility criteria will be assigned trial drug: nintedanib either 150 mg or 100 mg bid (refer to [Section 4.1.2](#)).

Boxes covering 4 weeks + 1 week reserve treatment will be dispensed to the patient:

- 1 box at day 1 (Visit 2);
- 2 boxes at Visit 4;
- 3 boxes at Visits 6, 7 and 8;
- 4 boxes at Visit 9 and following visits.

Please refer to the [Flow Chart](#) for dispensing schedule. The investigational product should only be dispensed to participating patients according to the protocol by authorised personnel as documented in the form "Trial Staff List".

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

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If a patient forgets to take one or several doses of nintedanib he/she should take the following dose according to the protocol: no catch up of missed doses is permitted.

Patients on the 150 mg bid dose may have their dose permanently or temporarily reduced to 100 mg bid during the course of the extension trial for tolerability reasons, i.e. to manage adverse events (refer to [Section 4.2.1](#)). Dose reduction/re-escalation will need to be assigned through IVRS/IWRS during an additional visit (refer to [Section 6.2.4](#)).

#### **4.1.5 Blinding and procedures for unblinding**

##### **4.1.5.1 Blinding**

This is an open-label trial.

The previous treatment (active drug or placebo) in the blinded parent trials will remain unknown until the database lock of the parent studies.

##### **4.1.5.2 Procedures for emergency unblinding**

Not applicable.

#### **4.1.6 Packaging, labelling and re-supply**

Primary study material will consist of capsules containing nintedanib 150 mg or 100 mg. The colour of capsules between the two doses is slightly different.

All study medication will be packaged in one-week blister cards. Blister cards will be labelled with a unique identifier for drug accountability and will be labelled according to the regulatory requirements of the participating countries. Blisters will be packaged in one month boxes.

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

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

#### **4.1.7 Storage conditions**

Nintedanib soft gelatin capsules will be stored in their original packaging under the recommended storage conditions, i.e. at room temperature at the study site. Detailed storage conditions are described on the study medication labels. The investigational product must be stored securely, e.g. in a locked cupboard or at a pharmacy.

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A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

If the storage conditions are found to be outside the specified range, immediately contact the sponsor as provided in the instructions for dispensing and storage in the ISF.

#### **4.1.8 Drug accountability**

Drug supplies, which will be provided by a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor.

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 study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Principal Investigator / Head of Trial Centre,
- 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 or immediately imminent signing of the clinical trial protocol,
- for countries where it is required, availability of the proof of a medical licence for the principal investigator,
- for US, availability of the Form 1572.

The investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product.

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 product 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.

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## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatment

An antidote against nintedanib is not available. Potential side effects of nintedanib have to be treated symptomatically.

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

#### 4.2.1.1 Management of diarrhoea

The guidelines for managing diarrhoea are the same as in the parent protocols.

##### 4-6 extra stools or i.v. fluid intake < 24 hours with no effect on daily living activities

Patients should be treated according to local standard (e.g. loperamide or equivalent).

If the severity of diarrhoea persists for 8 or more consecutive days despite optimal care, nintedanib treatment should be discontinued or reduced until return to less than 4 extra stools per day. Drug interruption is limited however to a maximum of 4 weeks and patients may restart treatment with nintedanib at a reduced dose (during a dose modification visit, refer to [Section 6.2.4](#)).

Dose re-escalation is allowed at any time after the beginning of the reduced dose if medically justified.

In case of re-occurrence of diarrhoea for 8 or more consecutive days despite dose reduction and after optimal or prophylactic therapy, patients have to permanently stop nintedanib and perform an End of Treatment Visit as soon as possible and a Follow-up Visit 28 days after last drug intake (refer to the [Flow Chart](#) for visit procedures).

##### > 6 extra stools or incontinence or i.v. fluid intake ≥ 24 hours or hospitalisation or decrease in daily living activities

Nintedanib has to be interrupted until return to less than 4 extra stools per day and patients should be treated with optimal supportive care (e.g. loperamide or equivalent). Thereafter, patients may restart treatment with nintedanib at a reduced dose.

In case of re-occurrence of diarrhoea for 8 or more consecutive days despite dose reduction and after optimal or prophylactic therapy, patients have to permanently stop nintedanib and perform an End of Treatment Visit as soon as possible and a Follow-up Visit 28 days after last drug intake (refer to the Flow Chart for visit procedures).

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#### 4.2.1.2 Management of liver enzyme elevation

The guidelines for managing liver enzyme elevations are the same as is in the parent protocols. The following procedures are based on the *FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation (P09-12413)*.

##### ALT or AST > 1.5 fold ULN and < 3 fold ULN

- Continue as planned

##### ALT or AST $\geq$ 3 fold ULN and < 5 fold ULN with no signs of severe liver damage

- Reduce to 100 mg bid or interrupt treatment (to be decided by investigator, based on individual risk assessment)
- Re-test ALT and AST, as well as alkaline phosphatase, total bilirubin and eosinophils within 48 to 72 hours, then at approximately 7 days, then at approximately 2 weeks, and assess signs of severe liver damage:
  - If ALT and AST < 3 fold ULN after 2 weeks, return to initial dose if reduced, restart at reduced dose if interrupted. Monitor lab (see above) every 2 weeks for at least 8 weeks.
  - If ALT and/or AST  $\geq$  3 fold ULN after 2 weeks or any time thereafter, permanently discontinue study medication.

##### ALT or AST $\geq$ 5 fold ULN and < 8 fold ULN with no signs of severe liver damage

- Interrupt treatment.
- Re-test ALT and AST, as well as alkaline phosphatase, total bilirubin and eosinophils within 48 to 72 hours, then at approximately 7 days, then at approximately 2 weeks, and assess signs of severe liver damage:
  - If AST and ALT < 3 fold ULN after 2 weeks, restart at reduced dose. Monitor lab (see above) every week for 4 weeks, then every 2 weeks for at least 8 weeks.
  - If AST and/or ALT  $\geq$  3 fold ULN after 2 weeks or any time thereafter, permanently discontinue study medication.

