# Clinical Trial Protocol

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| | **Document Number:** | **c34926326-01** |
| **EudraCT No.** | 2021-003152-16 | |
| **BI Trial No.** | 1199-0452 ([redacted] Trial No. [redacted] 204583) | |
| **BI Investigational Medicinal Product** | Nintedanib | |
| **Title** | A Phase I study for formulation selection and subsequent optimization of two different oral formulations of Nintedanib in healthy male subjects (open-label, randomised, single-dose study in three parts) | |
| **Lay Title** | A study in healthy men to find the best formulation for once daily intake of Nintedanib | |
| **Clinical Phase** | I | |
| **Trial Clinical Leader** | [redacted]<br>on behalf of<br>Boehringer Ingelheim Pharma GmbH & Co. KG<br>Department of Clinical Operations Corporate<br>Binger Straße 173<br>55216 Ingelheim am Rhein, Germany<br>Phone: [redacted]<br>Fax: [redacted] | |
| **Principal Investigator** | [redacted]<br>Tel: [redacted] (day)<br>Tel: [redacted] out of hours emergency) | |
| **Status** | Final Protocol | |
| **Version and Date** | Version: 1.0 | Date: 13 January 2022 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

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|---|---|
| **Company name** | Boehringer Ingelheim |
| **Protocol date** | 13 January 2022 |
| **Revision date** | Not applicable |
| **BI trial number** | 1199-0452 |
| **Title of trial** | A Phase I study for formulation selection and subsequent optimization of two different oral formulations of Nintedanib in healthy male subjects (open-label, randomised, single-dose study in three parts) |
| **Principal Investigator:** | [redacted] |
| **Trial site** | [redacted] |
| **Clinical phase** | I |
| **Trial rationale** | To assess two modified release formulations of oral Nintedanib and optimize a modified release (MR) profile to fit standard immediate release Nintedanib (twice daily) in healthy male subjects |
| **Trial objective** | To test two modified release formulations of Nintedanib (formulation X slow/fast release and Y slow/fast release) and further optimize release profile and dose of one modified formulation to ultimately fit exposure to the immediate release reference product, oral Nintedanib [redacted] mg twice daily. |
| **Trial design** | Open-label, randomised, single-dose (qd for test and bid for reference treatment) study in up to three parts; trial part 1: two parallel groups, each a randomised three-period crossover; trial part 2 (optional): one group of randomised three-period crossover; trial part 3 (optional): one group of randomised two-period crossover |
| **Trial endpoints:** | Primary endpoint: $AUC_{0-\infty}$ of Nintedanib<br>Secondary endpoints: $AUC_{0-tz}$ , $C_{max}$ and $C_{24}$ of Nintedanib |
| **Number of subjects**<br>**total entered**<br>**each treatment** | <br>30 (optional 59)<br>Trial part 1: 2 x 15 = 30<br>Trial part 2 (optional): 1 x 15 = 15<br>Trial part 3 (optional): 1 x 14 = 14 |
| **Diagnosis** | Not applicable |
| **Main criteria for inclusion** | Healthy male subjects (Caucasian and Black only), age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 $kg/m^2$ (inclusive, absolute body weight at least 65 kg) |

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|---|---|
| **Test product (TP) 1** | **Nintedanib Modified Release 1 (MR1)[1], Prototype 1 Tablet (MR1-1)** |
| **dose** | [redacted] mg (1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Test product 2** | **Nintedanib MR1[1], Prototype 2 Tablet (MR1-2)** |
| **dose** | [redacted] mg (1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Test product 3** | **Nintedanib MR2[2], Prototype 1 Tablet (MR2-1)** |
| **dose** | [redacted] mg (1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Test product 4** | **Nintedanib MR2[2], Prototype 2 Tablet (MR2-2)** |
| **dose** | [redacted] mg (1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Test product 5, optional** | **Nintedanib selected MRX[3], Prototype 3[4] Tablet (MRX-3)** |
| **dose** | [redacted] to [redacted] mg (approximate dose range, 1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Test product 6, optional** | **Nintedanib selected MRX, Prototype 4[4] Tablet (MRX-4)** |
| **dose** | [redacted] to [redacted] mg (approximate dose range, 1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Test product 7, optional** | **Nintedanib selected MRX, Prototype 5[4] Tablet (MRX-5)** |
| **dose** | [redacted] to [redacted] mg (approximate dose range, 1 tablet) as single dose |
| **mode of admin.** | Oral with 240 mL of water after light breakfast |
| **Reference product (RP)** | **Ofev® [redacted] mg soft capsules[5]** |
| **dose** | [redacted] mg (1 capsule) twice per day (*b.i.d.*) |
| **mode of admin.** | Oral with 240 mL of water after light breakfast/dinner |

