# CLINICAL TRIAL PROTOCOL

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| | **Document Number:** | **c03736471-03** |
| **EudraCT No.:** | 2015-003360-37 | |
| **BI Trial No.:** | 1199.247 (INBUILD®) | |
| **BI Investigational Product(s):** | Nintedanib | |
| **Title:** | A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) | |
| **Brief Title:** | Efficacy and safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) | |
| **Clinical Phase:** | Phase III | |
| **Trial Clinical Monitor:** | [redacted]<br>Boehringer Ingelheim Pharma GmbH & Co. KG<br>Birkendorfer Straße 65<br>88397 Biberach an der Riss, Germany<br>Phone: [redacted]<br>Fax: | |
| **Coordinating Investigator:** | [redacted].<br>University of Michigan Health System<br>1500 E. Medical Center Drive, 3916 Taubman Center<br>Ann Arbor, MI 48109-0360, USA<br>Phone: [redacted]<br>Fax: | |
| **Status:** | Final Protocol (Revised Protocol based on global amendment 2) | |
| **Version and Date:** | **Version: 3.0** | **Date: 08 Jun 2018** |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | | | |
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| **Name of company:** | | **Boehringer Ingelheim** | |
| **Name of finished product:** | | Nintedanib | |
| **Name of active ingredient:** | | Nintedanib | |
| **Protocol date:**<br>13 Sep 2016 | **Trial number:**<br>1199.247 | | **Revision date:**<br>08 Jun 2018 |

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|---|---|
| **Title of trial:** | A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) |
| **Coordinating Investigator:** | [redacted] |
| **Trial site(s):** | Multi-centre trial; approximately 14 participating countries Worldwide |
| **Clinical phase:** | Phase III |
| **Objective:** | To investigate the efficacy and safety of 150 mg bid nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD). |
| **Methodology:** | Placebo controlled, randomized, double-blind, parallel design trial comparing 150 mg nintedanib bid to placebo over a 52 week treatment period (Part A). Patients will continue on blinded randomized treatment (i.e. nintedanib or placebo) until the end of the trial (Part B).<br><br>The primary assessment of benefit- risk of nintedanib in PF-ILD will be based on the efficacy and safety data over 52 weeks. Additional data beyond the 52 week treatment period will provide supportive longer term information on secondary time to event efficacy endpoints and on safety. |

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| **Methodology continued:** | The study population will be enriched for patients with PF-ILD with Usual Interstitial Pneumonia (UIP) pattern. UIP pattern will be defined based on High Resolution Computed Tomography (HRCT) using the same HRCT criteria as in the Phase III IPF trials with nintedanib. Since these criteria differ slightly from the current definition of radiologic UIP provided in the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines, screening HRCT meeting the protocol criteria for UIP as confirmed by central review will be referred to as ”HRCT with UIP-like fibrotic pattern only” |
| **No. of patients:** | |
| **total entered:** | 600 |
| **each treatment:** | Nintedanib: 300<br>Placebo: 300 |
| **Diagnosis :** | Physician diagnosis of PF-ILD |
| **Main criteria for inclusion:** | Patients aged ≥ 18 years with PF-ILD, defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on HRCT and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD. |
| **Test product(s):** | Nintedanib |
| **dose:** | 150 mg bid (300 mg daily)<br>with optional dose reduction to 100 mg bid (200 mg daily) to manage adverse events |
| **mode of administration:** | Per os |

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| **Comparator products:** | Placebo matching nintedanib soft gelatine capsules |
| **dose:** | N/A |
| **mode of administration:** | Per os |
| **Duration of treatment:** | For each patient, the study will consist of two parts: Part A and Part B. Part A will be of 52 weeks duration. Part B will be a variable treatment period beyond 52 weeks.<br>In Part B, patients will continue on blinded randomized treatment (nintedanib or placebo) until the end of the trial or until a reason for treatment withdrawal is met. The trial will end once the last randomized patient completes the $EOT_B$ or Follow- up Visit, as applicable. |
| **Endpoints:** | Primary:<br>• Annual rate of decline in Forced Vital Capacity (FVC; in mL) over 52 weeks<br>Main secondary:<br>• Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score at week 52<br>• Time to first acute ILD exacerbation or death over 52 weeks<br>• Time to death over 52 weeks<br>Other secondary:<br>• Time to death due to respiratory cause over 52 weeks<br>• Time to progression or death over 52 weeks<br>• Proportion of patients with a relative decline from baseline in FVC % pred of >10% at week 52<br>• Proportion of patients with a relative decline from baseline in |

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| **Endpoints continued:** | FVC % pred of >5% at week 52<br>• Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnea domain score at week 52<br>• Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52 |
| **Safety criteria:** | • Vital signs, physical examination, body weight<br>• Clinical laboratory tests (haematology, clinical chemistry and urinalysis)<br>• Reporting of adverse events<br>• Others, e.g. 12 lead electrocardiogram |
| **Statistical methods:** | There will be two co-primary analysis populations: the first will comprise all patients (the overall population); the second will comprise PF-ILD patients with HRCT with UIP-like fibrotic pattern only. A Hochberg procedure will be used to adjust the significance level for the multiple testing. For the primary endpoint, statistical significance will be declared if the analyses in both co-primary populations are significant at the two-sided 5% level, or if the analyses in either co-primary population are statistically significant at the two-sided 2.5% level.<br><br>Random coefficient regression (random slopes and intercepts) model for the primary endpoint, Mixed Effects Models for Repeated Measures (MMRM) for all other continuous secondary endpoints, Cox proportional hazards models as well as Kaplan-Meier plots for time to event secondary endpoints, and logistic regressions for binary secondary endpoints. |

# FLOW CHART PART A: 52 WEEKS TREATMENT PERIOD

| **Visit** | | **1** | **2** | **3** | **4** | **5** | **6** | **6a** | **7** | **7a** | **8** | **8a** | **9** | **EOT$_A$**[1] | **FU**[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening**[*] | | **Treatment**[#] | | | | | | | | | | | | **FU** |
| **Weeks of treatment** | | | **0** | **2** | **4** | **6** | **12** | **18** | **24** | **30** | **36** | **44** | **52** | | **+4** |
| **Day** | Before or at the latest at visit 1 | ≥ 4d before V 2 | **1** | **15** | **29** | **43** | **85** | **127** | **169** | **211** | **253** | **309** | **365** | | **+28** |
| **Time window** | | | | **±3** | **±3** | **±3** | **±3** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | | **+7** |
| Informed consent | X* | | | | | | | | | | | | | | |
| HRCT sent to central review[2] | X | | | | | | | | | | | | | | |
| Demographics | | X | | | | | | | | | | | | | |
| Medical history | | X | X | | | | | | | | | | | | |
| Adverse events, concomitant medication | | X | X | X | X | X | X | | X | | X | | X | X | X |
| In-/exclusion criteria | | X | X | | | | | | | | | | | | |
| Physical examination, vital signs | | X | X | X | X | X | X | | X | | X | | X | X | X |
| Safety Laboratory (blood and urine) | | X[3] | X | X | X | X | X | X[4] | X | X[4] | X | X[4] | X | X | |
| Pregnancy test[5] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK sample[6] | | | | | X | | | | X | | | | | | |
| Serum and plasma biomarker samples[7] | | | X | | | | X | | X | | X | | X | X | |
| RNA sample[7] | | | X | | | | | | X | | | | X | X | |
| Serum banking samples (optional)[7, 8] | | | X | | | | X | | X | | X | | X | X | |
| DNA banking sample (optional)[8] | | | X | | | | | | | | | | | | |
| HCRU assessments | | | X | X | X | X | X | | X | | X | | X | X | |
| Non-elective hospitalization | | | | X | X | X | X | | X | | X | | X | X | X |
| Spirometry (FVC)[9] | | X | X | X | X | X | X | | X | | X | | X | X | X |
| $SpO_2$ (earlobe or forehead, resting) | | | X | | | | | | X | | | | X | X | |
| $DL_{CO}$[9] | | X | X | | | | | | X | | | | X | X | |
| HRCT (optional)[10] | | | X | | | | | | X | | | | X | X[11] | |
| Resting 12-lead ECG[12] | | X | X | | | | | | X | | | | X | X | |
| Questionnaires: K-BILD, L-PF Symptoms & Impact, EQ-5D, PF-IQOLS[13] | | | X | | | | X | | X | | X | | X | X | |

# FLOW CHART PART A: 52 WEEKS TREATMENT PERIOD (CONT.)

| **Visit** | | **1** | **2** | **3** | **4** | **5** | **6** | **6a** | **7** | **7a** | **8** | **8a** | **9** | **EOT$_A$**[1] | **FU**[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening*** | | **Treatment#** | | | | | | | | | | | | **FU** |
| **Weeks of treatment** | | | **0** | **2** | **4** | **6** | **12** | **18** | **24** | **30** | **36** | **44** | **52** | | **+4** |
| **Day** | Before or at the latest at visit 1 | ≥ 4d before V 2 | 1 | **15** | **29** | **43** | **85** | **127** | **169** | **211** | **253** | **309** | **365** | | **+28** |
| **Time window** | | | | **±3** | **±3** | **±3** | **±3** | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | | **+7** |
| Review questionnaires for completeness | | | X | | | | X | | X | | X | | X | X | |
| Acute ILD Exacerbations | | | | X | X | X | X | | X | | X | | X | X | X |
| Randomization | | | X | | | | | | | | | | | | |
| IRT call/notification | X[14] | | X | | X | | X | | X | | X | | X | (X) | |
| Administer 1st trial medication at the clinic | | | X | | | | | | | | | | | | |
| Dispense trial medication | | | X | | X | | X | | X | | X | | X | | |
| Collect trial drug | | | | | X | | X | | X | | X | | X | X | |
| Compliance / drug accountability | | | | X[17] | X | X[17] | X | | X | | X | | X | X | |
| Trial medication termination | | | | | | | | | | | | | | X | |
| Vital status assessment[15] | | | | | | | | | | | | | X | | |
| Conclude subject participation | | | | | | | | | | | | | | | X[16] |

* Informed consent needs to be signed before any procedure related to the study. When it is signed before visit 1, e.g. to allow shipment of images for central review, all AEs and Concomitant Treatments occurring after the informed consent have to be recorded. The Screening period (informed consent to Visit 2) must not be longer than 12 weeks. Upon obtaining informed consent, the patient will be instructed on the medication wash-out and other restrictions needed.

# In case of dose change (reduction or re-escalation) additional visits have to be included (refer to Section 6.2.4). In case of premature discontinuation of trial medication, the patient will be expected to attend all visits (Part A and Part B visits) as originally planned until the end of the trial (except for the laboratory visits 6a, 7a, 8a) (see Section 6.2.3).

[1] EOT$_A$ should be done in cases of premature trial medication discontinuation during Part A of the study with a follow-up Visit (FU) 4 weeks later. A scheduled visit (V3-V9) can be skipped if EOT$_A$ or Follow-up Visit occurs within 4 weeks prior to scheduled visits.

[2] Review of high resolution computed tomography (HRCT) for meeting the HRCT criteria for fibrosing lung disease, for extent of ILD in the lung (10% or more), and for HRCT pattern. Central review HRCT not older than 12 months should be sent. If the patient does not have a HRCT within 12 months of Visit 1 or the available HRCT scan fails to meet the required image acquisition specification, a new HRCT can be performed for the purposes of participation in the trial, provided the patient meets all other inclusion and no exclusion criteria.

[3] The safety lab of Visit 1 must be repeated if screening is longer than 6 weeks.

[4] Intermediate lab tests (a-Visit) to be done as needed for additional safety monitoring (see Section 4.2.2.2) at the discretion of the investigator.

[5] ß-HCG will be performed at Visit 2 only, at central laboratory. Urine dipstick pregnancy tests will be provided by central laboratory and should be performed in all women of childbearing potential every 4-6 weeks, i.e. at least at every visit and if necessary, additionally at home or at a local laboratory / local doctor. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory. Documentation will be done in patient's notes.

[6] PK samples will be taken at Visits 4 and 7 just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF. Patients will be provided (Visits 3 and 6) with a PK-card to support the record of the exact clock time of medication intake three days preceding PK sampling.

[7] Biomarker samples will be taken just before drug administration.

[8] Deoxyribonucleic Acid (DNA) and serum banking samples: will be taken from eligible patients who signed a separate informed consent at Visit 2, at the timepoints indicated in the Flowchart; participation is voluntary and is not a prerequisite for participation in the trial. DNA samples can be taken at Visit 2 or any subsequent visit.

[9] Order of lung function measurements: 1. FVC followed by patients rest; 2. DLCO. Measurements at approximately the same time each visit, reference time at Visit 2.

[10] High resolution CT scan will be done at baseline, 24 and 52 weeks in patients who agree as part of the informed consent. Participation is voluntary and is not a prerequisite for participating in the trial. Baseline scan will not be performed in patients where eligibility scan was performed during screening.

[11] If EOT takes place before Visit 7, HRCT should not be performed at EOT.

[12] Resting ECG will be performed (if possible prior to blood draw) at Visit 2 prior to randomization (only if abnormal at Visit 1).

[13] Self-reported outcomes / Questionnaires must always be done by the patients in a quiet place prior to any other visit procedure. Order of questionnaires: 1. K-BILD, 2. L-PF Symptoms and Impact, 3. EQ-5D, 4.PF- IQOLS.

[14] IRT needs to be notified at the latest at Visit 1 but can be notified upon informed consent's signature.

[15] Vital status at 52 weeks (Visit 9) should be available for all randomized patients. Consent for a vital status call at 52 weeks in case of premature discontinuation of trial participation will be requested for all patients as part of the informed consent.

[16] Conclusion of participation is only applicable for subjects who withdraw consent for trial participation.

[17] Compliance / drug accountability only in case of dose reduction / increase.

# FLOW CHART PART B[1]: VARIABLE TREATMENT PERIOD BEYOND 52 WEEKS

| Visit | Xa[2] | X[3] | $EOT_B$[4] | FU[4] |
|---|---|---|---|---|
| | Treatment[#] | | | |
| **Weeks of treatment from V9** | **8 + Every 16wk** | **16 + Every 16wk** | | **+4wk past $EOT_B$** |
| **Day** | | | | **+28** |
| **Time window** | **±7** | **±7** | | **+7** |
| Physical examination, vital signs | | X | X | X |
| Adverse events, concomitant medication | | X | X | X |
| Safety Laboratory (blood and urine) | X | X | X | |
| Pregnancy test[5] | X | X | X | X |
| Resting 12-lead ECG[6] | | X | X | |
| Spirometry (FVC)[7] | | X | X | X |
| DLCO[7] | | X | X | |
| HCRU assessments | | X | X | |
| Non-elective hospitalization | | X | X | X |
| Acute ILD Exacerbations | | X | X | X |
| Dispense trial medication | | X | | |
| Collect trial drug | | X | X | |
| Compliance / drug accountability | | X | X | |
| IRT call/notification | | X | X | |
| Trial medication termination | | | X | |
| Vital status assessment[8] | | | X | |
| Conclude subject participation | | | | X |

# In case of dose change (reduction or re-escalation) additional visits have to be included (refer to Section 6.2.4). Termination of trial medication data needs to be collected any time trial medication is permanently discontinued.

[1] After completion of the 52 weeks treatment period (V9), patients will continue on blinded treatment (nintedanib or placebo) until the end of the trial or until a reason for treatment withdrawal is met. In case of premature discontinuation of trial medication, the patient will be expected to attend all visits (Part B visits) as originally planned until the end of the trial (except for the laboratory visits Xa) (see Section 6.2.3).

[2] Intermediate lab tests ("a"-Visits) to be done as needed for additional safety monitoring (see Section 4.2.2.2) at the discretion of the investigator.

[3] Visit X stands for V10, 11 etc. Visits should occur every 16 weeks until the end of the trial. Same visit procedures should be repeated at every visit.

[4] In case of premature discontinuation of study medication, $EOT_B$ should be done as soon as possible after last drug intake and a Follow-up Visit should be completed 4 weeks after $EOT_B$. A scheduled visit can be skipped if $EOT_B$ or Follow-up Visit occurs within 4 weeks prior to scheduled visits. For patients who complete the study regularly, $EOT_B$ should be scheduled after the Sponsor's communication of the end of the trial. Only in case the patient does not roll-over in the separate open-label study a Follow-up Visit should be completed 4 weeks after $EOT_B$.

[5] Urine dipstick pregnancy tests will be provided by central laboratory and should be performed in all women of childbearing potential at least at every visit and if necessary; additionally at home or at a local laboratory / local doctor every 4-6 weeks. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory. Documentation will be done in patient's notes.

[6] Resting ECG should be done at every other scheduled visit (i.e. Visit X)

[7] Order of lung function measurements: 1. FVC followed by patients rest; 2. DLCO. Measurements at approximately the same time each visit, reference time at Visit 2.

[8] Vital status at the time of the data cut-off for the primary analysis and at the end of the trial should be available for all randomized patients. Consent for a vital status call at respective time points in case of premature discontinuation of trial participation will be requested for all patients as part of the informed consent.

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# ABBREVIATIONS

| | |
|---|---|
| AC | Adjudication Committee |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALK | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| aPTT | Activated Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| ATP | Adenosine Triphosphate |
| ATS / ERS | American Thoracic Society / European Respiratory Society |
| AUC | Area under the Curve |
| AZA | Azathioprine |
| BI | Boehringer Ingelheim |
| bid | bis in die (twice a day) |
| BLQ | Below Limit of Quantification |
| BNP | Brain natriuretic peptide |
| CA | Competent Authority |
| CHP | Chronic fibrosing Hypersensitivity Pneumonitis |
| CK | Creatine Kinase |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CML | Local Clinical Monitor |
| CNS | Central Nervous System |
| CRA | Clinical Research Associate |
| CrCL | Creatinine Clearance |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTD | Connective Tissue Disease |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DDI | Drug-Drug Interaction |
| DEDP | Drug Exposure During Pregnancy |
| DILI | Drug-Induced Liver Injury |
| DLCO | Carbon Monoxide Diffusion Capacity |
| DLT | Dose Limiting Toxicity |
| DMARD | Disease-Modifying Anti-Rheumatic Drug |
| DMC | Data Monitoring Committee |
| DNA | Desoxyribo Nucleic Acid |
| DPLD | Diffuse Parenchymal Lung Diseases |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDTA | Ethylenediamine-Tetraacetic Acid |
| EOT | End of Treatment |
| ePRO | Electronic Patient Reported Outcome |
| EudraCT | European Clinical Trials Database |

| | |
|---|---|
| EQ5D | EuroQol 5-Dimensional quality of life Questionnaire |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FGFR | Fibroblast Growth Factor Receptor |
| FU | Follow-up |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transferase |
| GI | Gastro Intestinal |
| GLI | Global Lung Initiative |
| GP | General Practitioner |
| Hb | Haemoglobin |
| HCG | Human Chorionic Gonadotropin |
| HCRU | Health Care Resource Utilization |
| HCT | Haematocrit |
| HP | Hypersensitivity Pneumonitis |
| HR | Hazard Ratio |
| HRCT | High Resolution Computed Tomography |
| IEC | Independent Ethics Committee |
| IIPs | Idiopathic Interstitial Pneumonias |
| ILD | Interstitial Lung Disease |
| INR | International Normalized Ratio |
| iNSIP | Idiopathic Nonspecific Interstitial Pneumonia |
| IPAF | Interstitial Pneumonia with Autoimmune Features |
| IPF | Idiopathic Pulmonary Fibrosis |
| IQOLS | Impact on Quality of Life Scale |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ISF | Investigator Site File |
| K-BILD | King's Brief Interstitial Lung Disease Questionnaire |
| Lck | Lymphocyte-specific Tyrosine-protein Kinase |
| LDH | Lactate Dehydrogenase |
| L-PF | Living with Pulmonary Fibrosis Scale |
| LPLVPE | Last Patient Last Visit Primary Endpoint |
| Lyn | Lymphocyte antigen receptor-associated tyrosine kinases |
| MACE | Major Adverse Cardiovascular Events |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MMF | Mycophenolate Mofetil |
| MMRM | Mixed Effects Models for Repeated Measures |
| NAC | N-Acetylcysteine |
| NOA | Not Analyzed |
| NOR | No Valid Result |
| NOS | No Sample |
| OCS | Oral Corticosteroides |
| PD | Pharmacodynamics |
| PDGFR | Platelet-derived Growth Factor Receptor |

| | |
|---|---|
| P-gp | P-glycoprotein |
| PF-ILD | Progressive Fibrosing Interstitial Lung Disease |
| PF-IQOLS | Pulmonary Fibrosis Impact on Quality of Life Scale |
| PIT | Partial Thromboplastin Time |
| PK | Pharmacokinetics |
| PRO | Patient Reported Outcome |
| PT | Prothrombin Time |
| QoL | Quality of Life |
| QOLS | Quality of Life Scale |
| RA-ILD | Rheumatoid Arthritis-associated ILD |
| RBC | Red Blood cell Count |
| REP | Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present |
| REML | Restricted Maximum Likelihood |
| RNA | Ribo Nucleic Acid |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| s.c. | Subcutaneous |
| SD | Standard Deviation |
| SGRQ | Saint George's Respiratory Questionnaire |
| SMQ | Standard MedDRA Query |
| SOP | BI Standard Operating Procedures |
| $SpO_2$ | Saturation of oxygen |
| Src | proto-oncogene tyrosine-protein kinase src |
| SSc-ILD | Systemic Sclerosis-associated ILD |
| STPD | Standard Temperature and Pressure, Dry |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TOEP | Toeplitz |
| TOEPH | Heterogeneous Toeplitz |
| TS | Treated Set |
| TSAP | Trial Statistical Analysis Plan |
| UIP | Usual Interstitial Pneumonia |
| ULN | Upper Limit of Normal |
| VAS | Visual Analogue Scale |
| VEGF / R | Vascular Endothelial Growth Factor / Receptor |
| wk | Week |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

The aim of the current study is to investigate the efficacy and safety of 150 mg bid nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT) and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD. Section 1.1.1 below provides background information on ILDs in general, Section 1.1.2 on the concept of PF-ILD and Section 1.1.3 on the target study population of the current study.