##### ALT or AST $\geq$ 8 fold ULN or signs of severe liver damage

- Permanently discontinue study medication.

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- Patients showing these lab abnormalities need to be followed up according to [Section 10.1.1](#) of this clinical trial protocol and the “DILI checklist” provided in ISF.

Signs of severe liver damage are defined as:

Increase of liver transaminases (ALT or AST  $\geq$  3 fold ULN) and:

- appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $> 5\%$ ); or
- Total bilirubin  $> 1.5$  fold ULN; or
- INR  $> 1.5$ ;

Please refer to [Section 10.1](#) for more detailed instructions.

Immediately refer to [Section 5.3.6.1](#) in case AST and/or ALT  $\geq$  3 fold ULN is combined with total bilirubin  $\geq$  2 fold ULN.

Initial assessment of liver enzyme elevation should be performed at the investigational site. Blood samples for additional monitoring may be collected at the investigational site, primary physician (GP or Pulmonologist) or external laboratory with specific study kits and sent to the central laboratory for analysis.

For patients continuing treatment with nintedanib within this trial after the database lock for the final analysis, the liver function monitoring is to be done locally in case of liver enzyme elevations.

#### 4.2.1.3 Management of acute exacerbations

In case of acute exacerbation (refer to [Section 5.2](#)), all treatment options considered adequate by the investigator / caregiver are allowed. The patient may interrupt study treatment for up to 8 weeks if this is considered necessary (e.g., if short-term full anticoagulation is performed).

#### 4.2.1.4 Management of other adverse events

Patients who develop an uncontrolled hypertension despite appropriate antihypertensive therapy should permanently discontinue study medication.

For AEs that are assessed drug related, a dose reduction or an interruption (of maximum 4 weeks) can be considered. Re-escalation is allowed at any time after start of dose reduction if medically justified.

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For non related AEs, drug interruption may occur for no longer than 12 weeks. Nintedanib should be re-started at the same dose as it was being taken before interruption.

#### Summary of allowed interruption periods:

- Acute IPF exacerbations: 8 weeks maximum interruption;
- Related AEs: 4 weeks maximum interruption, then dose reduction is recommended, then re-escalation to full dose (150 mg bid) is allowed at any time;
- Unrelated AEs: 12 weeks maximum interruption.

## 4.2.2 Restrictions

### 4.2.2.1 Restrictions regarding concomitant treatment

- Investigational therapy is not allowed during the entire study period and must not have been introduced in the interval between parent trial and enrolment into this extension trial.
- Nintedanib is an anti-fibrotic kinase inhibitor which has been shown to have anti-angiogenic properties. Inhibition of angiogenesis may increase susceptibility to bleeding. Therefore, concomitant anticoagulation, fibrinolysis or high-dose antiplatelet therapy is contra-indicated (refer to [Section 3.3.3](#) [4 weeks washout]). Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, heparin, hirudin), or high dose antiplatelet therapy are to be withdrawn. 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), as well as 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) should be allowed.
- The concomitant administration of nintedanib with any drugs which are likely to increase gastrointestinal events such as diarrhoea, nausea, vomiting, is discouraged.
- Washout of bronchodilators must be observed before spirometry: 24 hours for long acting and 8 hours for short acting bronchodilators, if applicable.

### 4.2.2.2 Restrictions on diet and life style

No restrictions on diet or life style.

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### 4.3 TREATMENT COMPLIANCE

Study medication will be dispensed to the patient at the study site by responsible site personnel. Details regarding dispensing of the study medication to each participating patient, including patient identification, the amount of study drug dispensed, the date the drug was dispensed, and the number of capsules returned to the site will be recorded in the drug accountability form.

Patients will be instructed to bring all study medication to the clinic at each visit (except Visits 3 and 5). The investigator will be responsible for the assessment of patient compliance and will be encouraged to counsel patients on the importance of taking study medication as directed at each visit.

Study medication will be counted by the investigator (or designated site personnel) and compliance will be calculated in a worksheet, which must be kept as a source document.

Compliance will be calculated according to the formula: Compliance (%) = Number of capsules actually taken since last count  $\times$  100 / Number of capsules which should have been taken in the same period. Compliance to nintedanib should be between 80% and 120%.

Patients should not be discontinued for lack of compliance without prior discussion with the clinical monitor.

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## 5. VARIABLES AND THEIR ASSESSMENT

### 5.1 TRIAL ENDPOINTS

#### 5.1.1 Primary Endpoint

The primary endpoint is the incidence (number and % of patients) of overall adverse events over the course of the study, including incidence (number and % of patients) of serious adverse events; adverse events leading to discontinuation and fatal adverse events.

#### 5.1.2 Secondary Endpoints

Not applicable.

### 5.2 ASSESSMENT OF EFFICACY

#### Measurements of FVC

Unique spirometry devices (identical to the ones used in the parent studies) will be supplied to all participating sites at trial initiation and spirometry performance will be centrally reviewed. During the course of the trial and specifically at each interim analysis, the sponsor will re-evaluate the use of central spirometry. If applicable, i.e. central spirometry will be no longer used, measurements of FVC will be performed using calibrated electronic spirometers at the investigational site or at a referral site.

Spirometers and usage of spirometers must meet ATS/ERS criteria ([P05-12782](#)), including daily calibration of the spirometer, and regular calibration of the calibration pump. Spirometry will be conducted while the patient is in a seated position. The test will be done in

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triplicate and selection of the best result done according to the guidelines. Spirometric results captured by spirometers provided by the sponsor will be electronically transmitted and confirmed by central reading.

For each patient, pulmonary function testing will always start at approximately the same time of the day (with  $\pm 60$  minutes maximum difference, time will be recorded). On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing.

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

#### Definition of Acute IPF Exacerbations

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

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

Acute IPF exacerbations will be collected as adverse events.