### 1.1.1 ILD Overview

ILDs, also referred to as diffuse parenchymal lung diseases (DPLD), encompasses a large group of over 200 pulmonary disorders. The clinical assessment of a patient with ILD requires a multidisciplinary approach: medical history including occupational, environmental, medication, smoking and family history, physical examination, laboratory investigation, lung function testing together with chest imaging studies and histologic/Bronchial Alveolar Lavage examinations are necessary to establish the diagnosis. Achieving a correct diagnosis is a dynamic process requiring close communication between clinician, radiologist and pathologist (R13-4145).

Classification

There is no universally accepted single classification of ILDs. Figure 1.1: 1 shows one of the many classifications to illustrate the complex nature of ILDs. This classification uses five categories:

- idiopathic interstitial pneumonias (IIPs) which includes the most studied idiopathic pulmonary fibrosis (IPF),
- hypersensitivity pneumonitis (HP),
- autoimmune ILD that includes systemic sclerosis-associated ILD (SSc-ILD) and rheumatoid arthritis-associated ILD (RA-ILD),
- sarcoidosis and
- the group of “other ILDs”.

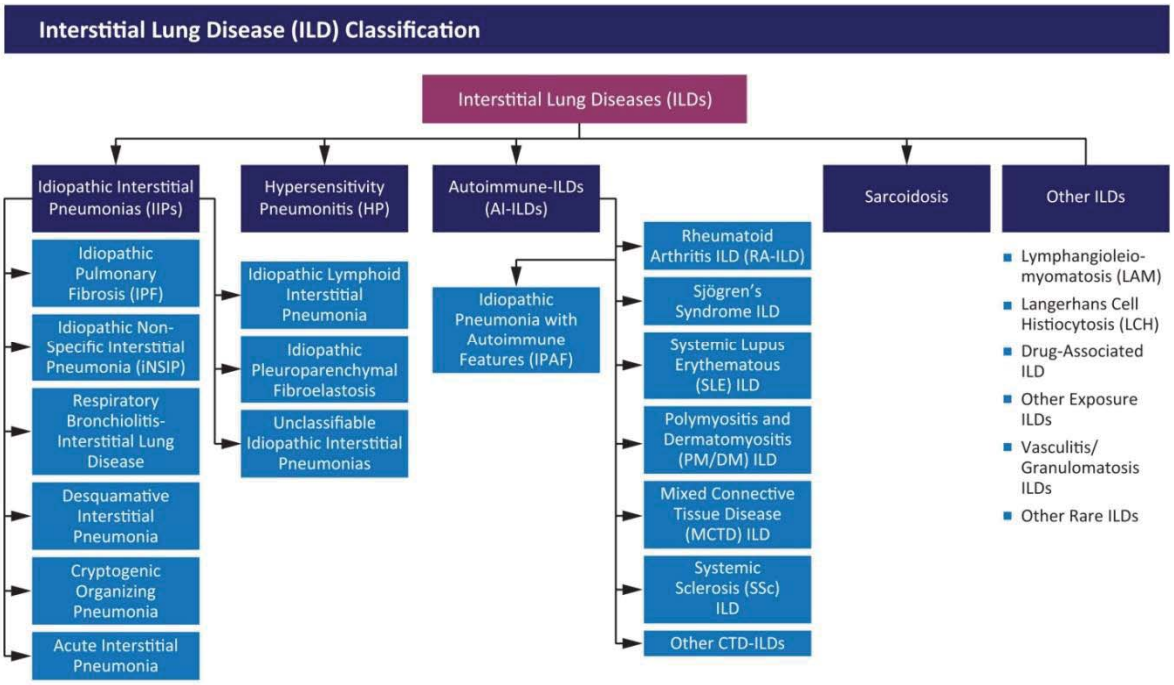


Figure 1.1: 1 Classification of interstitial lung disease

Pathomechanism

Overall, the major abnormality in ILDs is the disruption of the distal lung parenchyma. Although the pathogenesis, especially of the IIPs, remains unknown, it is generally agreed that some form of injury of the alveolar epithelial cells initiates an inflammatory response coupled with repair mechanisms. The initiating injury can be introduced via the airways (e.g. inhalation of mineral fibres or dust as in occupational diseases or sensitization to inhaled allergens as in hypersensitivity pneumonitis) or via the circulation (e.g. Connective Tissue Disease (CTD) and drug-induced ILDs). The injury-repair process is reflected pathologically as inflammation, fibrosis or a combination of both. However, irrespective of the underlying pathophysiology, the resulting alteration of the interstitial space leads to clinical symptoms such as dyspnoea and cough and physiologic abnormalities such as restrictive ventilatory deficit on pulmonary function testing (R16-0722).

Prognosis

Of all ILDs, IPF accounts for 20% to 30% and has the worst prognosis. IPF is a progressive, severely debilitating disease characterized by decline in lung function leading to respiratory failure and death. The median survival of IPF is 2.5–3.5 years from diagnosis (P11-07084).

The natural history of other ILDs is less well characterized because no large, prospective, controlled clinical trials have been performed in ILDs other than IPF and SSc-ILD.

The currently available data in different ILDs collectively suggest that the ILD injury pattern, and severity of lung involvement i.e. extent of fibrosis and longitudinal behaviour of lung function have major impact on prognosis. (P11-07084, R16-0557, R15-3264, R16-0553, R10-6539, R06-4127, R10-2727, P12-09611, R14-1149, R12-3648, R14-1150). The prognosis and clinical behaviour of fibrosing ILDs, particularly those with a Usual Interstitial Pneumonia (UIP) pattern, seem to be similar to that of IPF (R06-4129, R15-3262, R16-0553, R16-0496).

### 1.1.2 PF-ILD disease concept

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

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

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

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

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

Nintedanib is a kinase inhibitor indicated for the treatment of IPF, which has been shown to slow the progression of IPF. Based on the similarity in both the underlying pathophysiology and clinical course of PF-ILD and IPF, it is anticipated that nintedanib will elicit similar effects in PF-ILD as it demonstrated in IPF. This assumption is supported by the pre-clinical data indicating that nintedanib impacts fundamental processes of lung fibrosis and that the anti-fibrotic activity of nintedanib is independent of the cause of the fibrosing lung disease (P14-02860, P14-17410, P15-02392, P15-06100).

### 1.1.3 Patient population to be studied in the current trial

The current clinical trial will include patients with PF-ILD defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT) and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD (see Section 3.3.2).

The selection criteria (see Section 3.3) mirror the physicians' assessment in the clinical practice as they are based on a composite of the three dimensions of the disease activity i.e. worsening of symptoms, worsening of lung function and increasing fibrosis on chest images. Patients with physician diagnosis of ILD who fulfil at least one of the following criteria for PF-ILD within 24 months of the screening visit as assessed by the investigator will be eligible:

- clinically significant decline in FVC % predicted (%pred) based on ≥10% relative decline
- marginal decline in FVC %pred based on ≥5 – <10% relative decline in FVC combined with worsening of respiratory symptoms
- marginal decline in FVC %pred based on ≥5 – <10% relative decline in FVC combined with increasing extent of fibrotic changes on chest imaging
- worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging

Further, the following additional inclusion criteria will be used to ensure that patients with progressive fibrosing phenotype are selected for the study:

- Features of fibrosing lung disease with >10% extent on HRCT as confirmed by central review
- Baseline diffusing capacity of the lungs for carbon monoxide (DLCO) (%pred) <80%

Although patients with IPF exhibit a progressive phenotype, patients with clinical diagnoses of IPF will be excluded from the study (see Section 3.3). The rationale for this is based on the fact that the efficacy and safety of nintedanib has already been established in IPF. The current study will focus on patients with PF-ILD in whom the effects of nintedanib have not yet been assessed or demonstrated.

Nintedanib is hypothesized to have the same relative effect in all patients with PF-ILD i.e. an approximately 50% reduction in the annual rate of decline in FVC. However, it is expected that the absolute effect difference between groups will be the largest in the patients with PF-ILD with UIP pattern since these patients are assumed to have a larger annual rate of decline in FVC than patients with other fibrotic patterns. Based on this, the study will be enriched for patients with UIP pattern to maintain a high statistical power to detect a clinically meaningful effect of nintedanib in the rare disease of PF-ILD (see Section 3.2).

UIP pattern can be assessed either by surgical biopsy or HRCT. However, given the challenges associated with surgical sampling in clinical practice in patients with impaired lung function, availability of surgical biopsy is often limited. In contrast, HRCT assessment

of extent of fibrosis and fibrotic pattern has become an essential part of the evaluation and diagnosis of patients with ILDs. Since HRCT diagnosis of UIP has been shown to correlate with both histologic UIP (P11-07084) and prognosis in patients with ILDs (R16-0560, R16-0756, R14-3529), the proposed Phase III study will be enriched for patients with UIP pattern based on HRCT.

As described in the 2011 ATS/ERS Guidelines for IPF (P11-07084), the HRCT pattern of "definite UIP" requires the presence of honeycombing. However, recent evidence suggests that an HRCT pattern of fibrosing ILD defined by the presence of traction bronchiectasis is independently correlated with histologic UIP as well as prognosis in patients with IPF, CTD-ILD and CHP (R16-1567, R14-3529, R16-0752, R16-1568). These data are also supported by findings from the nintedanib Phase III studies in IPF. In a post-hoc pooled analysis, patients with traction bronchiectasis without evidence of honeycombing ("possible UIP" in the guidelines) were found to have similar lung function decline and response to therapy compared to those with "definite UIP" pattern on HRCT (P15-04977, P15-05695). These data suggest that both honeycombing and traction bronchiectasis may predict the presence of histologic UIP and have similar prognostic value.

Accordingly, the same HRCT criteria for UIP pattern as the Phase III IPF trials for nintedanib (P15-04977, P15-05695) will be used and the study will be enriched for patients meeting either criteria A, B and C, or criteria A and C, or criteria B and C as described below:

A. Definite honeycomb lung destruction with basal and peripheral predominance
B. Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C. Atypical features are ABSENT, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Since these criteria differ slightly from the current definition of radiologic UIP provided in the ATS/ERS guidelines (P11-07084), screening HRCT meeting the above criteria will be referred to as "HRCT with UIP-like fibrotic pattern only". Patients with HRCT patterns not meeting the above criteria will be referred to as "patients with other HRCT fibrotic patterns".

## 1.2 DRUG PROFILE

Mechanism of Action

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling. In addition nintedanib inhibits Fms-like tyrosine-protein kinase 3 (Flt 3), lymphocyte-specific tyrosine-protein kinase (Lck), tyrosine-protein kinase lyn (Lyn) and proto-oncogene tyrosine-protein kinase src (Src).

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

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

Pharmacokinetics

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

Co-administration of nintedanib with the P-glycoprotein (P-gp) inhibitor ketoconazole increased exposure to nintedanib by 60-70% based on area under the curve (AUC) and by 80% based on $C_{max}$ in a dedicated drug-drug interaction (DDI) study. Patients taking potent P-gp inhibitors (e.g. ketoconazole, erythromycin or cyclosporine) should be monitored closely for tolerability of nintedanib.

In a DDI study with the P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on $C_{max}$ upon co-administration with rifampicin compared to administration of nintedanib alone.

Based on population pharmacokinetic (PK) analysis, age and body weight were correlated with nintedanib exposure. However, their effects on exposure are not sufficient to warrant an a priori dose adjustment. There was no influence of sex or mild and moderate renal impairment (creatinine clearance (CrCL) > 30 mL/min) on the exposure of nintedanib. In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib was approximately 2-fold higher in volunteers with mild hepatic impairment (Child Pugh A) and approximately 8-fold higher in volunteers with moderate hepatic impairment (Child Pugh B). Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Clinical experience

Nintedanib (trade name: Ofev) was approved for the treatment of IPF in the US, EU, Japan and a large number of additional countries. Nintedanib has been in clinical development for

the treatment of several types of cancer. It is currently being evaluated for the treatment of systemic sclerosis in patients with SSc-ILD as part of a separate study.

Summary of the efficacy results in IPF

The main evidence of the efficacy of nintedanib in IPF is provided by the 2 randomized, double-blind, placebo-controlled confirmatory phase III trials 1199.32 (U13-2381-01) and 1199.34 (U13-2382-01), which were of identical design and investigated the efficacy and safety of nintedanib 150 mg bid versus placebo over 52 weeks. Patients were randomized at 2:3 ratio (placebo: nintedanib). The primary endpoint in these trials was the annual rate of decline in Forced Vital Capacity (FVC) expressed in mL over 52 weeks and the key secondary endpoints were the change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at 52 weeks and the time to first acute IPF exacerbation over 52 weeks. Additional evidence of efficacy is provided by the 52-week randomized, double-blind, placebo-controlled, proof-of-concept phase II trial 1199.30. The primary endpoint in this trial was the same as the phase III trials; the annual rate of decline in FVC (expressed in L over 52 weeks). Change from baseline in SGRQ total score at 52 weeks and time to first acute IPF exacerbation over 52 weeks were also investigated as secondary endpoints in trial 1199.30 (U11-1225-02).

In both phase III trials, nintedanib significantly reduced the annual rate of decline in FVC compared with placebo. The adjusted difference in the annual rate of decline between nintedanib and placebo in the 2 trials was similar: 125 mL (95% CI 78, 173; p <0.0001) in trial 1199.32 and 94 mL (95% CI 45, 143; p=0.0002) in trial 1199.34. Of note, the consistent phase III results for the primary endpoint are further supported by the results of the phase II trial 1199.30. In this trial, the difference in the annual rate of decline in FVC between nintedanib 150 mg and placebo was 0.131 L/year (95% CI 0.027, 0.235; nominal p=0.0136).

The difference in the adjusted mean change in SGRQ total score at 52 weeks was statistically significant and in favour of nintedanib in trial 1199.34 (-2.69; 95% CI -4.95, -0.43; p = 0.0197); there was no treatment difference in trial 1199.32 (-0.05; 95% CI -2.50, 2.40; p = 0.9657). In the phase II trial 1199.30, the difference in the adjusted mean change from baseline in SGRQ total score at 52 weeks was -6.12 (95% CI -10.57, -1.67; p=0.0071) in favour of nintedanib.

In trial 1199.34, the frequency of patients with at least 1 acute IPF exacerbation over 52 weeks based on Investigator reporting was lower in the nintedanib group (3.6%) than in the placebo group (9.6%). The hazard ratio (HR) of 0.38 (95% CI 0.19, 0.77) indicated a significantly lower risk of having a first acute IPF exacerbation in the nintedanib group than in the placebo group at any time point over 52 weeks. In trial 1199.32, the frequency of patients with at least 1 acute IPF exacerbation based on Investigator reported adverse events was 6.1% in the nintedanib group and 5.4% in the placebo group; the HR was 1.15 (95% CI 0.54, 2.42), indicating no significant difference in the risk of first acute IPF exacerbation between the treatment groups. In the phase II trial 1199.30, the number of patients with acute IPF exacerbations over 52 weeks was lower in the nintedanib group (2.3%) compared to placebo (13.8%). The estimated HR of nintedanib versus placebo was 0.16 (95% CI 0.04,

0.71; p=0.0054) indicating a significantly lower risk of having an acute IPF exacerbation in the nintedanib group than in the placebo group.

In the pre-specified pooled analysis of the Phase III studies 1199.32 and 1199.34, consistent with the effect of nintedanib on the decline in lung function, overall mortality over 52 weeks was numerically lower in the nintedanib group (5.5%) than in the placebo group (7.8%). The analysis of the time to death resulted in a hazard ratio (HR) of 0.70 (95% CI 0.43, 1.12; p=0.1399) indicating a 30% reduction in the risk of death in the nintedanib group compared with placebo. The results of all survival endpoints (such as on-treatment mortality and respiratory mortality) showed a consistent numerical difference in favour of nintedanib.

A post-hoc time to progression analysis, defined as time to ≥10% absolute decline of FVC % predicted (% pred) or death was performed on data from the phase III trials, 1199.32 and 1199.34. This showed that the risk of progression was statistically significantly reduced for patients treated with nintedanib compared with placebo in both trials. The results were consistent across the 2 Phase III trials with a HR of 0.53 (95% CI 0.39, 0.72; p=0.0001) in study 1199.32 and a HR of 0.67 (95% CI 0.51, 0.89; p=0.0054) in 1199.34. In the pooled analysis of the Phase III trials, there was a 40% reduction in the risk of progression for patients treated with nintedanib compared to placebo (HR: 0.60; 95% CI 0.49, 0.74; p<0.0001).

In conclusion: nintedanib has shown robust, reproducible, statistically significant, and clinically meaningful effects on the decline in lung function as measured by FVC. In 2 large, international, placebo controlled phase III trials of identical design, nintedanib statistically and clinically significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo, with a similar treatment effect, about 100 mL/year, i.e. a relative difference of 50% between nintedanib and placebo, in both trials. These consistent phase III results are further supported by 1-year data from the phase II trial 1199.30, which showed comparable results for nintedanib 150 mg bid in regard to annual rate of decline in FVC.

As the natural history of IPF has been described as a progressive decline in pulmonary function until eventual death from respiratory failure or complicating comorbidity (P11-07084), the effects of nintedanib are considered consistent with slowing disease progression.

Summary of the safety results in IPF

The safety profile of nintedanib has been investigated comprehensively based on the pooled data of the two phase III studies 1199.32 and 1199.34. The proportion of patients with Adverse Events (AEs) and Serious Adverse Events (SAEs) was comparable between the nintedanib and placebo groups.

During the nintedanib trials 1199.32 and 1199.34, the most commonly reported adverse events (≥ 10% and ≥1.5 times placebo) experienced with nintedanib were diarrhoea (nintedanib 62.4% vs placebo 18.4%) , nausea (24.5% vs 6.6%), abdominal pain (15.0% vs 6.1%), vomiting (11.6% vs 2.6%) and decreased appetite (10.7% vs 5.7%). Most of these AEs were of mild or moderate intensity, reported as non-serious, and were managed by symptomatic treatment and/or temporary interruption and/or reduction of the nintedanib

dosage. 19% of patients treated with nintedanib had an adverse event leading to treatment discontinuation (compared to 13% in the placebo treatment group). The most commonly reported adverse events (≥ 1% and more than for placebo) leading to nintedanib discontinuation were diarrhoea (4.4%), nausea (2.0%) and decreased appetite (1.4%).

Liver enzyme elevations (AST and/or ALT ≥3 x ULN) were experienced by 5.0% of patients treated with nintedanib in the phase III trials (versus 0.7% of patients treated with placebo).

Arterial thromboembolic events were infrequently reported: in 0.7% of patients in the placebo and 2.5% in the nintedanib treated group. While adverse events reflecting ischemic heart disease were overall balanced between the nintedanib and placebo groups, within this group of terms a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%).

For further details refer to the current version of the Investigators Brochure

In conclusion: the most frequent AEs were gastrointestinal events which were manageable by the proposed dose regimen that includes dose reduction and dosing interruption. This dosing regimen was also effective in the management of liver enzyme and bilirubin elevations that are associated with nintedanib treatment.

Overall, the evidence available from the clinical development programme demonstrates a favourable benefit-risk balance for nintedanib in the treatment of patients with IPF.

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

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

Nintedanib is a kinase inhibitor indicated for the treatment of IPF. Based on the similarity in both the underlying pathophysiology and clinical course of PF-ILD and IPF, the established efficacy and safety profile of nintedanib in IPF is considered Proof of Concept for PF-ILD.

As nintedanib is expected to impact the final common pathogenic mechanisms of progressive fibrosis similarly as in IPF, it is anticipated that nintedanib will elicit similar effects in PF-ILD as it demonstrated in IPF.

Based on data suggesting that the HRCT pattern has a major impact on prognosis, the study population will be enriched for patients with HRCT with UIP-like fibrotic pattern only (see Section 1.1.3).

## 2.2 TRIAL OBJECTIVES

The objective of the trial is to investigate the efficacy and safety of 150 mg bid nintedanib in patients with PF-ILD compared to placebo over 52 weeks (Part A).

The primary objective is to demonstrate a reduction in lung function decline, as measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52 weeks.

The main secondary objectives of the trial are to investigate the effect of treatment on quality of life using the King's Brief Interstitial Lung Disease Questionnaire (K-BILD), and to assess the effect of nintedanib on time to first acute ILD exacerbation and overall survival over 52 weeks. Other objectives include the assessment of other lung function parameters and other symptoms of the disease such as dyspnea and cough (L-PF) over 52 weeks.

PK, safety and tolerability of nintedanib and biomarkers (e.g. serologic and imaging) will also be assessed.

The objectives of Part B (variable treatment period beyond 52 weeks) will be to collect supportive, longer term efficacy (time to event endpoints) and safety data on the effect of nintedanib compared to placebo.

## 2.3 BENEFIT - RISK ASSESSMENT

In the group of patients with PF-ILD the natural history of the disease appears to follow a course similar to IPF with worsening of respiratory symptoms, lung function, quality of life (QoL) and functional status, as well as early mortality. With the exception of nintedanib and pirfenidone which are available for patients with IPF, there is no approved therapy for PF-ILD.

In patients with IPF, a typical example of PF-ILD, nintedanib has shown robust, reproducible, statistically significant, and clinically meaningful effects on the decline in lung function consistent with slowing disease progression. The safety profile of nintedanib has been investigated comprehensively. The most frequent AEs were gastrointestinal events (nausea, vomiting, diarrhoea, abdominal pain) which were manageable by symptomatic treatment or adjustment of the dose regimen that includes dose reduction and dosing interruption. This dosing regimen adjustment was also effective in the management of liver enzyme and bilirubin elevations that are associated with nintedanib treatment (see Section 4.2.1). Cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. The majority of patients presented with mild to moderate liver enzyme elevation, which was in most cases transient upon dose reduction or treatment discontinuation. However, severe DILI with fatal outcome has also been reported.

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

Risks of nintedanib treatment also include hypertension, bleeding, thrombocytopenia, gastrointestinal perforations, thrombo-embolism and bleeding, pancreatitis, decreased appetite and decreased weight.

The safety assessments and evaluation plan in the current protocol are based on the information available to date from the IPF program. Important identified risks and important potential risks described for nintedanib in IPF are taken into account by the definition of eligibility criteria and will be closely monitored during the conduct of the study. No effect of nintedanib is expected on the underlying conditions e.g. RA. Hence potential changes in the course of the underlying diseases will be captured via AE reporting and safety laboratory assessments; no specific monitoring tools will be applied.

A placebo arm is needed to allow for a true assessment of the effects of nintedanib on the rate of decline in FVC. Treatment with unapproved anti-inflammatory/immunomodulatory treatment for ILD will be required to be discontinued and a wash-out period will be observed, if applicable, before randomization of the patient to either placebo or to nintedanib. The use of placebo comparator is justified by the following: there is no approved treatment for ILD except for IPF. The management of ILD has been based on the suppression of inflammation with corticosteroids and immunomodulator/steroid-sparing agents or both. However, there are no controlled clinical trials to support the efficacy and safety of these therapies. It is hypothesized that in PF-ILD the response to lung injury includes fibrosis which becomes self-sustaining and the current unapproved medications used in clinical practice to treat ILD are not / are no longer effective at this stage. In the proposed study, patients whose fibrosing ILD has worsened despite use of unapproved treatment of ILD will be eligible (see Section 3.3). In case of clinically significant deterioration, initiation of additional therapy for ILD is allowed after 6 months (see Section 4.2.2).

Based on the similarity in both the underlying pathophysiology and clinical course of PF-ILD and IPF, it is anticipated that nintedanib will elicit comparable efficacy in PF-ILD as

demonstrated in IPF. To achieve a positive benefit-risk profile, a similar safety profile in PF-ILD to that in IPF will be required.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, prospective, randomized, placebo-controlled, double blind clinical trial to investigate the efficacy and safety of nintedanib at a dose of 150 mg bid, in patients with PF-ILD over 52 weeks.

A total of approximately 600 patients will be randomized, 300 in the active treatment arm and 300 in the placebo group. The study population will be enriched for patients with HRCT with UIP-like fibrotic pattern only applying the criteria used in the Phase III IPF studies for nintedanib, and as determined by the central reviewers (see Section 3.3.4). It is planned to enrol 400 patients with PF-ILD with HRCT with UIP-like fibrotic pattern only, i.e. two thirds (66.7%) of the randomized patients and 200 patients with PF-ILD with other HRCT fibrotic patterns.

After signing informed consent (IC), the initial screening visit (Visit 1) will be performed to determine eligibility. Following completion of Visit 1, patients with established PF-ILD, as assessed by the Investigator, will enter a screening period of maximum 12 weeks to confirm HRCT eligibility and determine HRCT pattern for randomization (see Section 3.3.4), and to allow for wash-out of treatment for ILD, if applicable (see Section 4.2.2).

Written confirmation by the central readers that the protocol criteria for qualifying HRCT are met will be mandatory for randomization. For detailed procedural assessments of patient's eligibility, please refer to the Flowchart Part A and Section 6.2.1.

Once HRCT eligibility is confirmed, Visit 2 will be scheduled to collect all clinical and safety information, and review all inclusion and exclusion criteria. Patients will be randomized in 1:1 ratio to either nintedanib or placebo and then enter the treatment phase for a minimum of 52 weeks. Randomization (stratified by HRCT pattern: "UIP-like fibrotic pattern only", or "Other fibrotic patterns") will be performed by phone or Internet, using an Interactive phone/web Response System (IRT).

Part A of the study will consist of Visits 2 through 9, which will occur within one year of randomization. Following completion of the week 52 visit (Visit 9), patients will continue to have study visits every 16 weeks (Part B) until the end of the trial. Intermediate laboratory tests for safety monitoring will be performed as needed for additional safety monitoring until the end of the trial.

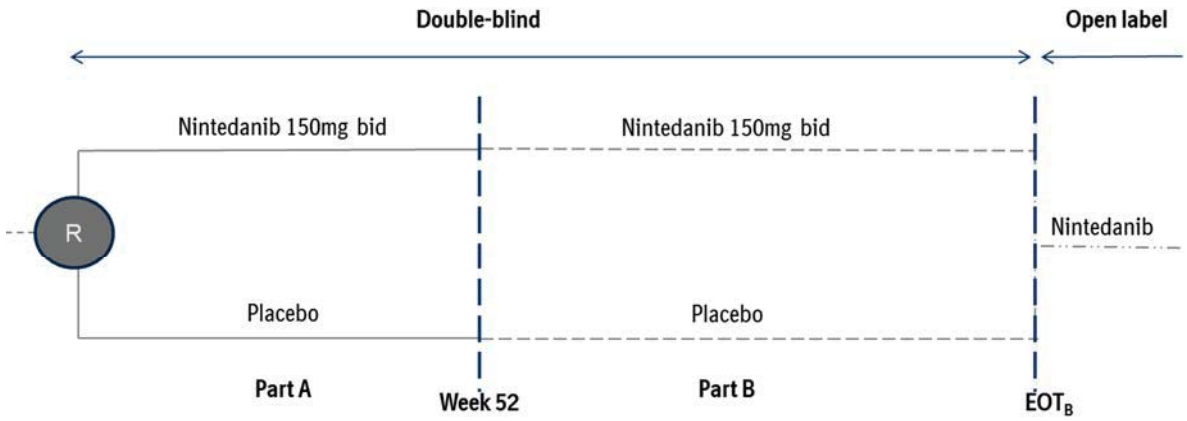


Figure 3.1: 1 Study design schematic of study 1199.247 followed by a separate open label trial (optional): Part A (Visit 1 through 9 over 52 weeks) and Part B (Visit 10 through EOT Visit over variable period for each patient)

The primary assessment of benefit-risk of nintedanib in patients with PF-ILD will be based on efficacy and safety data over 52 weeks.

The primary analysis of this study will therefore be performed once the last randomized patient reaches the Week 52 Visit (Visit 9 at the end of Part A). At that time, a first database lock will occur and all the data will be unblinded. Efficacy and safety analyses will be performed on the data from Part A of the trial to assess the benefit-risk of nintedanib over 52 weeks. In addition, data collected in Part B of the trial (after 52 weeks) and available at the time of data cut-off for the primary analysis will be reported together with data from Part A (i.e. over the whole trial) (see Section 5.1).

After review of the efficacy and safety data available after the first data base lock, the Sponsor will communicate the end of the trial and an $EOT_B$ visit has to be performed in all ongoing patients. Depending on the results of the evaluation, patients receiving trial medication until the end of Part B will be eligible for open-label treatment with nintedanib in a separate study.

Trial 1199.247 i.e. Part B will continue until all patients have completed the $EOT_B$ visit and the Follow-up Visit as applicable. A final database lock will then occur and Part B data collected between the data cut off for the primary analysis and the final database lock will be reported together with data from Part A i.e. over the whole trial (see Section 5.1).

Concomitant treatment rules, dose reduction procedures and short term drug interruptions in case of adverse events are described in Section 4.2.

For each patient, the study period is from the signature of the Informed Consent until their last visit. Adverse events are collected during the entire study period and are considered treatment-emergent from first study drug intake until 28 days after drug discontinuation.

All patients who prematurely discontinue trial medication will need to complete an End of Treatment (EOT) visit and a Follow-up (FU) visit 4 weeks later. Patients who prematurely discontinue trial medication will be asked to remain in the study and to return to all regularly scheduled visits until the end of the trial. This request will be outlined in the patient information / informed consent procedure prior to randomization.

For those patients who are unable to complete the scheduled visits, every attempt will be made to get information on vital status at 52 weeks after randomization, as well as at the time of the data cut-off for the primary analysis and at the end of the trial. The need for vital status information will be explained to patients prior to their participation in the trial and will be part of the patient information / informed consent procedure prior to randomization.

### 3.1.1 Administrative structure of the trial

Study sites will consist of specialized referral centres experienced in the management of ILD. A Coordinating Investigator, chosen among experts in the field of ILD, will be nominated and will be responsible for providing expert medical support for Investigators at different centres participating in this multicentre trial. Tasks and responsibilities of the Coordinating Investigator will be defined in a contract. Relevant documentation on all participating (Principal) Investigators and other important study personnel, including their curricula vitae, will be filed in Investigator Site File (ISF).

*For Japan:*
*Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF.*

HRCT eligibility criteria and HRCT pattern will be confirmed by central review prior to randomization (see Section 3.3.4). Central review of the HRCT images will be performed by two independent specialists in thoracic radiology with extensive expertise in the interpretation of HRCT. The reviewers will be blinded to demographic and clinical data of the patient. Cases of disagreement will be adjudicated by a third reviewer.

An independent blinded Adjudication Committee (AC) will review all fatal cases and adjudicate all deaths to either cardiac, respiratory or other causes (see Section 5.3.7). The AC will also review all adverse events categorized as major adverse cardiovascular events (MACE) (see Section 5.3.7).

A Data-Monitoring Committee (DMC), independent of the Sponsor will be in place until the database lock for the primary analysis after the last patient reaches the Week 52 visit (Part A: Visit 9) and will assess the progress of the clinical trial, including safety assessment at specified intervals, to recommend to the Sponsor whether to continue, modify, or stop the trial (see Section 5.3.7). The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

Central laboratory facilities will handle all laboratory analyses of the trial. Samples for intermediate measurements (liver enzymes, creatinine) and pregnancy tests may be collected at the office of a local doctor using trial specific lab kits that will be sent to a central laboratory for analyses. These kits will be provided at each study visits as applicable to women of childbearing age.

An IRT (interactive response technology) vendor will be used in this trial.

The Sponsor has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by Boehringer Ingelheim (BI) according to BI SOPs.

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

Placebo control

There is no approved treatment for ILD except for IPF. The management of ILD has been based on the suppression of inflammation with corticosteroids and immunomodulator/steroid-sparing agents or both. However, there are no controlled clinical trials to support the efficacy and safety of these therapies. In the current study, patients whose fibrosing ILD has worsened despite use of unapproved treatment for ILD will be eligible (see Section 3.3.2). To minimize potential impact on efficacy and safety assessments, treatment with unapproved anti-inflammatory/immunomodulatory treatment for ILD will be required to be discontinued and a wash-out period will be observed, if applicable, before randomization of the patient to either placebo or to nintedanib (see Section 4.2.2). As there is no targeted antifibrotic therapy currently indicated for the treatment of ILD in these patients, the use of placebo comparison in PF-ILD is considered justified. However, similar to the Phase III IPF studies, initiation of concomitant immunomodulatory treatment as medically indicated will be allowed for the management of worsening of the disease after the first six months of the trial (see Section 4.2.2).

Dose regimen

The dosing regimen to be investigated is the same as approved for IPF indication, i.e. 150 mg bid with the option of dose reduction to 100 mg and/or interruptions to manage adverse events (AEs). Exploration of higher dose(s) is not regarded feasible due to dose-limiting

toxicities (DLTs) observed in the oncology development program; testing of lower dose(s) is not considered based on lack of efficacy in IPF.

12 months treatment duration for primary assessment of benefit-risk of nintedanib in PF-ILD

The primary assessment of benefit-risk of nintedanib in patients with PF-ILD will be based on efficacy and safety data over 52 weeks (12 months) of study treatment. This is based on the assumptions that PF-ILD is similar to IPF and the treatment effect of nintedanib demonstrated in IPF will be reproduced in PF-ILD.

In IPF, the association between decline in FVC over one year and clinical outcome has been examined in the scientific literature (R10-6539, R06-4127, P12-10347, R14-1150, P14-06844, R14-1149). While these publications do not, by stringent statistical criteria, prove that reduction in the annual rate of FVC decline is a surrogate for improved survival, they do strongly suggest that an increased rate and extent of decline in FVC at 12 months is associated with an increased risk of death. Due to the expected similarity in disease progression, especially for FVC decline and mortality, between PF-ILD patients and IPF patients, the proposed benefit-risk assessment over12 months is regarded as the most appropriate period to detect a difference in the reduction of FVC decline between nintedanib and placebo in PF-ILD patients.

Additional data beyond 12 months will be collected while patients remain on blinded treatment to provide supportive longer term efficacy and safety data on the effect of nintedanib in a controlled manner, especially for the early enrollers to the study. Due to the varying length of follow-up in Part B of the trial, the efficacy measures incorporating data from Part A and Part B will focus on time to event endpoints.

The use of placebo control for this extended period is justified by the lack of approved ILD treatments and by the provision of the protocol that allows for the use of any of the unapproved medications utilized in the clinical practice to treat ILD, in case of worsening of the patient's ILD as assessed by the investigator (see Section 4.2.2.1).

Primary and main secondary endpoints

The primary endpoint of the study is the annual rate of decline in forced vital capacity (FVC). In clinical trials in IPF, FVC is an established efficacy parameter; mean changes in FVC over time are considered relevant to assess the effect of a pharmacologic intervention at population level (P11-13635, P12-10347, R06-4126, R06-4127). FVC as primary endpoint has served as basis for worldwide regulatory approvals for nintedanib and pirfenidone in IPF (P14-07514, P10-13367).

Similar to IPF, in other interstitial lung diseases (ILDs) the accelerated decline in lung function over time is considered consistent with disease progression and is thought to be associated with mortality (R10-6539, R06-4127, P12-10347, R14-1150, P14-06844, R14-1149). In PF-ILD, and even more so for patients with PF-ILD with histologic usual interstitial pneumonia (UIP) pattern, it is expected that the placebo decline in FVC is similar to the

decline observed in patients with IPF and that nintedanib will slow the decline in FVC in a similar way as it does in IPF.

The main secondary endpoints are the absolute change from baseline in King's Brief Interstitial Lung Disease (K-BILD) total score at week 52, time to first acute ILD exacerbation or death over 52 weeks and time to death over 52 weeks. These endpoints are considered relevant to the assessment of the effect of nintedanib in PF-ILD and will provide the main supportive evidence to the primary endpoint assessment.

Enrichment design

Based on data suggesting that the HRCT pattern has a major impact on prognosis (see Section 1.1), the study population will be enriched for patients with HRCT with UIP-like fibrotic pattern only (see Section 3.3.4). An enrichment design will be used in order to increase the likelihood of detecting a clinically meaningful effect of nintedanib with the greatest statistical efficiency, therefore ensuring feasibility of the enrolment of patients with this rare disease. This enrichment design is consistent with the considerations for prognostic enrichment strategies in the Food and Drug Administration (FDA) Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drug and Biological Products (R13-0580).

## 3.3 SELECTION OF TRIAL POPULATION

A total of approximately 600 patients with PF-ILD will be randomized (300 in the active dose group and 300 in placebo) in approximately 14 countries. Approximately 100 sites are each expected to include a minimum of 4-5 patients.

The study population will be enriched for patients with HRCT with UIP-like fibrotic pattern only: about 400 patients with PF-ILD with HRCT with UIP-like fibrotic pattern only and about 200 patients with PF-ILD with other HRCT fibrotic patterns will be randomized.

Patients with clinical diagnosis of IPF will be excluded from the current study (see Section 1.1.3).

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

### 3.3.1 Main diagnosis for trial entry

Outpatients aged ≥ 18 years with PF-ILD, defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on HRCT and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD, 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).

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

### 3.3.2 Inclusion criteria

1. Written Informed Consent consistent with ICH-GCP and local laws signed prior to entry into the study (and prior to any study procedure including shipment of HRCT to reviewer).
2. Male or female patients aged ≥ 18 years at Visit 1.
3. Patients with physician diagnosed ILD who fulfil at least one of the following criteria for PF-ILD within 24 months of screening visit (Visit 1) despite treatment with unapproved medications used in clinical practice to treat ILD, as assessed by the investigator (refer to Exclusion Criteria):
   a. Clinically significant decline in FVC % pred based on a relative decline of ≥10%
   b. Marginal decline in FVC % pred based on a relative decline of ≥5-<10% combined with worsening of respiratory symptoms
   c. Marginal decline in FVC % pred based on a relative decline of ≥5-<10% combined with increasing extent of fibrotic changes on chest imaging
   d. Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging
   [Note: Changes attributable to comorbidities e.g. infection, heart failure must be excluded. Unapproved medications used in the clinical practice to treat ILD include but are not limited to corticosteroid, azathioprine, mycophenolate mofetil (MMF), n-acetylcysteine (NAC), rituximab, cyclophosphamide, cyclosporine, tacrolimus].
4. Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 12 months of Visit 1 as confirmed by central readers.
5. For patients with underlying CTD: stable CTD as defined by no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1.
6. DLCO corrected for Haemoglobin (Hb) [visit 1] ≥ 30% and <80% predicted of normal at Visit 2 (refer to Appendix 10.1).
7. FVC ≥ 45% predicted at Visit 2 (refer to Appendix 10.1).

### 3.3.3 Exclusion criteria

1. AST, ALT > 1.5 x ULN at Visit 1
2. Bilirubin > 1.5 x ULN at Visit 1
3. Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula at Visit 1 (refer to Appendix 10.2).

   [Note: Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. Visit 2 laboratory results will be available only after randomization. In case at Visit 2 the results do no longer satisfy the entry criteria, the Investigator has to decide whether it is justified that the patient remains on study drug. The justification for decision needs to be documented. Laboratory parameters that are

found to be abnormal at Visit 1 are allowed to be re-tested (once) if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign) or the result of a temporary and reversible medical condition, once that condition is resolved].

4. Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment).
5. Previous treatment with nintedanib or pirfenidone.
6. Other investigational therapy received within 1 month or 6 half-lives (whichever was greater) prior to screening visit (Visit 1).
7. Use of any of the following medications for the treatment of ILD: azathioprine (AZA), cyclosporine, MMF, tacrolimus, oral corticosteroids (OCS) >20mg/day and the combination of OCS+AZA+NAC within 4 weeks of Visit 2, cyclophosphamide within 8 weeks of Visit 2, rituximab within 6 months of Visit 2.
   Note: Patients whose RA/CTD is managed by these medications should not be considered for participation in the current study unless change in RA/CTD medication is medically indicated (refer to Inclusion Criterion #5)
8. Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 Guidelines (P11-07084).
9. Significant Pulmonary Arterial Hypertension (PAH) defined by any of the following:
   a. Previous clinical or echocardiographic evidence of significant right heart failure
   b. History of right heart catheterization showing a cardiac index ≤ 2 l/min/m²
   c. PAH requiring parenteral therapy with epoprostenol/treprostinil
10. Primary obstructive airway physiology (pre-bronchodilator FEV1/FVC < 0.7 at Visit 1).
11. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
12. Major extrapulmonary physiological restriction (e.g. chest wall abnormality, large pleural effusion)
13. Cardiovascular diseases, any of the following:
    a. Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 month of Visit 1
    b. Myocardial infarction within 6 months of Visit 1
    c. Unstable cardiac angina within 6 months of Visit 1
14. Bleeding risk, any of the following:
    a. Known genetic predisposition to bleeding.
    b. Patients who require
       i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
       ii. High dose antiplatelet therapy.
       [Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited].
    c. History of haemorrhagic central nervous system (CNS) event within 12 months of Visit 1.

d. Any of the following within 3 months of Visit 1:
   i. Haemoptysis or haematuria
   ii. Active gastro-intestinal (GI) bleeding or GI – ulcers
   iii. Major injury or surgery (Investigators judgment).
e. Coagulation parameters: International normalized ratio (INR) >2, prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) by >1.5 x ULN at Visit 1.

15. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1.
16. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin)
17. Patients with peanut allergy.
18. Other disease that may interfere with testing procedures or in the judgment of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial.
19. Life expectancy for disease other than ILD < 2.5 years (Investigator assessment).
20. Planned major surgical procedures.
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
22. Women of childbearing potential* not willing or able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to and 3 months after nintedanib administration. A list of contraception methods meeting these criteria is provided in the patient information.
23. In the opinion of the Investigator, active alcohol or drug abuse.
24. Patients not able to understand or follow trial procedures including completion of self-administered questionnaires without help.

*A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

### 3.3.4 Imaging criteria

Patients with original physician diagnosis of different fibrosing ILDs, i.e. CTD-ILD, chronic fibrosing HP, iNSIP, unclassifiable IIP and environmental/ occupational fibrosing lung disease will be included if they meet the protocol criteria for PF-ILD. While the clinical ILD diagnosis will not be verified, central review of the screening HRCT images will ensure that relevant lung fibrosis is present and the HRCT pattern is not indicative of other causes of progression.

At screening the most recent (not older than 12 months at screening) HRCT image of the patient will be evaluated; previous HRCT images will not be collected or reviewed. Hence inclusion based on increasing extent of fibrotic changes on chest imaging within 24 months will reflect the investigator's judgement.

Eligible patients will have fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing with disease extent of >10%.

The following co-existing features will be accepted:

- ground glass opacity
- upper lung or peribronchovascular predominance
- mosaic attenuation
- air trapping
- centrilobular nodules

The following co-existing features will not be allowed:

- widespread consolidation
- progressive massive fibrosis

In addition, determination of the HRCT pattern will also be done by central review and will be used for randomization stratification. The study will be enriched for patients meeting either criteria A, B and C, criteria A and C, or criteria B and C as described below. These patients will be referred to as "patients with HRCT with UIP-like fibrotic pattern only". Patients with PF-ILD who do not meet these criteria will be referred to as "patients with other HRCT fibrotic patterns".

A=Definite honeycomb lung destruction with basal and peripheral predominance
B=Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C=Atypical features are ABSENT, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Specifications for the HRCT acquisition will be provided in the ISF. Screening HRCT can be performed as part of the study in case the available HRCT does not meet the required image acquisition specifications.

### 3.3.5 Removal of patients from therapy or assessments

3.3.5.1 Removal of individual patients from therapy

The trial medication has to be permanently discontinued in the following circumstances:

- The patient experiences signs of hepatic injury, defined in Section 5.3.6.1.
- In the opinion of the Investigator, the patient experiences unacceptable adverse events despite dose adjustments and supportive care.
- Use of restricted concomitant treatment: as defined in Section 4.2.2 "restrictions".
- Pregnancy: If a patient becomes pregnant during the trial the investigational product needs to be stopped and the patient should be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report (CTR) until patient´s last visit and any events thereafter will be reported in the BI drug safety database. Refer to Section 5.3.6 for detailed information on event reporting in case of pregnancy.

Premature discontinuation: in case the patient discontinues study drug, it is of utmost importance for the robustness and integrity of the trial results that his/her lung function parameters and safety data are recorded until the end of the 52 weeks period. Thus all patients will be asked to follow their visit schedule until the end of the trial (refer to Section 6.2.3).

For patients who prematurely discontinue trial medication and are unable to complete the scheduled visits, every attempt will be made to get information on vital status at 52 weeks after randomization, as well as at the time of the data cut-off for the primary analysis and at the end of the trial.

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

- Major surgery, including any abdominal or intestinal surgery.
- Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, etc.), or high-dose antiplatelet therapy. (Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy is allowed.).
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
- Increased risk of bleeding e.g. haemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or GI-ulcers.