### **5.3 ASSESSMENT OF SAFETY**

#### **5.3.1 Physical examination**

Physical examination includes assessment of heart, lung, abdomen and measurement of weight. Abnormal findings in the parent trial which were recorded as an adverse event and are still ongoing at the time of screening, as well as any new abnormal finding at the time of screening, will be recorded as baseline conditions on the appropriate eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

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### 5.3.2 Vital signs

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

### 5.3.3 Safety laboratory parameters

The laboratory tests will include:

- Haematology: red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, white blood cell count including differential, platelet count.
- Chemistry: creatinine, AST, ALT, total protein, alkaline phosphatase, total bilirubin.
- Coagulation: International normalized ratio (INR) and partial thromboplastin time (PTT).

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.

Additionally, all patients will have intermediate liver function monitoring visits (AST, ALT and bilirubin) when the interval between 2 regular visits exceeds 8 weeks. At these visits blood may be collected at the investigational site, primary physician (GP or Pulmonologist) or external laboratory. However analysis will still be performed by the central laboratory.

In case of liver enzymes elevation, close monitoring must be ensured by the investigator (please refer to [Section 4.2.1.2](#)).

For patients continuing treatment with nintedanib within this trial after the database lock for the final analysis, laboratory tests will no longer be part of the trial related procedures. However investigators are encouraged to monitor liver function locally according to the recommendations provided in the Investigators Brochure and to manage liver enzyme elevations according to the recommendations provided in [section 4.2.1.2](#) Management of liver enzyme elevations.

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#### 5.3.4 Electrocardiogram

Regular ECGs are to be conducted during the first year of the trial. Rate, rhythm and repolarisation changes have to be looked at, compared to previous one, and assessed for clinical relevance. Clinically relevant findings at baseline of this trial will be recorded as baseline conditions, new abnormal findings thereafter will be recorded as adverse events.

#### 5.3.5 Other Safety parameters

Not applicable.

#### 5.3.6 Assessment of adverse events

##### 5.3.6.1 Definitions of adverse events

###### Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

###### Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

###### Intensity of adverse event

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

Mild: Awareness of sign(s) or symptom(s) which 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

###### Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge,

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confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

*Additional information for Japan: The reason for the decision on causal relationship needs to be provided in the eCRF.*

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.

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

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF.

#### Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator.

#### Protocol-specified significant events

Similar to the parent trials, the following are considered as Protocol-specified significant events:

- Hepatic injury defined by an elevation of AST and/or ALT  $\geq 3$  fold ULN combined with an elevation of bilirubin  $\geq 2$  fold ULN measured in the same blood draw sample.

Patients showing these lab abnormalities need to be followed up according to [Section 10.1.1](#) of this clinical trial protocol and the “DILI checklist” provided in ISF.

- Adverse events relating to gastrointestinal perforation.

Protocol-specified significant events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria – for details please see [Section 5.3.7](#).

#### Expected Adverse Events

Expected (listed) AEs are described in Section 7.9 of the Investigator’s Brochure ([U07-1248](#)).

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### 5.3.7 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational period of 28 days) will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the ‘Adverse Event Reporting’ section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in [Section 5.3.6.1](#).

The investigator also has the responsibility to report AEs occurring in a certain period (28 days) after a patient completes the study drug administration. After this defined period all SAEs related to the study drug and/or study design have to be reported by the investigator.

The investigator must report the following events via telephone/fax using the SAE form immediately (within 24 hours or the next business day whichever is shorter) to the sponsor: SAEs and non-serious AEs occurring at the same time as an SAE and/or which are medically related to the SAE(s), and protocol-specified significant events.

Boehringer Ingelheim has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these “always serious adverse events”, if a non serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item “serious” needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found in the ISF.

*Additional information for Japan: This information must be also reported immediately to the head of the trial site.*

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified significant events becomes available.

#### Pregnancy

As mentioned above, due to the reprotoxic potential of nintedanib, a patient must not become pregnant while treated with nintedanib and until 3 months after end of treatment.

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However, generally, in rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

#### **5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS**

Not applicable.

#### **5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)**

Not applicable.

#### **5.6 OTHER ASSESSMENTS**

Not applicable.

#### **5.7 APPROPRIATENESS OF MEASUREMENTS**

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

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



## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the [Flow Chart](#). Some flexibility is allowed in scheduling the visits according to visit time windows as specified in the Flow Chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule (calculated from Visit 2). The trial medication kits contain sufficient medication to allow for these time windows. All deviations from the planned visit schedule will be documented.

The trial will run until all patients have discontinued treatment or a stopping criterion is met according to [Section 3.3.4](#).

### 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

#### 6.2.1 Screening

The study will be explained to all patients who complete the parent trials and are willing to continue treatment with nintedanib. No study related procedure should be performed until the patient has signed the Informed Consent.

Patients will complete a 52 weeks treatment period with nintedanib (or placebo) at Visit 9 in the parent trial (1199.32 or 1199.34) and a follow-up period of at least 28 days without drug (Follow-up Visit).

After concluding all visits from the parent trial and in order to assess eligibility for the extension trial (1199.33), patients are required to perform a screening visit (Visit 1) which includes laboratory tests.

If the period between Visit 9 (End of Treatment) of the parent trial and the first visit of 1199.33 is  $\leq 6$  weeks, Visit 1 and Visit 2 may occur on the same date. In this case, eligibility assessment will be based on laboratory data from Visit 9 of the parent trial.

Please refer to the Flow Chart for complete procedures at Visit 1.

Patients who have a laboratory test value that is outside the range specified by the exclusion criteria may have the test repeated once to determine eligibility; however, the result must be available prior to Visit 2.

Details of any patient who has given informed consent for the trial but is found to be ineligible must be entered in the Enrolment log and documented in the eCRF.

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### 6.2.2 Treatment period

If the patient has been determined eligible by the investigator to enter the trial (refer to [Section 3.3](#)), the investigator will assign a medication number to the patient through IVRS/IWRS at Visit 2 (refer to [Section 4.1.2](#)). First dose of nintedanib will be administered at Visit 2 in the clinic (day 1).