For conditions that allow treatment interruption please refer to Section 4.2.1.

#### 3.3.5.2 Removal of individual patients from trial

All efforts should be made to continue to record safety data and lung function parameters for patients who withdraw study medication prematurely. Patients, will be asked to follow their original visit schedule (except the laboratory ‘a-Visits’; refer to Section 6.2.2).

Participation in the trial must be stopped if the patient withdraws his consent for all procedures of the study. There is no other pre-specified criterion to withdraw from the trial. Attempts to collect vital status will be made at Week 52, at the time of data cut-off for the primary analysis and at the end of trial for patients who have withdrawn consent as applicable (see Section 5.3.2).

For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the electronic Case Report Form (eCRF). These data will be included in the trial database and will be reported.
For final assessment and safety follow-up, please refer to Section 6.2.3.

#### 3.3.5.3 Discontinuation of the trial by the Sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of Good Clinical Practice (GCP), the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

The Investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

# 4. TREATMENTS

## 4.1 TREATMENTS TO BE ADMINISTERED

### 4.1.1 Identity of BI investigational product(s)

Table 4.1.1: 1 Identity of BI investigational products

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

### 4.1.2 Method of assigning patients to treatment groups

During Visit 2 after eligibility has been confirmed including the criterion of presence of features of fibrosing lung disease with >10% extent on HRCT and the HRCT pattern has been determined by central review, patients will be randomized to receive nintedanib or placebo in a 1:1 ratio according to a randomization plan. The randomization list will be generated using a validated system. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT). Access to the codes will be controlled and documented.

Technical and statistical features of the process of treatment allocation are described in Section 7.6.

To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

Dose reductions or re-escalation (refer to Section 6.2.4) will need to be assigned through IRT and require a patient visit.

### 4.1.3 Selection of doses in the trial

Based on the efficacy, safety and dose-finding from trials investigating nintedanib in IPF, a dose of 150 mg bid is selected for the PF-ILD program. With 150 mg bid, acceptable tolerability in PF-ILD patients is expected based on the risk profile seen in IPF patients. Lower starting doses are not expected to demonstrate efficacy based on the dose ranging trial in IPF. However, to manage adverse events, the dose may be reduced to 100 mg bid temporarily or permanently (see Section 4.2.1 and Section 6.2.4).

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

The treatment for an individual patient will be assigned by means of an IRT contact during Visits 2, 4, 6, 7, 8, 9 to X. Patient will receive either active drug at a dosage of 150 mg bid or placebo bid.

Trial medication will consist of 1 capsule twice daily (bid) administered orally throughout the study. Wallets covering 4 weeks + 1 week reserve treatment will be dispensed to the patient:

- 1 wallet at Day 1 (randomization = Visit 2) (30 days plus 5 days reserve)
- 2 wallets at Visit 4 (60 days plus 10 days reserve)
- 3 wallets at Visit 6 and Visit 7 (90 days plus 15 days reserve)
- 4 wallets at Visit 8 (120 days plus 20 days reserve)
- 4 wallets at Visit 9 (120 days plus 20 days reserve)
- 4 wallets at Visit X (120 days plus 20 days reserve)

Trial medication will be administered orally on a twice daily basis (bid). The patients should swallow the trial medication, without chewing, together with a glass of water (~250 mL), and should observe a dose interval of 12 hours. Trial medication needs to 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 trial medication after food intake.

A forgotten dose should be skipped if the time window to the next dose is less than 8 hours. The following dose should be taken according to the protocol. No catch up of missed doses is permitted.

The investigational product should only be dispensed to participating patients according to the protocol by authorized personnel as documented in the form “Investigator’s Trial Staff”.

In case of adverse events requiring dose reduction between planned visits, an additional site visit is required. 100 mg bid (or matching placebo) will be assigned by means of an IRT call from the Investigator (see Section 6.2.4). The colour of capsules (100 mg capsule or corresponding placebo) will be slightly different but the packaging will remain the same (same number of capsules per blister and same number of blisters per wallet).

The dose can be reduced without prior interruption, i.e., immediately stepping down from 150 mg bid to 100 mg bid if necessary due to adverse events which require a special trial visit according to procedures described in Section 4.2.1.

If the reduced dose is well tolerated, re-escalation is possible within 4 weeks (after the dose reduction visit) or 8 weeks in case of AEs not considered drug related, which if it occurs between scheduled trial visits will also require a special trial visit according to procedures described in Section 4.2.1.

Patients experiencing adverse events requiring temporary interruption of trial medication may re-start trial medication according to procedures described in Section 4.2.1.

### 4.1.5 Blinding and procedures for unblinding

#### 4.1.5.1 Blinding

This trial is a double-blind trial.
Trial medication is identified by a medication code number. Packaging and labelling is otherwise identical. Colour, size and shape of nintedanib and placebo capsules are indistinguishable within dose strength, but are different between dose strengths.

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (apart from the DMC) will remain blinded with regard to the randomized treatment assignments until after database lock.

When the last randomized patient reaches the Week 52 Visit (Part A: Visit 9), the trial data base will be locked and unblinded by the sponsor for the primary assessment of benefit-risk of nintedanib over 52 weeks in patients with PF-ILD. With exception of the sponsor, the trial conduct will continue blinded until the end of the trial when the final database lock occurs.

The randomization codes will be provided to Bioanalytics prior to last patient out to allow for the exclusion from the analyses of PK samples taken from placebo patients. Bioanalytics will not disclose the randomization code or the PK analysis results until after the final database lock.

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

#### 4.1.5.2 Unblinding and breaking the code

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

To avoid unblinding of the study team through drug safety reports which are to be unblinded as per regulatory requirements, a procedure will be maintained to keep code-breaking in these cases invisible to study team.

The independent statistician of the DMC will receive the randomization code to allow the required analyses on unblinded data upon request of DMC. [redacted] will ensure that all unblinded information remains within the DMC.

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

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

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

One wallet covers for one month of treatment.

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

Initial supply and further re-supplies will be managed by IRT. The IRT will assign an appropriate kit to each patient according to the randomization list that are generated by the Sponsor and not known by the study personnel.

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

### 4.1.7 Storage conditions

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

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

All unused trial medication must be returned to the Sponsor or appointed Contract Research Organization (CRO). Receipt, usage and return must be documented on the respective forms/IRT system. Account must be given for any discrepancies.

### 4.1.8 Drug accountability

The Investigator will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Investigational site must be trained to perform site-related procedures,
- In countries where it is required, availability of the proof of a medical license for the Principal Investigator,
- In the US, availability of Form 1572.

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

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator will maintain records that document adequately that the patients were provided the doses specified in Section 4.1.4 and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed CRO, the Investigator must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

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

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

Treatment interruption, reduction and re-increase are allowed at multiple occasions.

Table 4.2.1: 1 Allowed treatment reduction / interruption periods:

| | **AEs considered related to study drug** | **AEs not considered related to study drug** |
|---|---|---|
| **Maximum interruption** | 4 weeks | 8 weeks |
| **Recommended restart** | with reduced dose (100 mg bid) | with the same dose as before interruption<br>(100 mg bid or 150 mg bid) |
| **Re-escalation** | within 4 weeks to 150 mg bid | N/A |

#### 4.2.1.1 Management of diarrhoea

Diarrhoea is a known side effect of nintedanib treatment (see Section 1.2). However, potential causes for diarrhoea other than study medication should always be considered and treated accordingly (e.g. viral infections, bacterial overgrowth, antibiotic treatment).

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

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and/or dose reduction of nintedanib to 100 mg bid should be considered according to the recommendations described in Table 4.2.1.1: 1.

Table 4.2.1.1: 1 Management of diarrhoea (considered related to trial medication)

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

**Footnotes:**

* Other potential causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment)

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

#### 4.2.1.2 Management of liver enzyme elevation

Nintedanib can be associated with increased liver enzymes (see Section 1.2). Concomitant use of other drugs known to cause liver enzyme elevations should be evaluated. For a detailed guidance on how to manage liver enzyme elevations, please refer to Table 4.2.1.2: 1.

Table 4.2.1.2: 1 Recommendations for managing liver enzyme elevations

| | **AST or ALT increase to** | | | Signs of hepatic injury* (Section 5.3.6) |
|---|---|---|---|---|
| | >1.5x to <3x ULN | ≥3x to <5x ULN and no signs of hepatic injury (see Section 5.3.6) | ≥5x to <8x ULN and no signs of hepatic injury (see Section 5.3.6) | |
| **Visit 2** (randomization) | Withdraw trial medication or justify continuation[1] | Withdraw trial medication | Withdraw trial medication | Withdraw trial medication |
| **Any other Visit** | Continue as planned[2] | Reduce dose or interrupt trial medication [3] | Interrupt trial medication | Withdraw trial medication |
| | | Close observation[4] After 2 weeks or any time later | Close observation[4] After 2 weeks or any time later | **CLINICAL EVALUATION OF HEPATIC-INJURY** (Section 5.3.6) |
| | <3x ULN | ≥3x ULN | < 3x ULN | ≥3x ULN |
| | Reduced: return to initial dose. Interrupted: restart at reduced dose. Monitor bi-weekly for at least 8 weeks | Permanently discontinue trial medication. Close observation[4] | Restart at reduced dose. Monitor weekly for 4 weeks, then bi-weekly for at least 8 weeks | Permanently discontinue trial medication. Close observation[4] |

**Footnotes:**

*Signs of hepatic injury are defined as

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold ULN and unexplained INR >1.5
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

[1] Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).
[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: Re-test ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks by using intermediate visit lab kit.

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 care physician or external laboratory with specific trial lab kits and sent to the central laboratory for analysis.

4.2.1.3 Management of acute ILD exacerbations

In case of acute ILD exacerbation (see Section 5.2.4), all treatment options considered adequate by the Investigator are allowed. The patient may interrupt study treatment for up to 8 weeks, if necessary (e.g. if short-term full anticoagulation is performed).

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The aim of the study is to investigate the efficacy and safety of nintedanib in patients whose progressive lung disease is the main contributor to morbidity.

Treatment of ILD

Immunomodulatory medications i.e. Azathioprine, cyclosporine, tacrolimus, Rituximab, Cyclophosphamide, mycophenolate mofetil, OCS have been utilized in the clinical practice for the treatment of ILD although their benefit-risk profiles in ILD have not been established and they are not approved for the treatment of ILD in most countries. In order to avoid the potential impact of these drugs on the assessment of the efficacy and safety of nintedanib in PF-ILD, their use will not be allowed at randomization and during the first six months of the treatment period.

Patients who receive any of these medications for the treatment of their ILD will have to discontinue these drugs prior to randomization. As the protocol requires that eligible patients progress despite treatment with these medications (i.e. do not or no longer benefit from these drugs), prohibition of these medications is considered justified. In case of acute worsening of PF-ILD during the treatment period, the use of any of these drugs after six months of study treatment will be allowed if judged necessary by the investigator.

Treatment of the underlying diseases associated with ILD

The largest group of patients with PF-ILD that has an underlying disease associated with ILD is the group of patients with CTD. Eligible patients with underlying CTD should have *stable* CTD defined as no initiation or withdrawal of therapy for CTD within six weeks prior to screening. In addition, investigators are encouraged to maintain the baseline treatment of CTD during the entire study unless change is medically indicated.

The majority of the eligible patients with CTD is expected to have RA and to be receiving disease-modifying anti-rheumatic drug (DMARD) e.g. methotrexate or TNF inhibitors. All approved RA/CTD medications are allowed at stable doses at Baseline (Visit 2) and during the study with the exceptions of the following, less frequently used medications: Azathioprine, cyclosporine, tacrolimus, high dose steroids, and Rituximab. The use of these medications will not be allowed in this study. In addition, the following drugs used off-label for the treatment of RA/CTD will not be allowed throughout the study: Cyclophosphamide and MMF.

The rationale for these limitations is that, as described above, these drugs have also been utilized in the clinical practice for the treatment of ILD. In order to avoid the potential impact of these drugs on the assessment of the efficacy and safety of nintedanib in PF-ILD, their use will not be allowed.

Patients whose RA/CTD is well managed by these medications should not be considered for participation in the current study. In case a change in the RA/CTD treatment to another non-restricted medication is indicated, the patient's disease has to be stable (i.e. no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1) before entering in the current trial.

Table 4.2.2.1: 1 Medication restrictions

| **Restricted medications:** Azathioprine, cyclosporine, tacrolimus, Rituximab, Cyclophosphamide, mycophenolate mofetil, OCS >20mg/day, investigational drugs | | |
|---|---|---|
| | **For ILD** | **For CTD** |
| **Baseline** | Not allowed at V2* | Not allowed |
| **Within first 6 months of study treatment** | Not allowed | Not allowed |
| **After 6 months of study treatment** | Allowed in case of significant deterioration[#] | Allowed case of significant deterioration [#] |
| **After EOT** | Allowed | Allowed |

* Wash-out periods to be observed as described in Table 4.2.2.1: 2 below

[#] All can be used in case of clinically significant deterioration of PF-ILD or worsening CTD at the discretion of the Investigator, except for investigational drugs. Introduction of new therapy for CTD should be minimized.

Table 4.2.2.1: 2 Wash-out schedule. Wash-out rules apply only for medications used for ILD treatment.

| **Medication** | **Wash-out period** |
|---|---|
| Azathioprine<br>Cyclosporine<br>Tacrolimus<br>Mycophenolate mofetil<br>OCS >20mg/day | 4 weeks prior to Visit 2 |
| Rituximab | 6 months prior to Visit 2 |
| Cyclophosphamide | 8 weeks prior to Visit 2 |
| Investigational drug(s) | 4 weeks or 6 half-lives (whichever is longer) prior to Visit 1 |

In case of clinically significant deterioration, initiation of additional therapy for ILD i.e. on top of the study medication is allowed after completion of the 6-month study visit (Visit 7) as described in Table 4.2.2.1:1, as determined by the Investigator. For example, introduction of additional therapy may be considered if the patient experiences ≥ 10% relative decline in FVC% pred from baseline that is not attributed to a reversible process (i.e. respiratory infection). Detailed (S)AE information following such events should be recorded in the eCRF. Please also refer to cautionary notes (Section 4.2.2.2).

Prohibited medications

As detailed in the exclusion criteria, patients receiving *pirfenidone, nintedanib, full dose therapeutic anticoagulation or high dose antiplatelet therapy* (e.g. acetyl salicylic acid >325 mg/day, or clopidogrel >75 mg/day, or equivalent doses of other antiplatelet therapy) are not eligible for participation in the study.

The use of pirfenidone and nintedanib are prohibited throughout the study, including the Follow-up period.

4.2.2.2 Cautionary notes

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Co-administration with oral doses of a potent P-gp and CYP3A4 inhibitors, e.g. ketoconazole, erythromycin, may increase exposure to nintedanib. In such cases, patients should be monitored closely. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with nintedanib.

Co-administration with oral doses of a potent P-gp and CYP3A4 inducers, e.g. rifampicin, carbamazepine, phenytoin, and St. John's wort may decrease exposure to nintedanib and should be avoided.

As the most common side effects known for nintedanib are GI effects i.e. diarrhoea, nausea and vomiting (see Section 4.2.1.1) the concomitant use of medication with an overlapping safety profile (e.g. mycophenolate mofetil) should be carefully considered.

Nintedanib is also associated with increases in liver enzymes and bilirubin. If in addition to the trial medication, a treatment is introduced that is known to induce AST/ALT elevations (e.g. methotrexate, bosentan), additional measurements of liver enzymes (ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils) every 2 weeks for approximately 6 weeks, by using intermediate (a-visit) trial lab kit are recommended.

#### 4.2.2.3 Restrictions on diet and life style

There are no restrictions on diet and life style.

#### 4.2.2.4 Restrictions regarding women of childbearing potential

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

## 4.3 TREATMENT COMPLIANCE

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

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

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

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

# 5. VARIABLES AND THEIR ASSESSMENT

## 5.1 TRIAL ENDPOINTS

### 5.1.1 Primary Endpoint

The primary efficacy endpoint is the annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks).

### 5.1.2 Secondary Endpoints

The main secondary efficacy endpoints are:

- Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score at week 52
- Time to first acute ILD exacerbation or death over 52 weeks
- Time to death over 52 weeks

The other secondary efficacy endpoints are:

- Time to death due to respiratory cause over 52 weeks
- Time to progression (defined as a ≥ 10% absolute decline in FVC % pred) or death over 52 weeks
- Proportion of patients with a relative decline from baseline in FVC % pred of >10% at week 52
- Proportion of patients with a relative decline from baseline in FVC % pred of >5% at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnea domain score at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52

### 5.1.3 Further Endpoints

5.1.3.1 Further Endpoints over 52 weeks (Part A)

Further efficacy endpoints over 52 weeks are:

- Time to first non-elective hospitalization or death over 52 weeks
- Absolute change from baseline in FVC (mL) at week 52
- Absolute change from baseline in FVC % pred at week 52
- Proportion of patients with an absolute decline from baseline in FVC % pred of >10% at week 52
- Proportion of patients with an absolute decline from baseline in FVC % pred of >5% at week 52

- Absolute change from baseline in DLCO % pred at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Total score at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Impact score at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms total score at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Fatigue domain score at week 52
- Absolute change from baseline in Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS) summary score at week 52

5.1.3.2 Further Endpoints over the whole trial (Part A and Part B)

Part B of the trial (variable treatment period beyond 52 weeks) will be conducted in order to collect supportive longer term data on the effect of nintedanib in patients with PF-ILD in a controlled manner, especially for the early enrollers. Due to the varying length of follow-up in Part B of the trial, the efficacy measures incorporating data from Part A and Part B will focus on time to event endpoints and will be referred to as time to event endpoints over the whole trial.

Those further efficacy endpoints are:

- Time to first acute ILD exacerbation or death over the whole trial
- Time to death over the whole trial
- Time to death due to respiratory cause over the whole trial
- Time to progression (defined as a ≥ 10% absolute decline in FVC % pred) or death over the whole trial
- Time to first non-elective hospitalization or death over the whole trial

More details will be provided and additional further endpoints may be defined in the trial statistical analysis plan (TSAP).

## 5.2 ASSESSMENT OF EFFICACY

### 5.2.1 Assessment of FVC

FVC will be assessed with the FlowScreen® spirometer which will be supplied to all participating sites.

Spirometry measurements must be performed according to ATS/ERS 2005 guideline (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 triplicate (three curves to be provided), and the best result selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of

the three blows meeting the ATS/ERS criteria with preferably a maximum of five manoeuvres.

Efforts should be made, to schedule the spirometric measurements at approximately the same time of the day, with reference to baseline measurement (Visit 2). 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 visit days (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). If treated with bronchodilators, wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

Spirometry results will be electronically transmitted. To ensure the quality of primary endpoint measurement a central spirometry review is put in place to provide feedback to the investigational site and the CRA on the quality of the data received from the site.

Further instructions regarding FVC measurements will be provided in the ISF.

### 5.2.2 Time to progression or death

Time to progression or death is based on the time of death as defined in section 5.2.3 and based on time to progression. Progression is defined as a ≥10% absolute decline in FVC % predicted.

### 5.2.3 Time to death

Time to death will be based either on the date of death on the AE report for patients with AEs leading to death or will be based on the information from the vital status assessment.

Analysis of time to death due to respiratory cause will be based on the adjudicated cause of death as determined by the Adjudication Committee.

### 5.2.4 Acute ILD exacerbations

Exacerbation of ILD has not been previously studied. Based on the similarity between IPF and PF-ILD, in the current study, the most recent definition of acute IPF exacerbation will be adapted for use as described below (P16-06899). For the endpoints evaluating the effect of nintedanib on these events, AEs reported by the Investigator will be used; the AEs will not be adjudicated.

Acute exacerbation will be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following:

- Previous or concurrent diagnosis of ILD
- Acute worsening or development of dyspnea typically less than one month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrosing ILD
- Deterioration not fully explained by cardiac failure or fluid overload

Events that are clinically considered to meet the definition of acute exacerbation but fail to meet all four diagnostic criteria due to missing CT data should be termed “suspected acute exacerbations”.

### 5.2.5 Assessment of DLCO

The site will use its own carbon monoxide diffusion capacity (DLCO) equipment and conduct all measurements with the same DLCO equipment in case that several devices are available at the site. Single-breath DLCO measurement will be carried out according to the ATS/ERS guideline on DLCO measurements (R06-2002). DLCO and the corresponding alveolar volume will be measured at time points given in the Flowcharts Part A and B. Before beginning the test, the manoeuvres should be demonstrated and the subject carefully instructed.

DLCO values will be adjusted for altitude, carboxyhaemoglobin (COHb) and the most recent haemoglobin value (Appendix 10.1). For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the calculation method used must be in compliance with the ATS/ERS guideline on DLCO measurements (R06-2002) and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

The DLCO assessment should always be performed after the FVC measurement and should always be started approximately the same time a day.

Further instructions regarding DLCO measurements will be provided in the ISF.

### 5.2.6 Time to hospitalization

Time to non-elective hospitalization assessment will be based on the date of hospitalization collected on a specific hospitalization CRF page. The CRF page will capture whether the non-elective hospitalization was due to respiratory cause, and the primary admission diagnosis.

### 5.2.7 Assessment of PRO questionnaires

The patient should complete patient reported outcome (PROs) questionnaires on his/her own in the pre-specified order defined in the Flowchart Part A in a quiet area/room prior to any other trial-related examination. Site personnel will check the answers of the patients in the questionnaires for completeness prior to the patient leaving the site, but the response to each item should not be scrutinized. In instances where a patient cannot give or decide upon a response, no response should be recorded. The scores will be transcribed into the eCRF by designated site-personnel.

The PRO questionnaires should be presented and filled out in the following order:

1. King's Brief Interstitial Lung Disease Questionnaire (K-BILD)

2. Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (L-PF)
3. EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D)
4. Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS)

5.2.7.1 King's Brief Interstitial Lung Disease Questionnaire (K-BILD)

The K-BILD is a self-administered health status questionnaire that was developed and validated specifically for patients with ILD (R12-4171). The questionnaire development and validation included a range of ILDs, including the ILD disease types that encompass the observed study population.

The questionnaire consists of 15 items and 3 domains: breathlessness and activities, psychological and chest symptoms. Possible score ranges from 0-100, with a score of 100 representing the best health status. The K-BILD (Appendix 10.3.1) will be self-administered by the patient and will be administered at study visits as indicated in the Flowchart Part A and in Section 6.