Additional clinic visits will be scheduled after 2, 4, 6, 12, 24, 36 and 48 weeks of treatment (Visits 3-9). Liver function monitoring visits will be performed at 18, 30 and 42 weeks of treatment (Visits 6a, 7a and 8a). After the first year of treatment, complete clinic visits will be scheduled every 16 weeks with intermediate liver function monitoring visits.

For detailed description of the trial procedures at each visit and dispensing schedule, please refer to the [Flow Chart](#).

#### End of Treatment (EOT)

If a reason for drug discontinuation is met (refer to [Section 3.3.4](#)) an EOT Visit should be scheduled as soon as possible after last drug intake. Reason for discontinuation must be documented in the eCRF.

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

### 6.2.3 End of trial and follow-up period

A Follow-up (FU) Visit should be planned for 28 days after last drug intake.

For detailed description of the trial procedures at the FU Visit, please refer to the Flow Chart.

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

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

### 6.2.4 Dose modification visit

Every time a dose should be reduced or increased (refer to [Section 4.1.4](#) and [Section 4.2.1](#)) patients will need to come to the site for a dose modification visit where the following will be performed:

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- Physical examination measuring weight;
- Vital signs;
- Assessment of adverse events, acute exacerbations and concomitant therapy since last visit;
- PFT (FVC);
- Assignment of new dose in IVRS/IWRS;
- Dispensing of trial drug;
- Drug accountability.

#### 6.2.5. Period after the database lock for the final analysis

After the database lock for the final analysis (refer to [section 7.3](#)) and once consent has been provided, the remaining patients in the trial (patients without access to nintedanib outside the clinical trial) will be offered continuation of treatment within the trial. This period will consist of study visits every 16 weeks ( $\pm 2$  weeks) where the following procedures will be conducted:

- Assessment of adverse events and concomitant therapy since last visit;
- Dispensing of trial drug.

Patients will continue to receive treatment until they meet a reason for discontinuation (refer to [section 3.3.4](#)) or until access to nintedanib is obtained outside the clinical trial.

Dose reductions, interruptions and re-escalations are possible at any time during the scheduled study visits or between visits to manage adverse events.

End of treatment and follow up visits have to be performed to conclude the treatment period and trial participation.

Study procedures per visit are described in the [Flow Chart](#) for patients who continue treatment after the database lock for the final analysis. Investigators are encouraged to monitor liver function locally according to the recommendations provided in the Investigators Brochure.

Only Adverse Events, Concomitant medications and reason of trial drug discontinuation and trial completion will be collected in the eCRF.

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## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN - MODEL

This is a multicenter, multi-national, open-label clinical trial to investigate the long term safety of nintedanib in patients with IPF previously treated in a double-blind phase III placebo controlled trial (1199.32 or 1199.34).

This statistical paragraph deals with the analyses to be performed on the extension trial only. Although data of parent trial will not be described in the scope of these analyses, they will be taken into account for adverse events analyses, as described in [Section 7.3.4](#).

As the main objective of this extension trial is to study long-term safety, only descriptive statistics will be used.

### 7.2 NULL AND ALTERNATIVE HYPOTHESES

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

### 7.3 PLANNED ANALYSES

The treated set (TS) will consist of all patients who received at least one dose of open-label study medication.

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

Patients will be analysed according to their randomized treatment group in previous studies 1199.32/34, and overall.

The last available value between visit 1 and visit 2 (before first trial drug intake) will be considered as the baseline, for this extension trial.

The main statistical analyses as described below will be performed based on all data collected up to the third interim database lock date ([see section 7.4](#)). Afterwards, only adverse events and concomitant treatments listings will be provided.

#### 7.3.1 Primary endpoint analyses

The primary objective of the study is to assess the safety of nintedanib, so please refer to [Section 7.3.4](#). Number of patients and % will be presented over the extension trial by

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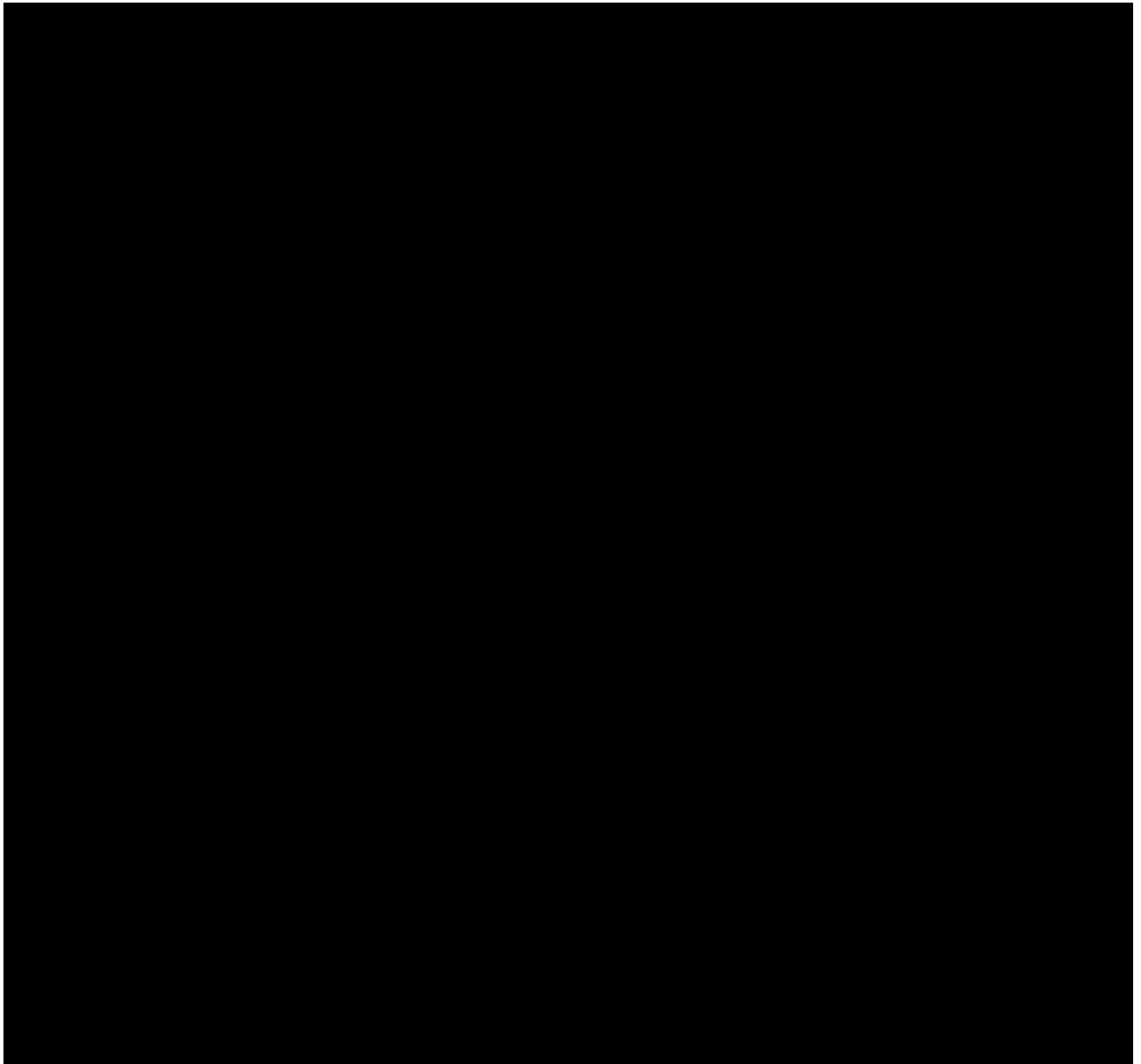
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category for adverse events overall; serious adverse events; adverse events leading to treatment discontinuation and fatal adverse events.