5.2.7.2 Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (L-PF)

The Living with Pulmonary Fibrosis (L-PF) questionnaire is a 44 item questionnaire with two modules: 1) symptoms (23 items) and 2) impacts (21 items). L-PF was developed with the input of patients with pulmonary fibrosis (PF) and thus is intended to capture perceptions specific to PF patients. The Symptoms module yields three domain scores: 1) dyspnea, 2) cough and 3) fatigue as well as a total Symptoms score. The Impacts module yields a single Impacts score. Symptoms and Impacts scores are summed to yield a total L-PF score. Scoring is performed as a summary score, the mean of the dimension ratings multiplied by 100. Summary score range from 0-100, the higher the score the greater the impairment.

The L-PF Symptoms and Impact Questionnaire (Appendix 10.3.2) will be self-administered by the patient at visits indicated in the Flowchart Part A and in Section 6.

5.2.7.3 EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D)

The EQ-5D was developed by the European Quality of Life Group (EuroQol Group) and is a standardized instrument for use as a measure of health outcome (R96-2382). The version used in this trial is the new five-level version (EQ-5D-5L).

The questionnaire essentially consists of 2 pages. The first page is the descriptive system with 5 questions to the patient´s health state today. Each question captures one dimension of health (e.g. mobility, self-care) and has five levels to answer. The second page records the patient´s self-rated health status of today on a vertical graduated (0 to 100) visual analogue scale.

The EQ-5D-5L (Appendix 10.3.3) will be self-administered by the patient at visits indicated in the Flowchart Part A and Section 6.

5.2.7.4 Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS)

The impact on quality of life scale (IQOLS) is based on the Quality of Life Scale (QOLS) that was developed by John Flanagan to measure current the quality of life of individuals. The IQOLS scale was developed to measure the impact of a disease and its treatment on the patient's quality of life. The quality of life dimensions used in the Flanagan IQOLS were identified using the critical incident methodology, and the QOLS was administered initially to a purposive sample of 3,000 American adults by personal interview (R16-2064, R16-2404). The questionnaire was subsequently adapted for use in chronic illness groups by addition of a 16th dimension (R16-2065), but that adaptation also used a response scale that differed from the Flanagan version and had problematic anchor descriptions. The IQOLS includes all 16 dimensions and a 5-point standard Likert-type response scale on which patients rate the impact of the disease on their quality of life (R16-2387, R16-2388). Unlike the most common disease-related quality of life instruments that measure only health/disease-related aspects of QoL (largely symptoms and physical and emotional functioning), the IQOLS measures the impact of a given disease on the full range of domains that are important to an individuals' life such as material and physical well-being, relationships with other people, work, social, community and civic activities, personal development, recreation and independence. The IQOLS approach has been used most extensively, to date, to study the quality of life impact of asthma and its treatment (the A-IQOLS). Versions have been developed to study the impact of other conditions as well (e.g., pulmonary fibrosis, breast cancer, heart failure), as well as the impact of a child's asthma on their parent's quality of life).

Scoring of IQOLS is performed as a summary score, the mean of the dimension ratings. Summary score range from 1-5 with greater scores meaning the worse quality of life.

The PF-IQOLS (Appendix 10.3.4) will be self-administered by the patient at visits indicated in the Flowchart Part A and Section 6.

## 5.3 ASSESSMENT OF SAFETY

The primary assessment of benefit-risk of nintedanib in patients with PF-ILD will be based on efficacy and safety data over 52 weeks. In addition to the assessment of safety after 52 weeks of treatment, selected safety analyses will be repeated to include data collected beyond 12 months, especially for the early enrollers to the study.

### 5.3.1 Physical examination

Physical examination will be performed at time points indicated in the Flowcharts Part A and B. All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

### 5.3.2 Vital Signs

Systolic and diastolic blood pressure and pulse rate will be measured with the patient seated after having rested. All abnormal findings at baseline will be recorded on the baseline condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

### 5.3.3 Safety laboratory parameters

The laboratory tests at regular site visits will include:

| Category | Laboratory test |
|---|---|
| Haematology | Red blood cell count (RBC)<br>Haemoglobin (Hb)<br>Haematocrit (Hct)<br>Mean corpuscular volume<br>White blood cell count including differential<br>Platelet count |
| Biochemistry | Aspartate aminotransferase (AST)<br>Alanine transaminase (ALT)<br>Gamma-glutamyl transferase (GGT)<br>Alkaline phosphatase (ALK)<br>Creatine kinase (CK)<br>Lactate dehydrogenase (LDH)<br>Total protein<br>Total bilirubin<br>Brain natriuretic peptide (BNP at V2, V7, V9 and EOT)<br>Creatinine<br>Glucose (non fasting)<br>Uric acid<br>Thyroid stimulating hormone (only at V2, V7, V9, and EOT)<br>ß-HCG (at Visit 2 only) |
| Electrolytes | Sodium<br>Potassium<br>Calcium<br>Chloride<br>Inorganic phosphorus |
| Coagulation | International normalized ratio (INR)<br>Activated partial thromboplastin time (aPTT)<br>Prothrombin time (PT) |
| Urinalysis | pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++) |
| Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory. | |

The laboratory tests at intermediate ‘a’ visits will include:

| Category | Laboratory test |
|---|---|
| Biochemistry | Total protein, creatinine, electrolytes and liver function (AST, ALT, GGT, alkaline phosphatase, and total bilirubin) |
| Urinalysis | pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi-quantitative measurements; -, +, ++, +++) |
| Local Urine dipstick pregnancy test in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory. | |

At 'a-Visits', safety blood, pregnancy tests and urine samples will be collected and submitted to the central laboratory if needed for additional safety monitoring at the discretion of the Investigator (see Section 4.2.2.2 for additional safety monitoring).
The samples and pregnancy tests may be collected at the office of a local doctor using trial specific lab kits that will be sent to a central laboratory for analyses. These kits will be provided to patients at study visits as applicable.

A maximum total amount of approximately 100 mL blood will be taken for standard safety laboratory during the course of Part A. In Part B, a maximum total amount of approximately 90 mL blood will be taken for standard laboratory depending of the time the patient will stay in Part B.

Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2).

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

In case of liver function value elevations, close monitoring must be ensured by the Investigator. Refer to Section 4.2.1.2 for monitoring elevations and Section 3.3.4 for withdrawal criteria.

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

### 5.3.4 Electrocardiogram

Resting 12 lead Electrocardiograms (ECGs) are conducted during the trial with site's own equipment. Rate, rhythm and repolarization changes have to be evaluated, compared to previous tracings, and assessed for clinical relevance.

Clinically relevant findings must be entered as adverse events.

### 5.3.5 Other safety parameters

Worsening of underlying CTD (if applicable) will be assessed via evaluation of adverse events / serious adverse events.

### 5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

**Adverse event**
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for

allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

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

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

The latest list of "Always Serious AEs" can be found in the RDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.

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

Adverse events relating to gastrointestinal perforation and hepatic injury will be considered AESIs.

Hepatic injury

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

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
- ALT and/or AST ≥3 fold ULN and unexplained INR > 1.5*
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication and need to be followed up according to the "drug-induced liver injury (DILI) checklist" provided in the ISF. The investigator is asked to collect requested information within 48 hours upon laboratory hepatic injury alert/notification.

Potential DILI cases are defined as AESIs, and are reported and processed following the SAE process on the respective SAE form.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST and total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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

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

In addition the intensity of diarrhoea adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for adverse events (CTCAE) version 4 (R10-4848, Table 5.3.6.1:1).

Table 5.3.6.1:1 CTCAE Categorization for diarrhoea

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

**Causal relationship of AEs**
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction, weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

### 5.3.7 Adverse event collection and reporting

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

- From signing the informed consent onwards until the end of treatment (including the Residual Effect Period, REP):
  - all AEs (non-serious and serious) and all AESIs.
  After the end of treatment (including the REP) until the individual patient's end of trial:
  - all AEs (non-serious and serious) and all AESIs should be collected.
- After the individual patient's end of the trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

The end of treatment will occur during Part B of the study, except in case of premature trial medication discontinuation during Part A.

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

**AE reporting to Sponsor and timelines**
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours ) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

**Information required**
For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.
The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease e.g. RA, other CTD or of other pre-existing conditions e.g. hypertension, diabetes.
- Changes in vital signs, resting ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

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

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

**Pregnancy**
In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-

specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

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

**Safety monitoring and adverse events with additional information collection:**

- An independent Data Monitoring Committee (DMC) will conduct regular reviews of the trial safety data as detailed in Section 3.1.1 and in the DMC charter.
- An independent Adjudication Committee (AC) will review all fatal cases and adjudicate all deaths to either cardiac, respiratory or other causes and will review all adverse events categorized as major adverse cardiovascular events (MACE). MACE is defined as non-fatal myocardial infarction, non-fatal stroke and cardiac death.
- Additional details (on top of standard AE and SAE reporting) will be collected in the eCRF for the adverse event 'Diarrhoea' and the adverse events in the subordinate Standard MedDRA Query (SMQ) 'Haemorrhage terms, excluding laboratory terms'.

## 5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

### 5.4.1 Assessment of Pharmacokinetics

Plasma concentration monitoring of nintedanib (BIBF 1120) will be performed in order to assess drug exposure in the PF-ILD patient population. PK plasma sampling will be conducted at Visits 4 and 7, just before drug administration and, hence, the pharmacokinetic parameter Cpre,ss will be determined at these time points. The pharmacokinetic parameter will be included in the clinical trial report.

### 5.4.2 Methods of sample collection

A detailed description of sample collection and handling is provided in the ISF. For quantification of drug plasma concentrations of nintedanib (BIBF 1120), venous blood will be collected using a pre-labelled potassium ethylenediamine-tetraacetic acid (EDTA) containing blood drawing tube. Overall, about 7 mL blood will be taken for pharmacokinetic measurement during the course of the trial.

No morning administration of nintedanib should be performed on Visits 4 and 7 before the pre-dose PK sample has been collected. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF. Additionally, the date and exact clock time of drug administration for the three days preceding the visit where blood sampling for PK is performed must be recorded by the patient on a PK-card.

### 5.4.3 Analytical determinations

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

The procedures and specifications of the analytical method are available at the bioanalytical site (Nuvisan GmbH & Co KG, Wegenerstraße 13, 89231 Neu-Ulm, Germany).

### 5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Exposure-response relationships will be explored. In case of a negative outcome of the trial, formal exposure-response analyses might be omitted. In addition, pharmacokinetic / pharmacodynamic (PK / PD) relationships might be explored with selected exploratory biomarkers and reported separately.

## 5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

The scientific working hypothesis is that the response to lung injury in PF-ILD includes the development of fibrosis which becomes progressive, self-sustaining and independent of the original clinical association or trigger. Due to the clinical and mechanistic parallels between PF-ILD and IPF, it is anticipated that nintedanib will elicit similar effects in PF-ILD as it demonstrated in IPF (see Section 1.1.2). The aim of the biomarker analyses is to provide further support of the scientific hypothesis of the protocol. In addition, these analyses may contribute to identification and validation of pharmacodynamic (PD) and patient selection biomarkers which may support future drug development.

Planned assessments include but are not limited to:

- determining the correlation between biomarkers and selected clinical parameters
- identifying potential predictors of disease progression
- characterizing similarities and differences between patient subgroups within the study and across patients in ILD projects

Accordingly, the following biomarkers related to lung fibrosis will be explored before and after treatment with the study medication and will be correlated with clinical endpoints. All biomarker analyses are considered exploratory.

Serum/plasma samples:
Biomarkers that will be evaluated will include but are not limited to:

- CRP, IL-8 , KL6, SP-D, ECM turnover biomarkers (such as BGM, C1M, C3M, C5M, C6M, CRPM, EL-NE), s-ICAM, MMP7

In addition, a metabolite panel and miRNAs related to lung fibrosis such as miR-29b may also be evaluated contingent upon availability of validated assays.

Ribonucleic Acid (RNA) samples:
Blood will be sampled for RNA extraction and subsequent gene expression analyses.

### 5.5.1 Methods and timing of sample collection

Serum and plasma collection:
Whole blood (approx. 16 mL) will be collected for the preparation of serum and plasma analysis. Collection time points are outlined in the Flowchart Part A. Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis. A detailed description of biomarker sample collection and sample handling is provided in the ISF.

RNA sample collection:
Whole blood will be collected for transcriptome-wide expression analyses. Collection time points are outlined in the Flowchart Part A. Approximately 2.5 mL blood will be collected per PAXgene Blood RNA Tubes. Samples in PAXgene Blood RNA Tubes must be stored at approximately -20°C/4°F or below.

Overall, a maximum total amount of approximately 90 mL blood will be taken for explorative biomarker assessment during the course of the trial.

### 5.5.2 Analytical determinations

Biomarkers will be analysed in EDTA plasma or serum using validated assays. The analytical methods of plasma, serum and RNA biomarkers will be given in detail in an analytical report.

All biomarkers will be analysed by the sponsor or by a contractor of the sponsor.

### 5.5.3 Biobanking

As scientific understanding of fibrosing lung diseases is expected to develop over time, all patients will be asked to provide additional samples to enable further biomarker analyses. Only if a separate, optional biobanking informed consent is given in accordance with local ethical and regulatory requirements, Desoxyribo Nucleic Acid (DNA) and serum banking samples will be taken, processed and stored. Patients will be informed about the purpose of banking serum and DNA samples and the procedures during the informed consent process. Participation in the biobanking part is voluntary and not a prerequisite for participation in the study.

The current study in patients with PF-ILD provides a unique opportunity to investigate exploratory biomarkers of disease progression in a large group of patients with physician

diagnoses of different fibrosing ILDs but the same clinical phenotype i.e. PF-ILD. Since the biomarker area has been rapidly evolving not all biomarker analyses can be pre-specified at this time. Banking serum samples will enable future analyses that may contribute to identification and validation of new biomarkers. Thereby future analyses of banked samples may, for example, contribute to better understanding of your and other lung diseases and to optimizing treatment of patients.

Banking of serum and DNA samples at BI is compliant with principles of Good Clinical Practice (GCP) as outlined in the guidance by the "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use" (CPMP/ICH/135/95) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf) which ensure oversight and that full compliance for the protection of patient data and interests are observed. This encompasses a tight standard operation procedure scheme including a sound scientific review/evaluation of any projects done with banked DNA samples and regular audits by a quality assurance unit.

BI's business model is the development of new innovative drugs; it does not include commercial trade of samples. Samples can be transferred to third party only for the purposes clearly stated in the Informed Consent Form.

The banking samples will be stored for up to 30 years after the final study report has been signed. Biomarker analyses of banked samples will be restricted to biomarkers relevant to the area of respiratory diseases.

DNA banking:
Only if a the separate, optional biobanking informed consent is given in accordance with local ethical and regulatory requirements, Desoxyribo Nucleic Acid (DNA) banking samples will be taken, processed and stored. Participation in the biobanking part is voluntary and is not a prerequisite for participation in the study.

One 8.5 mL blood sample for DNA banking will be collected in PAXgene blood DNA tube at or after Visit 2 for those patients who signed a separate informed consent for DNA banking (see Flowchart). Blood samples collected in PAXgene blood DNA tubes should be stored and shipped at a temperature of about -20°C/4°F or below.

The stored DNA may be analysed and assessed to retrospectively identify e.g. whether there are genetic factors that could contribute to a better therapeutic outcome or to a higher risk of developing treatment-related adverse drug reactions.
Serum banking:
All randomized patients who signed the separate, optional biobanking informed consent will be requested to provide blood samples for serum banking.
Approximately 10 ml additional blood will be collected in serum collection tubes according to the Flowchart Part A. Details on sample collection and processing will be given in the ISF. For serum banking the maximum total amount of blood taken during the course of the trial will be approximately 50mL.

Samples may be used for further biomarker investigations as the science of lung diseases evolves.

## 5.6 OTHER ASSESSMENTS

Health care resource utilization (HCRU)

For the purpose of a separate health economic analysis (such as cost-utility analysis), health care resource utilization (HCRU) data will be collected throughout the trial. Resource use data collected for calculating direct costs will include unscheduled hospitalizations, healthcare provider visits, and emergency room/intensive care unit use. Non-medical resource use data will include changes in work productivity.

The economic evaluation of the HCRU data will not be part of the clinical trial report but reported separately.

HRCT assessment

HRCT assessment of extent of fibrosis and fibrotic pattern has become an essential part of the evaluation and diagnosis of patients with ILDs. HRCT diagnosis of UIP has been shown to correlate with both histologic UIP (P11-07084) and prognosis in patients with ILDs (R16-0560, R16-0756, R14-3529). However, as the majority of the data currently available in the literature pertains to IPF, the present study provides an opportunity to explore the impact of extent of fibrosis and HRCT patterns on clinical makers of disease progression and response to treatment in other progressive fibrotic ILDs (i.e. patients with PF-ILD). In addition, exploratory HRCT analyses from this study may help identify prognostic imaging biomarkers to support future drug development and patient characterization.

Screening HRCT will be used in all patients to determine study eligibility and randomization stratification. In addition to confirmation of the presence of relevant fibrosis (>10% extent) and determination of the HRCT pattern for randomization stratification (see Section 3.3.4), visual and quantitative analyses of the screening HRCTs will be performed to explore potential predictors of clinical outcomes e.g. FVC decline, progression, exacerbation.

In patients who provide consent to optional longitudinal HRCT, HRCT scans will be performed at baseline, 6 months and/or 12 months (see Flowchart A). The planned assessments of the optional longitudinal HRCT include but are not limited to:

- identifying potential predictors of progression
- determining the correlation between HRCT-derived imaging biomarkers and selected clinical parameters
- investigating the performance of the computer aided analysis for the characterization and monitoring of ILDs

Details of the planned HRCT analyses and endpoints will be described in a specific SAP and are considered exploratory. All results will be reported separately.

The same acquisition protocol specifications will be used for all HRCT scans. Whenever possible, HRCT scans should be completed on the same scanner and by the same technician to minimize variability. Scans will be digitally transferred for central review. HRCT scans will be stored for up to 15 years at the sponsor facilities or by an external vendor for future scientific research.

## 5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted for primary and secondary endpoints are using standard methods. Refer to Section 3.2 for the discussion of the choice of FVC as primary endpoint. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used as measurements to assess drug exposure. Measures conducted for exploratory further endpoints might be new methodologies already used in clinical trials but not yet validated for this rare disease.

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

The trial consists of two parts: Part A and Part B. Part A will consist of Visits 2 through 9, which will occur within one year of randomization. Following completion of the week 52 visit (Visit 9), patients will continue to have study visits every 16 weeks (Part B) until the end of the trial. Intermediate lab tests for safety monitoring will be performed as needed until the end of the trial.

There is one screening visit (Visit 1; which may be preceded by a separate informed consent visit) and 8 visits (Visits 2 to 9) planned within the 52 weeks treatment period (Part A). Additional visits will occur every 16 weeks until the end of the trial. Furthermore, there are intermediate scheduled blood analyses and a follow-up Visit.

The trial will last until all patients completed the $EOT_B$ visit and the Follow-up Visit as applicable. (see Figure 3.1: 1).

After giving his/her informed consent, the patient will be screened for inclusion (see Section 3.3.2) and exclusion criteria (see Section 3.3.3) for the trial at Visit 1 and Visit 2 (refer to Flowchart Part A).

Visit 2 can be performed once the results from central laboratory of Visit 1 and central HRCT review are obtained. If for any reason the screening phase for an individual patient lasts for more than 6 weeks, then the laboratory examination for Visit 1 has to be repeated before randomization. The screening phase must be no longer than 12 weeks. The patient will be randomized at Visit 2 if all inclusion and none of the exclusion criteria are fulfilled.

The results of laboratory parameters from Visit 2 will become available only after Visit 2. Therefore, laboratory results from Visit 2 cannot qualify as exclusion criteria; laboratory results from Visit 1 will be used instead. In case laboratory results of Visit 2 would retrospectively fulfil an exclusion criterion, the patient should not continue receiving trial medication unless continuation is justified in writing by the Investigator.

Visits 2, 3, 4 and 5 will occur every 2 weeks. Visit 6 will be scheduled 6 weeks later, Visits 7 and 8 are planned every 12 weeks and Visits 9 is planned after further 16 weeks. Visits 6a, 7a, and 8a are intermediate laboratory control visits.

After Visit 9, study visits will occur every 16 weeks (Part B) until the end of the trial. Visit numbers will continue with Visit 10, Visit 11, etc.

The samples for the ‘a-Visits’ may be drawn locally (i.e. local general practitioner [GP]). The Investigator would in that case give the required documentation to the patient, with the corresponding trial kit for the respective ‘a-Visit’ to be sent to the central laboratory even if not at the trial site. Information, agreement and training of the respective local GP for blood draw will be ensured on an individual site basis consulting the Sponsor’s local monitor.

Pregnancy test will be performed in women of childbearing potential every 4-6 weeks. Urine dipstick test will be done at every visit and will be provided for at home pregnancy testing as soon as visit intervals are > 6 weeks (2 to 3 pregnancy test dipsticks to take home at Visit 7 and 8). Documentation will be done in patient's notes.

The primary endpoint Visit 9 is scheduled 52 weeks after randomization and occurs 16 weeks after Visit 8.

A window of ±3 days for Visits 3 to 6, ±7 days for Visits 6a to 9 is allowed to accommodate scheduling problems. If a delay is observed for a particular visit, the original calendar schedule should be kept for subsequent visits (delays should not accumulate). For visits in Part B, a window of ±7 days is allowed.

If treatment is discontinued, an end of treatment visit (EOT) will be performed in all patients. A follow-up Visit has to be organized 28 days (+ 7 days) after the end of treatment visit except for patients being transferred into the separate open-label extension study.

In case of a missed visit, the investigator should contact the local clinical monitor, these will be addressed on a case by case basis.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening

All trial procedures at selected visits will be done according to Flowchart Part A and footnotes and the CTP.

**Informed consent (before or at the latest at Visit1)**

- Informed consent will be obtained prior to patient participation in the trial, which includes any medication wash-out procedures or restrictions as well as HRCT transfer to central review. Upon obtaining informed consent, the patient will be instructed on the medication washout and other restrictions needed.
- Patients will be asked to give informed consent to the DNA banking sample (please note: the DNA banking sample must not be taken prior to Visit 2). Participation is voluntary and is not a prerequisite for participation in the trial.
- A preliminary check of in-/exclusion criteria is recommended at time of informed consent to avoid unnecessary wash-out procedures in non-eligible patients.
- An HRCT not older than 12 months will be sent for central review, after the Investigator's evaluation,
  - to confirm that the extent of features of fibrosis is >10% is in accordance with the inclusion criteria (see Section 3.3.4),
  - to assess HRCT pattern for stratification.

  Provided the patient meets all other eligibility criteria, the HRCT can be performed for the purposes of participation in the trial if the patient does not have a HRCT within

12 months at the time of the scheduled Visit 1 or the HRCT available does not meet the image acquisition specifications of the study.
- Site personnel will perform a screening call in IRT to ensure in-time trial medication shipment.
- Upon obtaining informed consent the patient will receive a trial identification card.

**Observations and procedures at Visit 1**

- If a separate informed consent Visit was not done, obtaining informed consent and the above mentioned procedures will be done prior to any further procedure at this visit.
- Demographics will be recorded.
- Medical history including pre-existing conditions will be recorded.
- Concomitant therapy including previous medications will be recorded.
- Any adverse events (since consent, if applicable) will be recorded.
- Local urine pregnancy test (dipstick) will be done, if applicable (see Section 5.3.3).
- Physical examination including vital signs will be performed.
- A resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated by the Investigator (if possible prior to blood draw).
- FVC measurement will be conducted with the FlowScreen® spirometer.
- DLCO measurement will be conducted. FVC measurement has to be done first, followed by patient's rest and subsequent DLCO measurement.
- Blood and urine samples (safety lab) will be collected and submitted to the central laboratory (for details refer to Section 5.3.3). Prior to blood draw a pre-assessment of all inclusion and exclusion criteria is highly recommended.
- Site personnel will send HRCT to central review (if not already done at time of informed consent).
- For patients qualified to enter the screening period, Visit 2 will be scheduled.

### 6.2.2 Treatment phase

At the beginning of each visit during treatment phase, Investigator and site personnel should ensure the well-being of the patient as well as prepare all requirements for conduct of the visits that are necessary.

The order of the different trial procedures should follow the protocol and should be planned for taking into account the specific structure of the investigational site and following the mandatory needs outlined in the clinical trial protocol.

Mandatory needs: the following has to be ensured during trial visits according to the study Flowchart:

- Patient reported outcome questionnaires have to be filled out always prior to any other procedures by the patient in a quiet area and in the following order:
  1. K-BILD
  2. L-PF Symptoms and Impact Questionnaire
  3. EQ-5D
  4. PF-IQOLS
- Urine pregnancy test and any laboratory sample collection must be performed prior trial medication administration.
- FVC and DLCO measurement at all visits should be performed approximately at the same time of the day to reference time point at Visit 2.
- Order of pulmonary function tests must always be
  1. FlowScreen® spirometry (FVC) followed by patient's rest
  2. DLCO with site's own equipment.

**Baseline Visit 2 (randomization)**

The following prerequisites must be available for randomization:

- Eligibility confirmation and HRCT pattern from central HRCT review.
- Safety laboratory results including haemoglobin and creatinine from Visit 1.

Procedures:

- All patients will be asked to fill out the patient reported outcome questionnaires prior to any other visit procedure. The order of the questionnaires will always be: 1. K-BILD, 2. L-PF Symptoms and Impact Questionnaire, 4. EQ-5D, 5. PF-IQOLS.
- Site personnel will review questionnaires for completeness.
- Physical examination including vital signs and HCRU interview will be performed.
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- Medical history will be reviewed.
- Repeated resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated if resting ECG was abnormal at Visit 1 (if possible prior to blood draw).
- $SpO_2$ will be recorded (earlobe or forehead, resting).
- FVC measurement will be conducted with the FlowScreen® spirometer.
- DLCO measurement with sites own equipment will be conducted.
- All in/exclusion criteria will be assessed based on Visit 1 laboratory and Visit 2 measures.
- HRCT will be performed in patients who agree to have follow-up HRCT done as part of the trial, unless a screening HRCT was done as part of the study to determine eligibility.

- Safety blood and urine samples will be collected and submitted to the central laboratory.
- Biomarker samples will be collected and submitted to the central laboratory.
- The time of blood collection for biomarker samples will be recorded in the eCRF. Note: blood samples should always be collected prior to drug administration.
- One blood sample for DNA banking will be collected in eligible patients and only after obtaining a separate informed consent.
- Local urine dipstick pregnancy test (if applicable).
- If a patient is eligible for the trial, randomization will be performed by using the IRT system.
- Treatment will be dispensed.
- The next visit will be scheduled and prepared.

**Visit 7, Visit 9 and $EOT_A$ ('big visits') procedures**

At Visit 7, Visit 9 and $EOT_A$ (primary endpoint visit), the same procedures will be performed as done at baseline Visit 2. Exceptions are the typical randomization measures, e.g. eligibility review, medical history assessment and randomization as well as DNA banking sample which is only taken once. In addition, if EOT takes place before Visit 7, HRCT should not be repeated. For Visit 7, Visit 9 and $EOT_A$ always refer to the Flowchart Part A.

*General rules*

- Treatment compliance will be reviewed by site personal.
- Trial medication will be collected and/or dispensed according to Flowcharts Part A.
- Visit 9 and end of treatment visit ($EOT_A$) are identical visits. $EOT_A$ is to be used in eCRF at any time a patient ends trial medication (scheduled or prematurely).
- Patient who prematurely discontinued trial medication will attend all originally planned visits until the end of the trial (except for the laboratory visits 6a, 7a and 8a).
- IRT should always be notified on end of treatment (EOT).
- Vital status will be collected for patients who prematurely discontinued trial medication and failed to attend future visits as planned, as well as for those who did not attend scheduled visits as planned at week 52 (scheduled Visit 9/$EOT_A$).
- PROs will always be scheduled prior to any other procedure and in the above described order and will be reviewed for completeness by site personal.
- Drug intake at visit days should always be performed at site and after blood and urine sample collection and pregnancy test.
- FlowScreen® spirometry (FVC) and DLCO measurements will always be in the allowed time window and the described order (reference visit = Visit 2).
- Non-elective hospitalization will be recorded.
- Acute ILD exacerbations will be recorded.
- Resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated (if possible prior to blood draw).
- At Visit 7, a PK sample will be collected. The patient needs to record exact date and clock time of medication intake the preceding three days on a PK-card provided at

Visit 6. The date and time of blood collection for PK and drug administration at the site will be recorded.
- Biomarker blood sampling will be done. The date and time of blood collection for biomarker samples will be recorded in the eCRF.
- For patients who agreed to the optional HRCT-follow-up, HRCT should be done at V7 and V9.

**Visit 3, 4, 5, 6, and 8 ('medium visits') procedures**

Please note that not all medium visits are drug dispensation visits (please always refer to Flowchart Part A). However, compliance of patients regarding drug intake should always be reviewed (see also treatment compliance in Section 4.3).

- Physical examination including vital signs and HCRU interview will be performed.
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- PROs will be scheduled prior to any other procedure and in the above described order and will be reviewed for completeness by site personal at Visits 6 and 8.
- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.
- At medium Visits 6 and 8, biomarker samples will be collected. The date and time of blood collection for biomarker samples will be recorded in the eCRF.
- At medium Visit 4, a PK sample will be collected. The patient needs to record exact date and clock time of medication intake the preceding three days on a PK-card provided at Visit 3. The date and time of blood collection and drug administration at the site will be recorded.
- At medium Visit 6, a PK-card will be provided to record exact date and clock time of medication intake three days preceding PK sampling at Visit 7.
- FlowScreen® spirometry (FVC) in the allowed time window will be performed.
- Non-elective hospitalization will be recorded.
- Acute ILD exacerbations will be recorded.
- 2 to 3 take home pregnancy tests (dipsticks) at Visit 8 will be dispensed.
- Treatment compliance will be reviewed by site personal at every visit (except at randomization visit and at 'a-Visits').
- Trial medication will be collected and/or dispensed according to Flowchart Part A.

**Visit X and $EOT_B$ procedures**

- Physical examination including vital signs and HCRU interview will be performed.
- Adverse events and concomitant therapy since last visit will be reviewed and recorded.
- Local dipstick pregnancy test (if applicable).
- Safety blood and urine samples will be collected and submitted to the central laboratory.

- Resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated (if possible prior to blood draw) at every other visit and EOT.
- The date and time of blood collection and drug administration at the site will be recorded.
- FlowScreen® spirometry (FVC) and DLCO measurements in the allowed time window will be performed.
- Non-elective hospitalization will be recorded.
- Acute ILD exacerbations will be recorded.
- Home pregnancy tests (dipsticks) will be dispensed.
- Treatment compliance will be reviewed by site personal at every visit.
- Trial medication will be collected and/or dispensed according to Flowchart Part B.
- Assessment of vital status at $EOT_B$ visit

**Intermediate 'a-Visit' procedures**

- Safety blood, pregnancy tests and urine samples will be collected and submitted to the central laboratory if needed for additional safety monitoring at the discretion of the Investigator (see Section 4.2.2.2).

### 6.2.3 Follow-up Visit and trial completion

A Follow-up Visit has to be scheduled 28 days after End of Treatment Visit for all patients except for patients transferred into a separate open-label extension study. This Follow-up Visit is the safety follow-up after treatment discontinuation.

- Physical examination including vital signs.
- Adverse events and concomitant therapy will be assessment since last visit.
- Local dipstick pregnancy test (if applicable).
- FlowScreen® spirometry (FVC) in the allowed time window will be performed.
- Non-elective hospitalization will be recorded.
- Acute ILD exacerbations will be recorded.
- Patient's participation will be concluded for patients who withdraw consent and do not attend future visits.

**Trial completion**

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

- For patients who complete all study visits, end of trial is $EOT_B$. A follow-up visit is only required for those who do not roll-over in the separate open-label study
- For patients who withdraw consent
  - at time of trial medication discontinuation, end of trial is an EOT visit followed by a follow-up visit.

– after EOT was already completed, then the patient should have a final visit based on their scheduled study visit.

**Patients who prematurely discontinued trial medication**

In case a patient has to permanently discontinue trial medication, for whatever reason, he/she will be encouraged to attend all future visits up to end of trial as originally planned (except for the laboratory 'a-Visits').

- During these visits, the patient will undergo all planned examinations according to Flowcharts A and B, especially FlowScreen® spirometry (FVC) and will fill in the PRO questionnaires (only Part A); however he/she will not have to do the resting ECG, safety laboratory, biomarker laboratory and PK blood draw.
- These visits will be regarded as part of the trial despite the patient having discontinued trial medication.

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

**Vital status information**

In case of premature discontinuation of trial medication, if the patient does not attend future visits as planned, every attempt will be made to get information on vital status at 52 weeks after his/her randomization, at the time of data cut-off for the primary analysis and at the end of the trial for patients who have withdrawn consent.

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

If death occurs, the Investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary and secondary causes of death. The cause of death will be adjudicated by the AC.

Collection of vital status will be performed in accordance with national ethical and regulatory guidelines.

### 6.2.4 Dose reduction visit / dose increase visit

If a patient experiences a drug related adverse event, the dose can be reduced and the dose can be re-increased after recovery as described in Section 4.2.1. In both cases, the patient will have to come back to a visit where the following will be performed:

- Physical examination including vital signs.
- Adverse events and concomitant therapy will be assessment since last visit.
- Local dipstick pregnancy test (if applicable).

- Safety blood and urine samples will be collected and submitted to the central laboratory.
- FlowScreen® spirometry (FVC) in the allowed time window will be performed.
- Trial medication will be collected and treatment compliance will be reviewed.
- IRT call for reduction or increase of the dose and trial medication dispensation.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN - MODEL

This is a multi-centre, multi-national, prospective, randomized, placebo-controlled, double blind trial to investigate the efficacy and safety of nintedanib 150 mg bid over 52 weeks in patients with PF-ILD.

The primary endpoint is the annual rate of decline in FVC estimated from readings taken over 52 weeks. The annual rate of decline in FVC will be analysed using a random coefficient regression (random slopes and intercepts) model including baseline FVC in mL and HRCT pattern (except for the analyses on the co-primary population assessing only patients with HRCT with UIP-like fibrotic pattern only) as covariates.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

The superiority of nintedanib 150 mg bid compared to placebo will be tested for the annual rate of decline in FVC in mL.

For the overall population, the null hypothesis is:
$H_0$: There is no difference in the annual rate of decline in FVC in mL between nintedanib 150 mg bid and placebo in the overall population.

The alternative hypothesis is:
$H_a$: There is a difference in the annual rate of decline in FVC in mL between nintedanib 150 mg bid and placebo in the overall population.

For the co-primary population of patients with HRCT with UIP-like fibrotic pattern only, the null hypothesis is:
$H_0$: There is no difference in the annual rate of decline in FVC in mL between nintedanib 150 mg bid and placebo in the patients with HRCT with UIP-like fibrotic pattern only.

The alternative hypothesis is:
$H_a$: There is a difference in the annual rate of decline in FVC in mL between nintedanib 150 mg bid and placebo in patients with HRCT with UIP-like fibrotic pattern only.

In order to maintain an overall type 1 error rate of 5%, a Hochberg procedure will be used (R97-1003). For the primary endpoint, statistical significance will be declared if the analyses in both co-primary populations are significant at the two-sided 5% level, or if the analyses in either co-primary population are statistically significant at the two-sided 2.5% level.

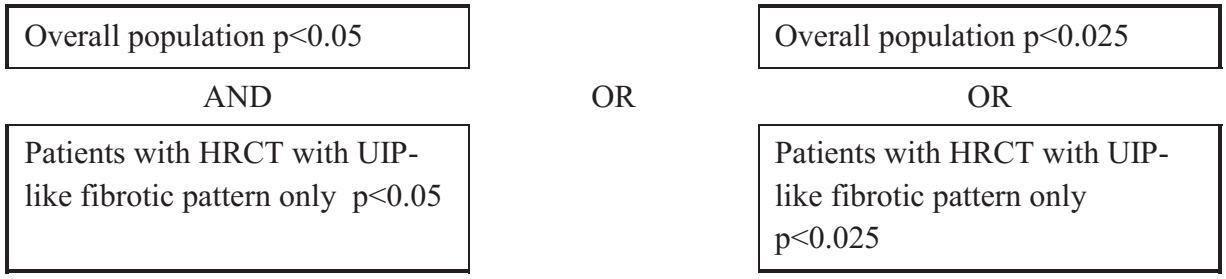


Figure 7.2: 1 Scenarios for statistical significance using Hochberg procedure

## 7.3 PLANNED ANALYSES

The efficacy and safety analyses will be conducted on the treated set (TS), which consists of patients who are randomized to a treatment group and receive at least one dose of study medication. There will be two co-primary analysis populations: the first will comprise all patients from the treated set (the overall population); the second will comprise all patients from the treated set with HRCT with UIP-like fibrotic pattern only.

The primary assessment of benefit-risk of nintedanib in patients with PF-ILD will be based on efficacy and safety data over 52 weeks (including data from part A only); assessments performed within the first 52 weeks (time-windowing rules will be defined in the TSAP) will be used.

The primary analysis is a random coefficient regression (random slopes and intercepts) model including baseline FVC (mL) and HRCT pattern (except for the analyses on the co-primary analysis population assessing only patients with HRCT with UIP-like fibrotic pattern only) as covariates.

Efficacy and safety data over the whole trial (including data from part A and part B) will be reported descriptively only. Data collected in Part B of the trial and available at the time of the primary analysis data cut-off will be reported after the first database lock. Selected analyses will be repeated after the final database lock and will include data collected until the end of the trial.

All analyses will be based on the treatment group (nintedanib 150 mg bid or placebo) as randomized by IRT.

Although there is no per protocol data set in the study, reasons for important protocol violations will be specified in the Trial Statistical Analysis Plan (TSAP). Patients with important protocol violations will be identified at Blinded Review Planning Meetings and listed in the CTR.

### 7.3.1 Primary endpoint analyses

The primary endpoint is defined in Section 5.1.1.

Baseline FVC in mL will be included as a covariate in the analysis model. Baseline FVC is defined as the FVC result recorded at Visit 2, unless missing in which case the screening result will be used. The HRCT pattern ("UIP-like fibrotic pattern only" or "Other fibrotic patterns") will also be used as a covariate for the analysis performed on the overall population and will not be a covariate for the analysis on the co-primary population assessing only patients with HRCT with UIP-like fibrotic pattern only. The primary analysis will also be performed on the complementary population of patients with other HRCT fibrotic patterns. A forest plot will present the three placebo-corrected, adjusted annual rates of decline in FVC with 95% confidence intervals from the analyses on the co-primary populations and on the complementary subgroup population.

The decrease in FVC is assumed to be linear within each subject over 52 weeks; this was also assumed in the IPF trials INPULSIS-1 and INPULSIS-2 (P14-07514). The intercepts and slopes will be assumed to be normally distributed with arbitrary covariance matrix. The within patient error will be assumed to be independent and normally distributed with mean zero and a common variance. The Kenward-Roger approximation will be used to estimate denominators degrees of freedom. Significant tests will be based on least-squares means; p-values and two-sided 95% confidence intervals for the difference between the treatment groups will be presented. An intent-to-treat principle will be used (i.e. all available data from the treated set within the first 52 weeks will be used, including baseline and data retrieved post treatment discontinuation for patients who prematurely discontinued randomized treatment). Analyses will be implemented using SAS® Version 9.4 or higher.

The assumptions for the primary analysis of decline in FVC will be tested; details will be provided in the TSAP. The primary analysis will be based on observed data (but including retrieved drop out measurements) and will assume remaining missing data are missing at random. The effect of missing data will be investigated using multiple imputation methods which assume that patients who discontinue treatment will no longer benefit from it in the future. See Section 7.5.1 for further details of these sensitivity analyses.

Subgroup analyses will be specified in the TSAP and will include:

- Age
- Gender
- Original diagnosis (e.g. IIP; CTD-ILD; other ILDs)

A cumulative distribution plot will be provided, showing the percentage of patients by the change from baseline in FVC in mL at Week 52.

Data will be summarized graphically and using summary statistics.

### 7.3.2 Secondary endpoint analyses

Secondary endpoints are defined in Section 5.1.2.

For all secondary endpoints, an intent-to-treat principle will be used (i.e. all available data from the treated set within the first 52 weeks will be used, including data for patients who prematurely discontinued randomized treatment).

Continuous endpoints will be analysed using a restricted maximum likelihood (REML) based repeated measures approach. Analyses will include the fixed, categorical effects of HRCT pattern (except for the analyses on the co-primary analysis population assessing only patients with HRCT with UIP-like fibrotic pattern only), treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient measurements.

If this analysis fails to converge, the following covariance structures will be tested in order: heterogeneous toeplitz (TOEPH), toeplitz (TOEP) and autoregressive 1 (AR[1]). The first model to converge will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals). In case the model fails to converge under PROC MIXED, the "singular" option will be considered. The treatment comparisons will be the contrast between treatments at week 52.

Time-to-event endpoints will be analysed using a Cox proportional hazards model. The equality of the hazard rates will be tested by the Wald test for the treatment effect at the two-sided 5% significance level. The model will include the treatment effect and HRCT pattern (except for the analyses on the co-primary analysis population assessing only patients with HRCT with UIP-like fibrotic pattern only) as covariates. Breslow's method for handling ties will be used. Kaplan-Meier plots by treatment group will also be presented. If the proportion of patients experiencing at least 1 acute ILD exacerbation over 52 weeks is less than 2%, then only frequencies of exacerbations by treatment group will be provided for the main secondary endpoint of time to first acute ILD exacerbation or death over 52 weeks and no statistical analysis will be performed.

Comparisons between treatment groups regarding the binary endpoint variables based on categorical declines in FVC % predicted (% pred) will be performed using a logistic regression model adjusting for the continuous covariate baseline FVC % pred and the binary covariate HRCT pattern (except for the analyses on the co-primary analysis population assessing only patients with HRCT with UIP-like fibrotic pattern only). The likelihood-ratio test will be used to test for differences between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing nintedanib 150 mg bid to placebo as the reference.

Any p-values presented for the secondary endpoints will be considered nominal in nature and no adjustment for multiplicity will be made.

### 7.3.3 Further endpoint analyses

All further endpoints will be considered exploratory in nature.

The analysis of further endpoints over 52 weeks will be performed with the same models and procedures as described for the secondary endpoints in Section 7.3.2.

Further time to event endpoints over the whole trial will be analysed in a descriptive manner. Frequency tables and Kaplan-Meier plots will be produced.

### 7.3.4 Safety analyses

The primary assessment of benefit-risk of nintedanib in patients with PF-ILD will be based on efficacy and safety data over 52 weeks (using data from Part A of the trial). All safety assessments described below will focus on data collected within the first 52 weeks of the study. In addition, selected safety analyses will be repeated to include data collected beyond 52 weeks (during Part B of the trial); further details will be specified in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All treated patients will be included in the safety analysis for the overall population and the safety analysis will be repeated for the co-primary population of patients with HRCT with UIP-like fibrotic pattern only. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Kaplan-Meier plots will be produced for the time to premature treatment discontinuation, for the time to first dose reduction and for the time to first treatment interruption.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as the 28 days after the date of the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered ‘treatment-emergent’. Based on the half-life of the study drug, the medical residual effect period is 7 days after the last dose of trial medication. Therefore, additional analysis of safety data will be made for adverse events that occur between the start of treatment and up to 7 days after the date of the last dose of trial medication will be analysed in addition.

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 MedDRA.

Summary tables will be produced for the adjudication results of MACE and deaths.

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

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

### 7.3.5 Pharmacokinetic analyses

Pre-dose plasma concentrations (Cpre,ss) of nintedanib will be tabulated with descriptive statistics in the CTR. For pharmacokinetic analysis and displays, concentrations will be used in the same format as reported in the bio-analytical report. Only concentrations within the validated concentration range will be used and these will be reported using actual sampling times.

## 7.4 INTERIM ANALYSES

No interim analysis is planned but the conduct of the trial will be monitored by a DMC until the primary analysis is performed. The purpose, scope and tasks of the DMC are described in Section 3.1.1.

The primary assessment of benefit-risk of nintedanib in patients with PF-ILD will be based on efficacy and safety data over 52 weeks. The primary analysis will therefore be performed once the last patient reaches the Week 52 Visit (Part A: Visit 9).