### 7.3.2 Secondary endpoint analyses

Not applicable



### 7.3.4 Safety analyses

The planned analysis is described in [section 7.3.1](#) and [7.3.3](#).

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All patients in the treated set will be included in the safety analysis. The analyses of adverse events will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events (in extension study), based on BI Guideline “Handling of Extension Trials”. To this end, all adverse events will be classified according to the following trial periods: previous trial, between-trials (from follow-up visit in previous trial up to date of informed consent in extension study), screening, on-treatment, post-treatment and post-study.

All adverse events with an onset date from the date of the first dose in the extension trial up to 28 days after the end of trial treatment will be assigned to the on-treatment period. Other adverse events will be assigned to the previous trial, between-trials, screening, post-treatment, or post-study period, as appropriate.

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

### 7.3.5 Pharmacokinetic analyses

Not applicable.

## 7.4. INTERIM ANALYSES

A first interim analysis will be performed to include safety data from this study in the regulatory submission documents of nintedanib in IPF. The appropriate analyses will be detailed in the Trial Statistical Analysis Plan; the timing of the interim database lock will be defined to allow for presentation of the most complete data.

A second interim analysis will be performed after the last patient entered into the trial has reached 48 weeks of treatment.

A third statistical analysis will be performed allowing the final assessment of all endpoints of this trial (refer to [section 5.1](#)). This will be the basis of the final Clinical Trial Report.

All the above mentioned analyses in [Section 7.3](#) will be presented at each interim analysis.

Data collected after the third interim DBL date will only be listed once all patients have discontinued the trial and then incorporated in a revision of the CTR. Details will be provided in the TSAP.

## 7.5 HANDLING OF MISSING DATA

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

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

For spirometry endpoints, missing data will not be imputed.

## **7.6 RANDOMISATION**

Not applicable as this is an extension trial.

## **7.7 DETERMINATION OF SAMPLE SIZE**

Not applicable as this is an extension trial. The number of patients included in this trial will correspond to the number of patients having completed 1199.32 and 1199.34 trials and willing to participate.

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## 8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH-GCP and, for Japan, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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 general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF.

### 8.1 STUDY 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.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

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*Additional information for Japan: The investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.*

*The following items need to be included:*

- 1. That the clinical trial is aimed at testing.*
- 2. Objectives of the trial.*
- 3. The name, title, and the address of the investigator to contact.*
- 4. Trial procedures.*
- 5. Anticipated benefits of the investigational products and anticipated disadvantages to the patient.*
- 6. Matters concerning other therapeutic measures.*
- 7. Duration of participation in the clinical trial.*
- 8. That the patient might withdraw from the trial at any time.*
- 9. That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantages to him or her.*
- 10. That the monitors, the auditors, and the institutional review board are given access to the relevant source documents on condition that confidentiality of the patient is fully secured.*
- 11. That privacy of the patient is kept.*
- 12. The office of the medical institution to contact in the event of trial-related injury.*
- 13. That necessary treatment is available to the patient in the event of trial-related injury.*
- 14. Matters concerning compensation in the event of trial-related injury.*
- 15. The type of the IRB which is used for the reviews and deliberations on the matters such as appropriateness of conducting the clinical trial, the matters to be reviewed and deliberated by each IRB, and other matters concerning the IRBs involved in the clinical trial.*
- 16. Other necessary matters concerning the clinical trial.*

## **8.2 DATA QUALITY ASSURANCE**

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance

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auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

To ensure good quality data, investigators and study site personnel will be familiarised with the study protocol, study procedures and principles of GCP during the Trial Initiation Visit. An Investigator Site File (ISF) with all necessary trial related documentation and handling procedures will be provided.

A central laboratory will be used to collect, analyze and report the results of all blood samples.

To ensure standardization in FVC measurement, a central spirometry review is put in place: unique spirometry devices will be supplied to all participating sites. Two procedures will be performed using a CRO to ensure high quality of collected FVC measurements:

- Quality Assurance (QA) process designed for providing feedback to the investigational site and the CRA on the quality of the data received from the site. During this process, a clinical specialist analyses and comments the data according to the ATS and study specific guidelines. A site gets an alert fax if all measurements of a patient during one visit are not acceptable.
- The Best Test Review (BTR) is designed to choose the best effort that will be used to represent the Best value for a particular test set. Only the acceptable efforts should be used to determine the best value. This choice is communicated to the Investigator whose confirmation is sought.