## 7.5 HANDLING OF MISSING DATA

### 7.5.1 Efficacy Endpoints

The effect of missing data on the primary endpoint will be investigated using multiple imputation techniques.

For the primary endpoint, for each co-primary analysis population, the following subsets of patients will be defined:

1. Patients with an FVC result at week 52 who received trial medication until week 52.
2. Patients with an FVC result at week 52 who prematurely discontinued trial medication prior to week 52.
3. Patients without an FVC result at week 52 who were alive at week 52.
4. Patients without an FVC result at week 52 who died prior to week 52.

These four subsets of patients will be used in sensitivity analyses to estimate the treatment effect under differing assumptions around the persistence of efficacy after withdrawal of trial medication. Table 7.5.1: 1 describes the planned sensitivity analyses for handling missing primary endpoint data. Sensitivity analyses 1 and 2 will only be performed if there are at least 10 patients included in patient subset 2 in each treatment group.

Table 7.5.1: 1 Sensitivity analyses for handling missing primary endpoint data

| **Analysis** | **Patient subset 3: No FVC result but alive at Week 52** | | **Patient subset 4: No FVC result and died prior to Week 52** | |
|---|---|---|---|---|
| | **Handling of missing FVC result** | **Underlying assumption** | **Handling of missing FVC result** | **Underlying assumption** |
| Primary analysis | Missing data handled by model. | Assumes missing at random. Discontinued patients would have behaved similarly to patients who did not discontinue. | Missing data handled by model. | Assumes missing at random. Discontinued patients would have behaved similarly to patients who did not discontinue. |
| Sensitivity analysis 1 | Based on the slope estimates for drug and placebo in patient subset 2. | Patients without a result would have behaved similarly to discontinued patients with a result who are in the same treatment group. | Based on the slope estimates for placebo patients in patient subset 2, but truncated so that those who died are more severe. | Patients who died before week 52 would have behaved in a similar or worse way to a placebo patient who prematurely discontinued. |
| Sensitivity analysis 2 | Based on the slope estimates for placebo in patient subset 2. | Patients without a result would have behaved similarly to discontinued placebo patients with a result. | | |
| Sensitivity analysis 3 | Based on the slope estimates for placebo in patient subsets 1 and 2. | Patients without a result would have behaved similarly to placebo patients with a result regardless of whether they prematurely discontinued treatment or not. | Based on slope estimates for placebo patients in subsets 1 and 2, but truncated so those who died are more severe. | Patients who died before week 52 would have behaved in a similar or worse way to a placebo patient regardless of whether they prematurely discontinued treatment or not. |

Further sensitivity analyses will be described in detail in the TSAP.

In the analysis of all other continuous endpoints, missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption".

In the analysis of time-to-event endpoints, missing or incomplete data will be handled using standard survival analysis techniques (i.e. censoring). Efficacy time-to-event endpoints will be calculated from the randomization date.

In the analyses of the categorical endpoints, missing data will be imputed using the worst case.

### 7.5.2 Safety

Missing or incomplete AE dates will be imputed according to BI standards. Other missing safety data will not be imputed.

### 7.5.3 Plasma concentrations

Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, and NOA are included).

## 7.6 RANDOMIZATION

Within each randomization HRCT pattern stratum (“UIP-like fibrotic pattern only” or “Other fibrotic patterns”), patients will be randomized in blocks to double-blind treatment in a 1:1 ratio. Approximately equal numbers of patients will be randomized to each treatment group. The randomization system will include caps for the two HRCT pattern strata so that approximately two thirds of the patients are randomized to the “UIP-like fibrotic pattern only” stratum and one third is randomized to the “Other fibrotic patterns” stratum (i.e. approximately 400 and 200 patients to each stratum, respectively). As a consequence of these caps randomization might be put on hold in one stratum temporarily and may mean that screened patients cannot be randomized immediately.

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

## 7.7 DETERMINATION OF SAMPLE SIZE

Lack of published data from randomized clinical trials in patients with PF-ILD leads to uncertainty both on the rate of forced vital capacity (FVC) decline and on its variability in the planned study population.

The main assumption of the study is that patients with PF-ILD, independent from their original ILD classification, at some point in time, exhibit a progressive fibrosing phenotype. In this group of patients with PF-ILD, the disease behaviour over time (e.g. lung function, mortality) appears to follow a course similar to IPF, a typical example of PF-ILD.

Based on the existing literature for IPF, the observed mean values for the annual rate of decline in FVC or the FVC change from baseline to 45–52 weeks in patients treated with placebo was approximately between 140 mL and 250 mL (see Section 10.5).

The currently available data in different ILDs show that the ILD injury pattern, in particular the presence of UIP, is associated with worse prognosis (P11-07084, R10-6539, R16-0554, R15-3264, R16-1567, R14-3529, R16-0752, R16-1568). Based on this, the study will be enriched for patients with UIP pattern. UIP pattern will be defined based on HRCT using the same HRCT criteria as in the Phase III IPF trials for nintedanib (P15-04977, P15-05695) and described in Section 1.1. Since these criteria differ slightly from the current definition of radiologic UIP provided in the ATS/ERS guidelines (P11-07084), patients with screening HRCT meeting the protocol criteria for UIP will be referred to as “patients with HRCT with UIP-like fibrotic pattern only”. Patients with HRCT patterns not meeting the protocol criteria for UIP will be referred to as “patients with other HRCT fibrotic patterns”.

For scenario planning for the sample size calculation, a rate of decline of 150-200 mL/year has been assumed for PF-ILD patients with HRCT with UIP-like fibrotic pattern only. For the patients with other HRCT fibrotic patterns, the FVC rate of decline is assumed to be slightly lower than in PF-ILD patients with HRCT with UIP-like fibrotic pattern only: between 120 and 150 mL/year.

Nintedanib is hypothesized to have the same relative effect on all patients with PF-ILD (an approximate 50% reduction in the annual rate of decline in FVC). However it is expected that the absolute effect difference between groups will be the largest in the patients with HRCT with UIP-like fibrotic pattern only since these patients are assumed to have a larger annual rate of decline than patients with other HRCT fibrotic patterns.

The treatment effect to detect is therefore in the range of 75-100 mL/year for the PF-ILD patients with HRCT with UIP-like fibrotic pattern only and of 60-75 mL/year in the PF-ILD patients with other HRCT fibrotic patterns.

Given some expected heterogeneity in the rate of decline across the PF-ILD subpopulations, the variability is assumed to be larger than in IPF for patients with other HRCT fibrotic patterns with a standard deviation (SD) of 400 mL/year. For patients with HRCT with UIP-like fibrotic pattern only, a more homogeneous group of patients, the variability is assumed to be the same as observed in IPF with a SD of 300 mL/year.

By enrichment, it is planned to recruit 400 PF-ILD patients with HRCT with UIP-like fibrotic pattern only, making up two thirds (66.7%) of the study population. This design will be used in order to maintain a high power to detect a clinically meaningful effect of nintedanib in the rare disease of PF-ILD.

There will be two co-primary analysis populations: the first will comprise all patients (the overall population); the second will comprise all patients with HRCT with UIP-like fibrotic pattern only. Since establishing an effect in either of these two populations is considered clinically relevant, the trial will be considered positive if it establishes efficacy in either one of the two populations or in both.

In order to maintain an overall type 1 error rate of 5%, a Hochberg procedure will be used (R97-1003). This multiplicity adjustment strongly controls the overall Type I error rate in clinical trials with a targeted subpopulation (R16-1041). For the primary endpoint, statistical significance will be declared if the analyses in both co-primary populations are significant at the two-sided 5% level, **or** if the analyses in either co-primary population are statistically significant at the two-sided 2.5% level. Given the proposed design properties it is calculated that applying this procedure, the overall alpha spent will be 4.35% so the overall Type I error control is below 5%. This is based upon the summation of the probabilities of rejecting $H_0$ under various combinations of results for the co-primary populations within the Hochberg procedure (calculated using SAS® Version 9.4, see Appendix 10.6 for details).

Table 7.7: 1 below presents the power properties of this study for several scenarios for the treatment effect in the two co-primary populations.

Table 7.7: 1: Power properties for several scenarios for the treatment effect in the two co-primary populations

| | **Patients with HRCT with UIP-like fibrotic pattern only**<br>**Co-primary** | **Patients with other HRCT fibrotic patterns** | **Overall patient population**<br>**Co-primary** | |
|---|---|---|---|---|
| **Scenario 1** | | | | |
| Assumed treatment difference in absolute change in FVC in mL/year (SD) | 100 (300) | 75 (400) | 92 (337) | |
| Individual test power | 90.2% | | 90.3% | |
| Overall Power* | | | | 92.6% |
| **Scenario 2** | | | | |
| Assumed treatment difference in absolute change in FVC in mL/year (SD) | 75 (300) | 60 (400) | 70 (337) | |
| Individual test power | 67.2% | | 68.2% | |
| Overall Power* | | | | 72.4% |
| **Scenario 3** | | | | |
| Assumed treatment difference in absolute change in FVC in mL/year (SD) | 75 (300) | 75 (400) | 75 (337) | |
| Individual test power | 68.2% | | 73.4% | |
| Overall Power* | | | | 75.8% |

FVC, forced vital capacity; SD, standard deviation.
Power calculations are based on Hochberg procedure at the overall type 1 error rate of 5% (two-sided), with 200 patients with HRCT with UIP-like fibrotic pattern only and 100 patients with other HRCT fibrotic patterns per treatment group.
*The overall power is the probability of concluding statistical significance for either of the co-primary populations.
Power calculated using SAS® Version 9.4 (see Appendix 10.6 for details)

Drop-out is not accounted for in the sample size calculation since all patients from the treated set are expected to have sufficient data to be included in the primary analysis.

With a sample size of 300 patients randomized per treatment group, and 600 patients in total including 400 patients with HRCT with UIP-like fibrotic pattern only and using a Hochberg procedure, there will be:

- more than 90% power to detect a treatment effect of 100 mL/year assuming a standard deviation of 300 mL/year in the patients with HRCT with UIP-like fibrotic pattern only ,
- more than 90% power to detect a treatment effect of 92mL/year assuming a standard deviation of 337 mL/year in the overall population, and

- more than 90% overall power (probability to conclude significance for the overall population or for the patients with HRCT with UIP-like fibrotic pattern only )

In fact with this sample size and study design, even in the scenario assuming the lowest rate of FVC declines for the patients with HRCT with UIP-like fibrotic pattern only and for the patients with other HRCT fibrotic patterns (scenario 2), there will be almost 80% overall power to detect an effect of nintedanib.

The proposed sample size will therefore provide adequate power to demonstrate a clinically important treatment benefit on the primary endpoint even in scenarios where the annual rate of decline in both PF-ILD co-primary patient populations is much lower than observed for IPF patients in the Phase III IPF trials.

In general, no key secondary endpoints are planned for the trial since there is no data in the published ILD literature on which to base assumptions for treatment effect and power for the proposed main secondary endpoints. However, the endpoints defined as main secondary are those which are considered most relevant to the assessment of the effect of nintedanib in PF-ILD. These endpoints will provide the main supportive evidence to the primary endpoint assessment.

The mortality rate in PF-ILD is anticipated to be similar to IPF (R15-3264, R16-0554). Power calculations based on the mortality rate expected and later observed in the IPF trials with nintedanib indicated that for demonstrating a statistically significant treatment benefit for nintedanib in all-cause mortality approximately 6,000 patients would be required for a placebo-controlled trial of 52-week duration in IPF (P14-06844). The current study in PF-ILD is powered for the primary endpoint, annual rate of decline in FVC with a total sample size of 600 patients. The study is therefore not powered to demonstrate a statistically significant reduction in mortality over 52 weeks. However, all-cause mortality as a main secondary endpoint will provide further clinically meaningful information on the effect of nintedanib in PF-ILD.

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

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and relevant regulations
*and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).*

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP
*and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).*

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

*For Japan:*
*The rights of the Investigator / trial site and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report.*
*The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."*

## 8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be

personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

*For Japan:*
*The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents.*
*The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.*

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

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

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

## 8.3 RECORDS

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

### 8.3.1 Source documents

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

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

All data must be derived from source documents.

Source documents in addition to the patient file are:

- Originals or copies of HRCT results
- Lung function test results
- Laboratory reports
- Resting ECG results (original or copies of printouts)
- DLCO results
- Patient reported outcome forms

### 8.3.2 Direct access to source data and documents

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

### 8.3.3 Storage period of records

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

## 8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

### 8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular 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 nintedanib in IPF for more details.

### 8.4.2 Expedited reporting to health authorities and IEC / IRB

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

## 8.5 STATEMENT OF CONFIDENTIALITY

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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.
Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB / IEC and the regulatory authorities.

## 8.6 END OF TRIAL

The end of the trial is defined as last patient out. The Last Patient Last Visit Primary Endpoint (LPLVPE) is defined as the date when the last randomized patient reaches the Week 52 Visit (Visit 9 at the end of Part A).

For EU member states:
The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

*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.*

## 8.7 PROTOCOL VIOLATIONS

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

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

*Mandatory in 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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# 10. APPENDICES

## 10.1 LUNG FUNCTION CRITERIA

At Visit 2, FVC must fulfil the following criteria:

- ≥ 45% of predicted normal

Predicted normal values will be calculated according to GLI (Global Lung Initiative) (R15-0845, R15-2073). FVC % predicted is a key inclusion criterion and a secondary endpoint using the following demographic information: race, age, gender and height.

At Visit 2, DLCO must fulfil the following criteria:

- ≥ 30% and <80% of predicted normal; corrected for Hb

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

Percent predicted DLCO corrected for haemoglobin (Hb) expressed in g·dL-1 (R06-2002) can be calculated as:

- Percent predicted DLCO corrected for Hb = Percent predicted DLCO x (10.22+Hb)/(1.7Hb) for males
- Percent predicted DLCO corrected for Hb = Percent predicted DLCO x (9.38+Hb)/(1.7Hb) for females

For decision on inclusion / exclusion, percent predicted DLCO results from Visit 2 will be corrected for haemoglobin (value obtained at Visit 1) by the site.

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

There should be at least two acceptable tests that meet the repeatability requirement of either being within 3 mL CO (Standard Temperature and Pressure, Dry - STPD)•min-1 •mmHg-1 (or 1 mmol•min-1•kPa-1) of each other or within 10% of the highest value.

## 10.2 CREATININE CLEARANCE

Creatinine clearance calculation is done according to Cockroft and Gault (R96-0690).

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

## 10.3 PATIENT REPORTED OUTCOME QUESTIONNAIRES

### 10.3.1 K-BILD

1

# King's Brief ILD Questionnaire (K-BILD)

**This questionnaire is designed to assess the impact of your lung disease on various aspects of your everyday life. Read each question carefully and answer by SELECTING the response that best applies to you. Please answer ALL questions, as honestly as you can.**

**PATIENT INFORMATION:**

**Name .....**

**Date: .....**

**1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.**

1. Every time
2. Most times
3. Several Times
4. Sometimes
5. Occasionally
6. Rarely
7. Never

**2. In the last 2 weeks, because of my lung condition, my chest has felt tight.**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**3. In the last 2 weeks have you worried about the seriousness of your lung complaint?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**4. In the last 2 weeks have you avoided doing things that make you breathless?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**5. In the last 2 weeks have you felt in control of your lung condition?**

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

**6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**8. In the last 2 weeks, my lung condition has made me feel anxious.**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**10. In the last two weeks how much of the time have you felt your lung disease is getting worse?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**12. In the last 2 weeks have you expected your lung complaint to get worse?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**14. In the last 2 weeks, has your lung condition made you think more about the end of your life?**

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

**15. Are you financially worse off because of your lung condition?**

1. A significant amount
2. A large amount
3. A considerable amount
4. A reasonable amount
5. A small amount
6. Hardly at all
7. Not at all

**Thank you for completing this questionnaire**

### 10.3.2 L-PF Symptoms and Impact Questionnaire



## Instructions for Completing the Living with Pulmonary Fibrosis (L-PF) Symptoms Questionnaire

Complete this questionnaire to assess the symptoms you may have experienced from Pulmonary Fibrosis (PF) over the last 24 hours.

Keep in mind:
- you are not being asked to compare yourself to anyone else
- you are not being asked to compare how you are now with any time in the past

---

**Items 1-12:** The first 12 items ask about your symptoms in relation to physical activities, some of which you may not have done in the **last 24 hours**. If you did not perform an activity, we would like to know whether it was because you did not have the opportunity to do it (for example, maybe your home doesn't have stairs, so you did not walk up a flight of stairs), or whether you avoided the activity because it was too difficult.

**If you did the stated activity, then reflect on the last 24 hours, and consider whether, on average, doing the activity at your usual pace or intensity level made you short of breath—and if so, how much.**

**If you normally use oxygen when you perform a given activity, then consider your response as if you were using supplemental oxygen.**

Please select the box that best describes your experience.

1. Did you get dressed in the last 24 hours?

☐ Yes How short of breath did getting dressed make you?

Not at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 Extremely

☐ No I did not get dressed in the last 24 hours because:

☐ A I avoided this activity because it was too difficult to perform

☐ B Not applicable, because I did not want or have the opportunity to do it

2. Did you walk up one flight of stairs in the last 24 hours?

Yes How short of breath did walking up one flight of stairs make you?

Not at all 0 1 2 3 4 Extremely

No I did not walk up one flight of stairs in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

3. Over the last 24 hours, how short of breath have you been while sitting down, relaxing, reading, or watching TV?

Not at all 0 1 2 3 4 Extremely

4. Did you walk up a short, gradual incline (like a wheelchair ramp into a building) in the last 24 hours?

Yes How short of breath did walking up a short, gradual incline make you?

Not at all 0 1 2 3 4 Extremely

No I did not walk up a short, gradual incline in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

5. Did you perform a grooming activity (e.g., brush teeth, shave, fix hair) in the last 24 hours?

Yes How short of breath did grooming make you?

Not at all 0 1 2 3 4 Extremely

No I did not perform a grooming activity in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

6. Did you walk outside on a level surface (approximately 150 feet/45 meters, or the distance of half a typical city block) in the last 24 hours?

Yes How short of breath did walking outside on a level surface make you?

Not at all 0 1 2 3 4 Extremely

No I did not walk outside on a level surface in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

7. Did you walk from room to room inside your home in the last 24 hours?

Yes How short of breath did walking from room to room inside your home make you?

Not at all 0 1 2 3 4 Extremely

No I did not walk from room to room inside my home in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

8. Did you leave your home in the last 24 hours?

Yes How short of breath did getting ready to leave your home (e.g., find keys, put on coat, lock doors) make you?

Not at all 0 1 2 3 4 Extremely

No I did not leave my home in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

9. Did you bathe or shower in the last 24 hours?

Yes — How short of breath did bathing or showering make you?

Not at all 0 1 2 3 4 Extremely

No — I did not bathe or shower in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

10. Did you do light cleaning around the house in the last 24 hours?

Yes — How short of breath did doing light cleaning around the house make you?

Not at all 0 1 2 3 4 Extremely

No — I did not do light cleaning around the house in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

11. Over the last 24 hours, how short of breath were you after eating a meal or snacks?

Not at all 0 1 2 3 4 Extremely

12. Did you lift and carry a light load (e.g., less than 10 lbs) a short distance (e.g., from one room to another) in the last 24 hours?

Yes — How short of breath did lifting and carrying a light load a short distance make you?

Not at all 0 1 2 3 4 Extremely

No — I did not lift or carry a light load a short distance in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

**Items 13-18**: Each item focuses on cough. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

**13.** Over the last 24 hours, how often did you cough?

**Not at all** 0 1 2 3 4 **Constantly**

**If you chose "0", please skip to Item 18.**

**14.** Over the last 24 hours, how often did you cough when you took a deep breath?

**Not at all** 0 1 2 3 4 **Constantly**

**15.** Over the last 24 hours, how often did you cough when you were breathing hard or fast?

**Not at all** 0 1 2 3 4 **Constantly**

**16.** Over the last 24 hours, how often did you cough when you over-exerted yourself?

**Not at all** 0 1 2 3 4 **Constantly**

**17.** Over the last 24 hours, how often did coughing make you short of breath?

**Not at all** 0 1 2 3 4 **Constantly**

**18.** Over the last 24 hours, how often did you feel an annoying tickle in your throat?

**Not at all** 0 1 2 3 4 **Constantly**

**19-23**: These items primarily focus on your energy level. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

**19.** Over the last 24 hours, how was your energy level?

**Extremely low** [0] [1] [2] [3] [4] **Excellent**

**20.** Over the last 24 hours, of all that you wanted to get done, how much did you actually get done?

**Nothing** [0] [1] [2] [3] [4] **Everything**

**21.** Over the last 24 hours, how much energy did you have to do all the things you like to do?

**No energy** [0] [1] [2] [3] [4] **A lot**

**22.** Over the last 24 hours, how much did coughing have a negative effect on your energy?

**No effect at all** [0] [1] [2] [3] [4] **A lot**

**23.** Did you become short of breath in the last 24 hours?

[Yes] How long did it take you to recover when you became short of breath?

**No time at all** [0] [1] [2] [3] [4] **An extremely long time**

[No] Please continue to the next page.

**Thank you for taking the time to complete the L-PF Symptoms Questionnaire.**

## Instructions for Completing the Living with Pulmonary Fibrosis (L-PF) Impacts Questionnaire

The goal of this questionnaire is to determine how Pulmonary Fibrosis affects your quality of life.

Quality of life refers to your perceptions of your overall position in life in relation to:

- your goals and expectations
- your standards and values
- your concerns and judgments

Among other things, quality of life encompasses:

- your physical health (conditions/diseases, symptoms, therapies)
- your psychological state (outlook, emotional well-being)
- your level of independence
- the relationships you have with pertinent features of your environment

Reflect on your life: has Pulmonary Fibrosis affected your quality of life? **As you respond to the items, reflect on your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.**

**Items 1-16**: For these items, reflect on the **last 7 days** as you consider where you are on the scale between the two statements.

**On average, over the last 7 days...**

1. How much did shortness of breath prevent you from doing things you wanted to do?

Not at all 0 1 2 3 4 Extremely

2. How much did fear of becoming too short of breath limit your physical exertion?

Not at all 0 1 2 3 4 Extremely

3. How was your stamina when you exerted physically?

Extremely poor 0 1 2 3 4 Excellent

4. How frustrated were you by the time it took you to complete a physical activity?

Not at all 0 1 2 3 4 Extremely

5. How frustrated were you by the speed it took you to complete a physical activity?

Not at all 0 1 2 3 4 Extremely

6. How frustrated were you by your need to rest during or after completing a physical activity?

Not at all 0 1 2 3 4 Extremely

7. How much did coughing embarrass you?

Not at all 0 1 2 3 4 Extremely

8. How much did coughing frustrate you?

Not at all 0 1 2 3 4 Extremely

**On average, over the last 7 days...**

9. How much did coughing interrupt your conversations (in person or on the phone)?

Never 0 1 2 3 4 All of the time

10. How frightening was your coughing to you?

Not at all 0 1 2 3 4 Extremely

11. How much was your cough a problem for you?

Not at all 0 1 2 3 4 Extremely

12. How much hassle or inconvenience has pulmonary fibrosis caused you in your day-to-day life?

None 0 1 2 3 4 A lot

13. How much did you have to rest in the middle of doing a simple chore inside the house?

Not at all 0 1 2 3 4 A lot

14. How much did you have to pace yourself to make it through the day?

Not at all 0 1 2 3 4 A lot

15. How much did it take to get yourself ready to leave the house?

Very little time 0 1 2 3 4 Extremely long time

16. How much were you forced to depend on other people to do things for you?

Not at all 0 1 2 3 4 A lot

**Only five more...**

**For Items 17-19:** Think broadly about your shortness of breath, cough and energy level over the last 7 days. Have these symptoms affected how you have felt physically? Psychologically? Have they disrupted your life? Or limited you in terms of what you would like to do or how you would like to do it? Now, please respond to Items 17-19.

**On average, over the last 7 days...**

**17.** How has shortness of breath affected your quality of life?

| | | | | | | |
|---|---|---|---|---|---|---|
| Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect |

**18.** How much has your cough affected your quality of life?

| | | | | | | |
|---|---|---|---|---|---|---|
| Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect |

**19.** How much has your energy level affected your quality of life?

| | | | | | | |
|---|---|---|---|---|---|---|
| Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect |

**For these last two Items:** Think broadly again about whether Pulmonary Fibrosis has affected you and your quality of life over the last 7 days. **Reflect on your symptoms and other aspects of your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.**

**On average, over the last 7 days...**

**20.** How have you felt in terms of physical health?

| | | | | | | |
|---|---|---|---|---|---|---|
| Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent |

**21.** How has your quality of life been?

| | | | | | | |
|---|---|---|---|---|---|---|
| Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent |

**The end.**
**Thank you for taking the time to complete the L-PF Impacts Questionnaire.**

### 10.3.3 EQ-5D


**Health Questionnaire**

**English version for the USA**

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Under each heading, please check the ONE box that best describes your health TODAY

**MOBILITY**

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

**SELF-CARE**

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

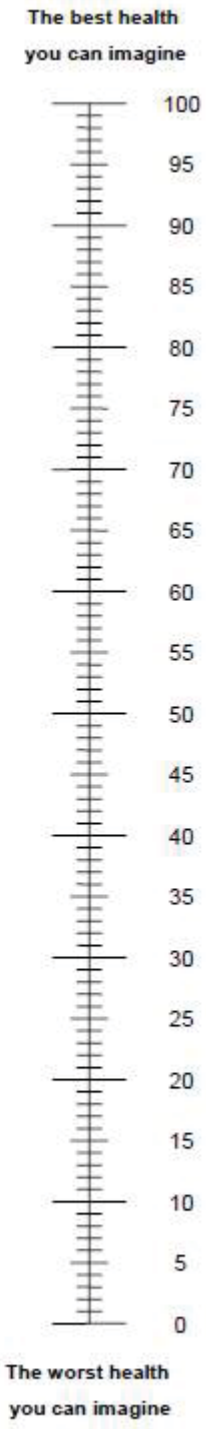
**ANXIETY / DEPRESSION**

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



### 10.3.4 PF-IQOLS

**Over the past four weeks, how much did your pulmonary fibrosis negatively affect your life in each of the following areas?**

**Consider the effects of the pulmonary fibrosis itself, the medications you take for pulmonary fibrosis (including supplemental oxygen if you use it), and anything you did to avoid, treat, or get medical care for symptoms of pulmonary fibrosis.**

| | No Negative Effect At All 1 | Slightly Negative Effect 2 | Moderately Negative Effect 3 | Very Negative Effect 4 | Extremely Negative Effect 5 |
|---|---|---|---|---|---|
| 1. *Material comforts* — things like a desirable home, good food, possessions, conveniences, an increasing income, and security for the future. | 1 | 2 | 3 | 4 | 5 |
| 2. *Health and personal safety* — being physically fit and vigorous, free from anxiety and distress, and avoiding bodily harm. | 1 | 2 | 3 | 4 | 5 |
| 3. *Relationships with your parents, brothers, sisters, and other relatives* — communicating, visiting, and doing things with, understanding, and helping and being helped by your relatives. | 1 | 2 | 3 | 4 | 5 |
| 4. *Having and raising children* — being a parent and helping, teaching, and caring for your children. | 1 | 2 | 3 | 4 | 5 |
| 5. *Close relationship with a husband, wife, or partner* | 1 | 2 | 3 | 4 | 5 |
| 6. *Close friends* — sharing activities, interests, and views; being accepted, visiting, giving and receiving help, love, trust, support, guidance. | 1 | 2 | 3 | 4 | 5 |
| 7. *Helping and encouraging others* — adults or children other than relatives or close friends. These can be your own efforts or efforts as a member of a church, club, or volunteer group. | 1 | 2 | 3 | 4 | 5 |
| 8. *Participation in activities relating to local and national government and public affairs.* | 1 | 2 | 3 | 4 | 5 |

IQOLS scale developed by Sandra R. Wilson, PhD. Dimensions from Flanagan, JC. *American Psychologist*. 1978;33:138-147, with addition by Burckhardt, CS, *et al*. *Research in Nursing & Health* 1989; 12:347-35.

**Over the past four weeks, how much did your pulmonary fibrosis negatively affect your life in each of the following areas?**

| | No Negative Effect At All | Slightly Negative Effect | Moderately Negative Effect | Very Negative Effect | Extremely Negative Effect |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| 9. *Learning*, attending school, improving your understanding, or gaining additional knowledge. | 1 | 2 | 3 | 4 | 5 |
| 10. *Understanding yourself* — knowing your assets and limitations, knowing what life is all about and making decisions on major life activities. For some people, this includes religious or spiritual experiences; for others, it is developing an attitude toward life or a philosophy. | 1 | 2 | 3 | 4 | 5 |
| 11. *Independence* — doing for yourself: being able to take care of and make decisions about your daily needs, personal care, where you live, and your financial affairs. | 1 | 2 | 3 | 4 | 5 |
| 12. *Work* in a job or at home that is interesting, rewarding, and worthwhile. | 1 | 2 | 3 | 4 | 5 |
| 13. *Expressing yourself* in a creative manner in music, art, writing, photography, practical activities, or in leisure time activities | 1 | 2 | 3 | 4 | 5 |
| 14. *Socializing* — meeting other people, doing things with them, and hosting or attending parties or other social gatherings. | 1 | 2 | 3 | 4 | 5 |
| 15. *Reading, listening to music, or observing* sporting events or entertainment. | 1 | 2 | 3 | 4 | 5 |
| 16. *Participation in active recreation* such as playing sports, traveling and sightseeing, playing games or cards, singing, dancing, playing an instrument, acting, and other such activities. | 1 | 2 | 3 | 4 | 5 |

IQOLS scale developed by Sandra R. Wilson, PhD. Dimensions from Flanagan, JC. *American Psychologist*. 1978;33:138-147, with addition by Burckhardt, CS, *et al*. *Research in Nursing & Health* 1989; 12:347-35.

## 10.4 HANDLING AND DERIVATION OF PHARMACOKINETIC PARAMETERS

### 10.4.1 Pharmacokinetic Methods

Concentrations will be used for calculations in the format that is reported in the bioanalytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of PK parameters, actual sampling times and only concentrations within the validated concentration range will be used. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then, the individual values, as well as the descriptive statistics, will be reported with three significant digits in the clinical trial report. For pre-dose samples, the actual sampling time will be set to zero. Descriptive PK analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software, version 9.4 (or later).

Analyte plasma concentrations will be plotted graphically versus time for all subjects as listed in the analyte plasma concentration-time tables. For the presentation of the mean profiles, the geometric mean and the planned blood sampling times will be used.

## 10.5 FVC DECLINE RESULTS IN IPF TRIALS

| Study | N treated placebo | FVC% pred at baseline | Mean absolute change from baseline in FVC |
|---|---|---|---|
| Acetylcysteine<br>PANTHER (P14-07665) | 131 | 73 % pred | Week 45 (observed):<br>-0.15 L<br>Week 60 (MMRM):<br>-0.19 L (SD=0.31 L*)<br>Week 60 (observed):<br>-0.15 L |
| Pirfenidone<br>CAPACITY 004 (P10-13367) | 174 | 76 %pred | Week 48 (without imputation):<br>-179 mL |
| Pirfenidone<br>CAPACITY 006 (P10-13367) | 173 | 73 %pred | Week 48 (without imputation):<br>-141 mL |
| Pirfenidone<br>ASCEND (R15-1725, R14-2103) | 277 | 69 % pred | Week 52 (without imputation):<br>-256 mL |
| Nintedanib<br>1199.30b (U11-1225-02) | 85 | 82 % pred | Week 52 (observed cases):<br>-188 mL (SD = 365 mL)** |
| Nintedanib<br>1199.32 (U13-2381-01) | 204 | 81% pred | Week 52 (observed cases):<br>-202 mL (SD = 306 mL) |
| Nintedanib<br>1199.34 (U13-2382-01) | 219 | 78% pred | Week 52 (observed cases):<br>-204 mL (SD = 280 mL) |

*SD was estimated based on the confidence interval
**FVC data were converted from L to mL by multiplying raw data by 1000

## 10.6 SAS CODE FOR SAMPLE SIZE CALCULATION

```
%MACRO PRBHOCH(a,b,d1,d2,sd1,sd2,f,n,dat);
*************************************************************************;
** a    = 1-sided Type 1 error used in powering                          **;
** b    = Type II error used in powering                                 **;
** d1   = hypothesized overall treatment effect                          **;
** d2   = hypothesized subpopulation treatment effect                    **;
** sd1  = assumed SD overall                                             **;
** sd2  = assumed SD subpopulation                                       **;
** f    = fraction in subpopulation                                      **;
** n    = Planned sample size per treatment group                        **;
** dat  = dataset name                                                   **;
*************************************************************************;

DATA x;
a=&a;
b=&b;
f=&f;
d1=&d1;
sd1=&sd1;
d2=&d2;
sd2=&sd2;
n=&n;
ns=round(f*n,1);
r=sqrt(f);   ** correlation between subpopulation and overall population test statistics **;

** under null using Hochberg**;
zhoc1= probit(1-0.025);
zhoc2= probit(1-0.025/2);

** critical values for Hochberg**;
choc1025=   zhoc1*sd1*sqrt(2/n);
choc10125=  zhoc2*sd1*sqrt(2/n);
choc2025=   zhoc1*sd2*sqrt(2/ns);
choc20125=  zhoc2*sd2*sqrt(2/ns);

**under alternative Hochberg**;
t1025=(choc1025-d1)/(sd1*sqrt(2/n));
t10125=(choc10125-d1)/(sd1*sqrt(2/n));
t2025=(choc2025-d2)/(sd2*sqrt(2/ns));
t20125=(choc20125-d2)/(sd2*sqrt(2/ns));

** Hochberg overall type 1 error**;
phoc1025= PROBBNRM(-zhoc1,50000,r);
phoc10125= PROBBNRM(-zhoc2,50000,r);
```

```
phoc2025= PROBBNRM(-zhoc1,50000,r);
phoc20125= PROBBNRM(-zhoc2,50000,r);
phoc1025nphoc2025= PROBBNRM(-zhoc1,-zhoc1,r);
phoc10125nphoc2025= PROBBNRM(-zhoc2,-zhoc1,r);
phoc20125nphoc1025= PROBBNRM(-zhoc1,-zhoc2,r);
pp1 = phoc10125 - phoc10125nphoc2025;
pp2 = phoc20125 - phoc20125nphoc1025;
phoc1sig = phoc1025nphoc2025 + pp1;
phoc2sig = phoc1025nphoc2025 + pp2;
HocTy1 = phoc1sig + phoc2sig - phoc1025nphoc2025; * 1-sided Type 1 error;

** Hochberg overall power **;
xhoc1025= PROBBNRM(-t1025,50000,r);
xhoc10125= PROBBNRM(-t10125,50000,r);
xhoc2025= PROBBNRM(-t2025,50000,r);
xhoc20125= PROBBNRM(-t20125,50000,r);
xhoc1025nxhoc2025= PROBBNRM(-t1025,-t2025,r);
xhoc10125nxhoc2025= PROBBNRM(-t10125,-t2025,r);
xhoc20125nxhoc1025= PROBBNRM(-t20125,-t1025,r);
xx1 = xhoc10125 - xhoc10125nxhoc2025;
xx2 = xhoc20125 - xhoc20125nxhoc1025;
xhoc1sig = xhoc1025nxhoc2025 + xx1;  * Power for overall population test;
xhoc2sig = xhoc1025nxhoc2025 + xx2;  * Power for sub-population test;
HocPow = (xhoc1sig + xhoc2sig - xhoc1025nxhoc2025); * Overall power;

run;

PROC PRINT;
RUN;

data &dat;set x;
Dat="&dat";
run;

%MEND;

%prbhoch(0.025,0.10,92,100,337,300,0.667,300 ,d1);
%prbhoch(0.025,0.10,70,75,337,300,0.667,300,d2);
%prbhoch(0.025,0.10,75,75,337,300,0.667,300,d3);


data all;set d1 d2 d3;
run;

proc print data = all;
run;
```

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

| | | |
|---|---|---|
| **Number of global amendment** | | 2.0 |
| **Date of CTP revision** | | 08 Jun 2018 |
| **EudraCT number** | | 2015-003360-37 |
| **BI Trial number** | | 1199.247 |
| **BI Investigational Product(s)** | | Nintedanib |
| **Title of protocol** | | A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
| | | |
| **Section to be changed** | | Synopsis |
| **Description of change** | | Administrative changes, corrections and clarification. |
| **Rationale for change** | | Add trial name 'INBUILD®' |
| | | |
| **Section to be changed** | I<br>II | Synopsis<br>Section 6.1(Visit Schedule) |
| **Description of change** | | The trial will last until all patients completed the $EOT_B$ visit and the Follow-up Visit as applicable |
| **Rationale for change** | | Clarification of end of trial |
| | | |
| **Section to be changed** | | Flowchart – Part A (Footnotes) |
| **Description of change** | | $EOT_A$ should be done in cases of premature trial medication discontinuation during Part A of the study with a follow-up Visit (FU) 4 weeks later. A scheduled visit (V3-V9) can be skipped if $EOT_A$ or Follow-up Visit occurs within 4 weeks prior to |

| | | |
|---|---|---|
| | | scheduled visits |
| **Rationale for change** | | Clarification of visit conduct in case of premature medication discontinuation |
| | | |
| **Section to be changed** | | Flowchart – Part A (Footnotes) |
| **Description of change** | | Compliance / drug accountability at Visit 3 and Visit 5 to be performed only in case of dose reduction / increase |
| **Rationale for change** | | Clarification what needs to be documented in regards of compliance / drug accountability |
| | | |
| **Section to be changed** | | Flowchart – Part A (Footnotes) |
| **Description of change** | | For biomarker sampling, date and exact clock time of drug administration and blood sampling needs not be recorded on the eCRF |
| **Rationale for change** | | Clarification of inconsistency between CTP and eCRF |
| | | |
| **Section to be changed** | | Flowchart – Part B |
| **Description of change** | | In case of premature discontinuation of study medication, $EOT_B$ should be done as soon as possible after last drug intake and a Follow-up Visit should be completed 4 weeks after $EOT_B$. A scheduled visit can be skipped if $EOT_B$ or Follow-up Visit occurs within 4 weeks prior to scheduled visits. For patients who complete the study regularly, $EOT_B$ should be scheduled after the Sponsor's communication of the end of the trial. Only in case the patient does not roll-over in the separate open-label study a Follow-up Visit should be completed 4 weeks after $EOT_B$.<br>The specific time window for $EOT_B$ was removed, the time intervals for Visits X and Xa corrected and the need for an IRT call included |
| **Rationale for change** | | Clarification of conduct and timing of $EOT_B$ |
| | | |
| **Section to be changed** | | Section 1.1.1 (ILD Overview), Figure 1.1: 1 |
| **Description of change** | | IPAF stands for Interstitial Pneumonia with Autoimmune Features |
| **Rationale for change** | | Correction |
| | | |
| **Section to be changed** | | 2.3 (Benefit risk assessment) |
| **Description of change** | | According to changes in the recent IB versions, adverse drug reactions and risks of nintedanib treatment have been added. Patients with low body weight (<65 kg), Asian and female patients have a |

| | | |
|---|---|---|
| | | higher risk of elevations in liver enzymes. It was clarified that cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. The majority of patients presented with mild to moderate liver enzyme elevation, which was in most cases transient upon dose reduction or treatment discontinuation. However, severe DILI with fatal outcome has also been reported |
| **Rationale for change** | | Clarification of inconsistency between IB and CTP |
| | | |
| **Section to be changed** | | Section 3.1 (Overall Trial Design and Plan) |
| **Description of change** | | After the Sponsor has communicated the end of the trial, an $EOT_B$ visit has to be performed in all ongoing patients. Depending on the findings, patients receiving trial medication until the end of Part B will be eligible for open-label treatment with nintedanib in a separate study |
| **Rationale for change** | | Clarification of the end of trial and roll-over into an open-label treatment |
| | | |
| **Section to be changed** | | Section 5.3.6.1 (Definitions of AEs) |
| **Description of change** | | Potential DILI cases are defined as AESIs and a DILI checklist has to be worked off |
| **Rationale for change** | | More detailed description of DILI handling |
| | | |
| **Section to be changed** | | Section 5.3.7 (Adverse event collection and reporting) |
| **Description of change** | | All AEs (non-serious and serious) and all AESIs should be collected after the end of treatment (including the Residual Effect Period until the individual patient's end of trial. Figure 5.3.7: 1will be deleted as no longer applicable |
| **Rationale for change** | | Clarification of AE documentation after end of treatment, with the goal to have all patients coming to the regular visits afterwards |
| | | |
| **Section to be changed** | | 6.2.1 (Screening) |
| **Description of change** | | Correct reference time point for historical HRCT within 12 month to Visit 1 |
| **Rationale for change** | | Correction for clarification and consistency with Inclusion criterion |
| | | |
| **Section to be changed** | | Section 6.2.3 (Follow-up Visit and trial completion) |
| **Description of change** | | A follow-up visit is only required for those patients who do not roll-over in the separate open- |

| | | |
|---|---|---|
| | | label study |
| **Rationale for change** | | To clarify by including new wording |
| | | |
| **Section to be changed** | | 7.3.4 (Safety analyses) |
| **Description of change** | | Clarification that based on the half-life of the trial drug, adverse events that occur between the start of treatment and up to 7 days after the date of the last dose of trial medication will be analysed in addition |
| **Rationale for change** | | Specification of an additional adverse event analyses to take the half-life of the trial drug into account |

| | | |
|---|---|---|
| **Number of global amendment** | | 1.0 |
| **Date of CTP revision** | | 21 Dec 2016 |
| **EudraCT number** | | 2015-003360-37 |
| **BI Trial number** | | 1199.247 |
| **BI Investigational Product(s)** | | Nintedanib |
| **Title of protocol** | | A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | ☒ |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | ☐ |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | | ☐ |
| | | |
| **Section to be changed** | | Flowchart A and footnote<br>Section 5.5.3 |
| **Description of change** | | Serum banking changed from mandatory to optional |
| **Rationale for change** | | To ensure that the trial can be conducted according to regulatory and ethical requirements in the participating countries |
| | | |
| **Section to be changed** | | Flowchart B |
| **Description of change** | | ECG will also be performed at EOT in Part B |
| **Rationale for change** | | To make sure that respective safety assessment is performed in Part B of the trial |
| | | |
| **Section to be changed** | | Appendix 10.1 |
| **Description of change** | | Correct criterion for FVC to ≥45% of predicted normal and delete <90% |
| **Rationale for change** | | To align with inclusion criterion in Synopsis and Section 3.3.2 |
| | | |
| **Section to be changed** | | Section 5.2.7.2 |

| | | |
|---|---|---|
| **Description of change** | | Adapt scoring information for the different L-PF domains |
| **Rationale for change** | | Scoring instructions update for L-PF |
| | | |
| **Section to be changed** | | Section 5.3.7 |
| **Description of change** | | Update role of Adjudication Committee under AE reporting an collection |
| **Rationale for change** | | To correct information provided for MACE |
| | | |
| **Section to be changed** | | Section 7.3.1 |
| **Description of change** | | The primary analysis will also be performed on the complementary population of patients with other HRCT fibrotic patterns |
| **Rationale for change** | | To address FDA requirement |
| | | |
| **Section to be changed** | | Section 8.1 |
| **Description of change** | | Information highlighted in cursive for Japan regarding ICF procedures |
| **Rationale for change** | | To adapt ICF handling for specific regulatory requirements in Japan |
| | | |
| **Section to be changed** | | Whole document |
| **Description of change** | | Change naming of HRCT to high resolution computed tomography |
| **Rationale for change** | | To use correct wording “computed” instead of “computer” |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c03736471** **Technical Version Number:3.0**

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

**Title:** A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Trial Clinical Monitor | [redacted] | 15 Jun 2018 08:48 CEST |
| Author-Trial Clinical Pharmacokineticist | [redacted] | 15 Jun 2018 10:26 CEST |
| Approval-Team Member Medicine | [redacted] | 15 Jun 2018 16:10 CEST |
| Author-Trial Statistician | [redacted] | 18 Jun 2018 10:53 CEST |
| Approval-Therapeutic Area [redacted] | [redacted] | 20 Jun 2018 14:13 CEST |
| Verification-Paper Signature Completion | [redacted] | 22 Jun 2018 07:09 CEST |

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

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|