Data will be collected using a Remote Data Capture (RDC) system. Training will be provided to all investigators, coordinators and field monitors to ensure consistency and accuracy of the data. The data will be source verified by the field monitors.

Diagnoses and adverse events will be coded using MedDRA, and concomitant medications will be coded using WHO Drug Reference List.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF.

### 8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the Sponsor via remote data capture. For drug accountability, refer to [Section 4.1.8](#).

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### 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 entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Current medical records must be available.

For eCRFs all data must be derived from source documents.

### 8.3.2 Direct access to source data and documents

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

### 8.3.3 Storage of records

#### Additional information for Japan:

#### *Storage period of records*

#### *Trial sites:*

*The trial sites must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and the sponsor's SOP.*

#### *Sponsor:*

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

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

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## 8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

### 8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For nintedanib this is the current version of the Investigator's Brochure ([U07-1248](#)). The current version of this reference document is provided in the ISF. No AEs are classified as listed for study design or invasive procedures.

### 8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

## 8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

## 8.6 COMPLETION OF TRIAL

*Additional information for Japan: When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.*

*Additional information for EU member states: The EC/competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.*

## 8.7 PROTOCOL VIOLATIONS

*Additional information for Japan: The investigator or sub-investigator should record all CTP violations. The investigator should provide and submit the sponsor and the head of the trial*

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*site the records of violations infringing the Japanese GCP or violations to eliminate an immediate hazard to trial subjects and for other medically inevitable reasons.*

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

*Additional information for Japan: In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.*

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## 9. REFERENCES

### 9.1 PUBLISHED REFERENCES

- P05-12782 Miller MR; Hankinson J; Brusasco V; Burgos F; Casaburi R; Coates A; Crapo R; Enright P; Grinten CPM van der; Gustafsson P; Jensen R; Johnson DC; MacIntyre N; McKay R; Navajas D; Pedersen OF; Pellegrino R; Viegi G; Wanger J. Standardisation of spirometry. *Eur Respir J* 2005; 26 (2), 319-338
- P07-00109 Nathan SD. Therapeutic management of idiopathic pulmonary fibrosis: an evidence-based approach. *Clin Chest Med* 2006 Mar; 27 [1 Suppl 1]: S27-35
- P09-12413 Guidance for industry: drug-induced liver injury: premarketing clinical evaluation (July 2009). Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) 2009
- 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, Klueglic M, Bois RM du. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; 365(12):1079-1087.
- P14-07514 Richeldi L, du Bois RM, Raghu G et al, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014; 370(22):2071-2082.
- R07-0002 Papaioannou AI, Kostikas K, Kollia P, Gourgouljanis KI. Clinical implications for Vascular Endothelial Growth Factor in the lung: friend or foe? *Respir Res* 2006 Oct 17; 7:128

### 9.2 UNPUBLISHED REFERENCES

- U07-1248 [REDACTED] Investigator's brochure: BIBF 1120, Indication: Idiopathic Pulmonary Fibrosis. 1199.P3.
- U13-2381-01 [REDACTED]: A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF). Study 1199.32. 07 April 2014
- U13-2382-01 [REDACTED]: A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF). Study 1199.34. 08 April 2014

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## 10. APPENDICES

### 10.1 GUIDANCE FOR HEPATIC ENZYME INCREASES

Immediately refer to [Section 5.3.6.1](#) in case AST and/or ALT  $\geq 3$  fold ULN is combined with total bilirubin  $\geq 2$  fold ULN.

Table 10.1:1 Handling of transaminase increases

AST or ALT			
> 1.5 fold ULN to < 3x ULN	$\geq 3$ fold ULN to < 5 fold ULN	$\geq 5$ fold ULN to < 8 fold ULN	$\geq 8$ fold ULN <u>or</u> signs of severe liver damage <sup>1</sup>
Continue as planned <sup>2</sup>	Reduce dose or interrupt treatment <sup>3</sup>	Interrupt treatment	Permanently discontinue study medication!
	Close observation <sup>4</sup>	Close observation <sup>4</sup>	CLINICAL EVALUATION OF LIVER INJURY ( <a href="#">Section 10.1.1</a> )
After 2 weeks or any time later			
< 3 fold ULN	$\geq 3$ fold ULN	< 3 fold ULN	$\geq 3$ fold ULN
<u>Reduced:</u> return to initial dose.  <u>Interrupted:</u> restart at reduced dose.  Monitor bi- weekly for at least 8 weeks  Please refer to <a href="#">Section 4.2.1.2</a>	Permanently discontinue study medication!  Close observation <sup>4</sup>	Restart at reduced dose  Monitor weekly for 4 weeks, then bi-weekly for at least 8 weeks  Please refer to Section 4.2.1.2	Permanently discontinue study medication!  Close observation <sup>4</sup>

1. Signs of severe liver damage

Increase of liver transaminases (ALT or AST  $\geq 3$  fold ULN) and:

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- Appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) or;
  - Total bilirubin > 1.5 fold ULN or;
  - INR > 1.5.
2. According to visit schedule. Consider additional control visits as adequate.
  3. To be decided by Investigator, based on individual risk assessment.
  4. Close observation:
    - Repeat within 48-72 hours all of the following: ALT, AST, alkaline phosphatase, total bilirubin, eosinophils.
    - Re-testing once a week or less if abnormalities stabilize or return to normal.

## 10.1.1 Clinical Evaluation of Liver Injury

### 10.1.1.1 Introduction

Alterations of liver laboratory parameters, as described in [Section 4.2.1.2](#) and [Section 5.3.6.1](#) (Protocol-Specified Significant Events), are to be further evaluated using the following procedures.

### 10.1.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient's repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) must be evaluated by local laboratory and results must be made available to the investigator and to BI as soon as possible.

If ALT and/or AST  $\geq 3$  fold ULN combined with an elevation of total bilirubin  $\geq 2$  fold ULN are confirmed, the laboratory parameters described below will be made available to the investigator and to BI as soon as possible.

#### Clinical chemistry

Alkaline phosphatase, albumin, PT or INR, CK, CK-MB, ceruloplasmin,  $\alpha$ -1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides

#### Serology

Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody

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(titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Antimitochondrial antibody

Hormones, tumour marker

TSH

Haematology

Thrombocytes, eosinophils

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF;
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the ISF;
- provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm;
- initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgment and Good Clinical Practices (GCP),

and report these via the CRF.

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## 11. DESCRIPTION OF GLOBAL AMENDMENTS

<b>Number of global amendment</b>		1
<b>Date of CTP revision</b>		15 October 2012
<b>EudraCT number</b>		2011-002766-21
<b>BI Trial number</b>		1199.33
<b>BI Investigational Product(s)</b>		BIBF 1120 (nintedanib)
<b>Title of protocol</b>		An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>
<b>Section to be changed</b>	I) II) III) IV) V) VI)	Flow chart (footnote 1) Abbreviations, Section 2.1, Section 2.3, Section 3.2, Section 3.3, Section 4.1.2, Section 4.1.7, Section 4.2.1.1, Section 5.2.4, Section 5.2.5, Section 5.3.2 and Section 7.3.2 Section 3.3.4.1 Section 4.2.1.2 and Appendix 10.1 Section 4.2.1.2 Section 7.3

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<b>Number of global amendment</b>		1
<b>Description of change</b>	<p>I)</p> <p>II)</p> <p>III)</p> <p>IV)</p> <p>V)</p> <p>VI)</p>	<p>Addition of guidance for patients requiring washout of bronchodilators at study entry.</p> <p>Administrative changes, corrections and clarifications.</p> <p>Addition of individual withdrawal criterion based on FVC% predicted decline over time.</p> <p>Liver “disease” replaced by liver “damage”; “withdraw treatment” replaced by “permanently discontinue study medication” and correction of formatting mistake in the definition of “signs of severe liver damage”.</p> <p>Clarification on which blood collections may be performed outside the investigational site in the occurrence of a liver enzyme elevation.</p> <p>Addition of definition of important protocol violations.</p>
<b>Rationale for change</b>	<p>I)</p> <p>II)</p> <p>III)</p> <p>IV)</p> <p>V)</p> <p>VI)</p>	<p>Ensure that washout of bronchodilators does not occur before obtaining a signed informed consent.</p> <p>Administrative changes, corrections and clarifications.</p> <p>Provide recommendation to investigators to discontinue study medication in case of disease progression.</p> <p>Provide consistency in the same terminology used across protocol sections.</p> <p>Facilitate the logistics related to study procedures, especially for patients who need to travel a long distance to the investigational site.</p> <p>Clarify on how and where important protocol violations will be defined and specified.</p>

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<b>Number of global amendment</b>		2
<b>Date of CTP revision</b>		09 January 2015
<b>EudraCT number</b>		2011-002766-21
<b>BI Trial number</b>		1199.33
<b>BI Investigational Product(s)</b>		BIBF 1120 (nintedanib)
<b>Title of protocol</b>		An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>
<b>Section to be changed</b>	I)	Section 1
	II)	Section 2.3
	III)	Section 3.3.3
	IV)	Section 4.1.2
	V)	Section 4.2.1.1
		Section 4.2.1.4
	VI)	Section 5 and Section 7.3
	VII)	Section 7.4
	VIII)	Section 9

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<b>Number of global amendment</b>		2
<b>Description of change</b>	I) II) III) IV) V) VI) VII) VIII)	Medical Background updated. Ratio benefit/risk updated according to the new version of Investigator Brochure. Removal of men's contraception method. Allow dose reescalation to 150mg bid to patients entered in the extension trial at a reduced dose from the placebo or active arm of the parent trial. Allow dose reescalation to 150mg bid at any time after a dose reduction for AE. Clarification of efficacy and safety endpoints. Frequency of iDBL changed. Update to include new references.
<b>Rationale for change</b>	I) II) III) IV) V) VI) VII) VIII)	Approval of Pirfenidone in US and inclusion of phase III results. Updating information on efficacy and safety. Update in accordance to the last IB version. Provide patients with the opportunity to receive the optimal dose even after V2 and unblinding of parent trials. Provide patients with the opportunity to receive the optimal dose even after a period of drug reduction > 4 weeks. Administrative changes. New iDBL will be set up if requested by Health Authorities. New references available.

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<b>Number of global amendment</b>		3
<b>Date of CTP revision</b>		28 March 2017
<b>EudraCT number</b>		2011-002766-21
<b>BI Trial number</b>		1199.33
<b>BI Investigational Product(s)</b>		BIBF 1120 (nintedanib)
<b>Title of protocol</b>		An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)
<b>To be implemented only after approval of the IRB/IEC/Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>
<b>Section to be changed</b>		FLOW CHART FOR PATIENTS WHO CONTINUE TREATMENT AFTER THE DATABASE LOCK FOR THE FINAL ANALYSIS
<b>Description of change</b>		Was added:

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<b>Number of global amendment</b>		3																																												
		<table border="1"> <tr> <td><b>Visit</b></td> <td>X<sup>3</sup></td> <td>EOT<sup>4</sup></td> <td>FU<sup>5</sup></td> </tr> <tr> <td><b>Week</b></td> <td>every 16w</td> <td></td> <td>EOT +28 days</td> </tr> <tr> <td><b>Day Time window (days)</b></td> <td>±14</td> <td></td> <td>+7</td> </tr> <tr> <td>Informed consent</td> <td>X<sup>2</sup></td> <td></td> <td></td> </tr> <tr> <td>IVRS/IWRS</td> <td>X</td> <td>X</td> <td></td> </tr> <tr> <td>Dispense trial drug</td> <td>X</td> <td></td> <td></td> </tr> <tr> <td>Collect used and unused trial drug</td> <td>X</td> <td>X</td> <td></td> </tr> <tr> <td>Adverse events</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Concomitant therapy</td> <td>X</td> <td>X</td> <td>X</td> </tr> <tr> <td>Trial medication termination</td> <td></td> <td>X</td> <td></td> </tr> <tr> <td>Conclusion of patient participation</td> <td></td> <td></td> <td>X</td> </tr> </table>	<b>Visit</b>	X <sup>3</sup>	EOT <sup>4</sup>	FU <sup>5</sup>	<b>Week</b>	every 16w		EOT +28 days	<b>Day Time window (days)</b>	±14		+7	Informed consent	X <sup>2</sup>			IVRS/IWRS	X	X		Dispense trial drug	X			Collect used and unused trial drug	X	X		Adverse events	X	X	X	Concomitant therapy	X	X	X	Trial medication termination		X		Conclusion of patient participation			X
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<b>Rationale for change</b>		As access to nintedanib outside of the clinical trial is now available in most of the participating countries, the sponsor has decided to terminate the trial in these countries and conduct the final trial analysis. However in order to ensure continuation of treatment with nintedanib, patients without access to treatment will continue to receive nintedanib in this trial until a reason for discontinuation is met.																																												
<b>Section to be changed</b>		4.2.1.2 Management of liver enzyme elevation																																												
<b>Description of change</b>		For patients continuing treatment with nintedanib within this trial after the database lock for the final analysis, the liver function monitoring is to be done locally in case of liver enzyme elevations.																																												
<b>Rationale for change</b>		Instruction for local monitoring of liver function.																																												
<b>Section to be changed</b>		5.3.3 Safety laboratory parameters																																												
<b>Description of change</b>		Was added:  For patients continuing treatment with nintedanib within this trial after the database lock for the final analysis, laboratory tests will no longer be part of the trial related procedures. However investigators are encouraged to monitor liver																																												

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		function locally according to the recommendations provided in the Investigators Brochure and to manage liver enzyme elevations according to the recommendations provided in section 4.2.1.2 Management of liver enzyme elevations.
<b>Rationale for change</b>		Instruction for local monitoring of liver function.
<b>Section to be changed</b>		6. INVESTIGATIONAL PLAN
<b>Description of change</b>		<p>Was added:</p> <p>6.2.5. Period after the database lock for the final analysis          After the database lock for the final analysis (refer to section 7.3) and once consent has been provided, the remaining patients in the trial (patients without access to nintedanib outside the clinical trial) will be offered continuation of treatment within the trial. This period will consist of study visits every 16 weeks (<math>\pm 2</math> weeks) where the following procedures will be conducted:</p> <ul style="list-style-type: none"> <li>- Assessment of adverse events and concomitant therapy since last visit;</li> <li>- Dispensation of trial drug.</li> </ul> <p>Patients will continue to receive treatment until they meet a reason for discontinuation (refer to section 3.3.4) or until access to nintedanib is obtained outside the clinical trial.</p> <p>Dose reductions, interruptions and re-escalations are possible at any time during the scheduled study visits or between visits to manage adverse events.</p> <p>End of treatment and follow up visits have to be performed to conclude the treatment period and trial participation.</p> <p>Study procedures per visit are described in the Flow chart for patients who continue treatment after the database lock for the final analysis.</p> <p>Investigators are encouraged to monitor liver function locally according to the recommendations provided in the Investigators Brochure.</p> <p>Only Adverse Events, Concomitant medications and reason of trial drug discontinuation and trial</p>

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		completion will be collected in the eCRF.
<b>Rationale for change</b>		As access to nintedanib outside of the clinical trial is now available in most of the participating countries, the sponsor has decided to terminate the trial in these countries and conduct the final trial analysis. However in order to ensure continuation of treatment with nintedanib, patients without access to treatment will continue to receive nintedanib in this trial until a reason for discontinuation is met.
<b>Section to be changed</b>		7.3 PLANNED ANALYSES
<b>Description of change</b>		Was added:  The main statistical analyses as described below will be performed based on all data collected up to the third interim database lock date (see section 7.4). Afterwards, only adverse events and concomitant treatments listings will be provided.
<b>Rationale for change</b>		To specify the handling data collected on patients continuing treatment with nintedanib in this trial after the database lock for the final analysis.
<b>Section to be changed</b>		7.4 INTERIM ANALYSES
<b>Description of change</b>		The first Interim analysis will occur when the last patient entered will reach 48 weeks of treatment. Additional interim analyses could be performed upon request from Health Authorities or for publication purpose. All the above mentioned analyses will be presented at each interim analysis.  Was changed to:  A first interim analysis will be performed to include safety data from this study in the regulatory submission documents of nintedanib in IPF. The appropriate analyses will be detailed in the Trial Statistical Analysis Plan; the timing of the interim database lock will be defined to allow for presentation of the most complete data. A second interim analysis will be performed after

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		<p>the last patient entered into the trial has reached 48 weeks of treatment.</p> <p>A third statistical analysis will be performed allowing the final assessment of all endpoints of this trial (refer to section 5.1). This will be the basis of the final Clinical Trial Report.</p> <p>All the above mentioned analyses in Section 7.3 will be presented at each interim analysis.</p> <p>Data collected after the third interim DBL date will only be listed once all patients have discontinued the trial and then incorporated in a revision of the CTR. Details will be provided in the TSAP.</p>
<b>Rationale for change</b>		To specify the handling data collected on patients continuing treatment with nintedanib in this trial after the database lock for the final analysis.

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**APPROVAL / SIGNATURE PAGE**
**Document Number: c01765254**
**Technical Version Number:9.0**
**Document Name: clinical-trial-protocol-revision-03**

**Title:** An open-label extension trial of the long term safety of oral BIBF 1120 in patients with Idiopathic Pulmonary Fibrosis (IPF)

**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medical Affairs		29 Mar 2017 10:17 CEST
Author-Trial Statistician		29 Mar 2017 10:30 CEST
Approval-Trial Clinical Monitor		29 Mar 2017 11:31 CEST
Approval-  Medical Affairs		29 Mar 2017 16:27 CEST
Verification-Paper Signature Completion		05 Apr 2017 10:37 CEST

**(Continued) Signatures (obtained electronically)**

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>
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