[1] MR1 = Monolithic Nintedanib Modified Release Prototype Tablet

[2] MR2 = Polyox Nintedanib Modified Release Prototype Tablet

[3] MRX = Placeholder for Polyox and/or Monolithic Nintedanib Modified Release Prototype Tablet

[4] Further prototypes will be selected from a design space describing formulation variables. Each prototype will be given a number assigned sequentially as dosed

[5] Immediate Release

| | |
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| **Duration of treatment** | One day (single dose) for each treatment:<br>**Trial part 1**<br>Trial part 1A (cohort 1, n=15)<br>• RP (Ofev® [redacted] mg soft capsules) *b.i.d.*: [redacted] mg Nintedanib *b.i.d.* after light breakfast and dinner, respectively<br>• TP1 (Nintedanib MR1, Prototype 1): [redacted] mg Nintedanib after light breakfast<br>• TP2 (Nintedanib MR1, Prototype 2): [redacted] mg Nintedanib after light breakfast<br>Trial part 1B (cohort 2, n=15)<br>• RP (Ofev® [redacted] mg soft capsules) *b.i.d.*: [redacted] mg Nintedanib *b.i.d.* after light breakfast and dinner, respectively<br>• TP3 (Nintedanib MR2, Prototype 1): [redacted] mg Nintedanib, after light breakfast<br>• TP4 (Nintedanib MR2, Prototype 2): [redacted] mg Nintedanib, after light breakfast<br>*Decision point: either (a) stop here or (b) proceed to trial part 2 with one selected formulation.*<br>**Trial part 2** (optional, cohort 3, n=15)<br>• RP (Ofev® [redacted] mg soft capsules) *b.i.d.*: [redacted] mg Nintedanib *b.i.d.* after light breakfast and dinner, respectively<br>• TP5 (Nintedanib selected MRX, Prototype 3): [redacted] mg Nintedanib, after light breakfast<br>• TP6 (Nintedanib selected MRX, Prototype 4): [redacted] mg Nintedanib, after light breakfast<br>*Decision point: either (a) stop here or (b) proceed to trial part 3 with one selected formulation.*<br>**Trial part 3** (optional, cohort 4, n=14)<br>• RP (Ofev® [redacted] mg soft capsules) *b.i.d.*: [redacted] mg Nintedanib *b.i.d.* after light breakfast and dinner, respectively<br>• TP7 (Nintedanib selected MRX, Prototype 5): [redacted] mg Nintedanib, after light breakfast<br>In any trial part, there will be a washout period of at least 14 days between treatments, i.e. the morning dose in the preceding treatment period and the morning dose in the following treatment period will be separated by at least 14 days. |

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| **Statistical methods** | Preliminary pharmacokinetic analyses and simulations will be performed between trial part 1 and 2 as well as between part 2 and 3, if appropriate.<br><br>Relative bioavailability will be estimated by the ratios of the geometric means (test/ reference) for primary, secondary and further selected endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subject nested within sequence, period and treatment.<br><br>CIs will be calculated based on the residual error from the ANOVA.<br><br>Descriptive statistics will be calculated for all endpoints. |

# FLOW CHART - REFERENCE TREATMENT OFEV® IR

| Period | Visit | Day | Planned time (relative to drug administration) [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory [7] | PK blood | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|
| SCR | 1 | -28 to -1 | | | Screening (SCR)[1] | A | | x | x | |
| 1/2/3 (2 or 3 periods separated by a wash-out of at least 14 days) | 2 or 3 or 4* | -1 | -12:00 | 20:00 | **Admission to trial site** | x[5] | | | | x |
| | | | -11:30 | 20:30 | Snack (voluntary) | | | | | |
| | | 1 | -1:30 | 06:30 | Allocation to treatment[2] (visit 2 only) | B[2] | x[2] | x[2] | x[2] | x[2] |
| | | | -0:30 | 07:30 | Light breakfast | | | | | |
| | | | **0:00** | **08:00** | **Drug administration (with 240 mL fluid intake)** | | | | | |
| | | | 1:00 | 09:00 | | | x | | | |
| | | | 2:00 | 10:00 | 240 mL fluid intake | | x | x | x | x |
| | | | 3:00 | 11:00 | | | x | | | |
| | | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x | x | x | x |
| | | | 6:00 | 14:00 | | | x | | | |
| | | | 8:00 | 16:00 | Snack (voluntary)[3] | | x | | | |
| | | | 10:00 | 18:00 | | | x | | | |
| | | | 11:30 | 19:30 | Dinner | | | | | |
| | | | **12:00** | **20:00** | **Drug administration** | | x[8] | | | x |
| | | | 13:00 | 21:00 | | | x | | | |
| | | | 14:00 | 22:00 | | | x | | | x |
| | | | 15:00 | 23:00 | | | x | | | |
| | | 2 | 16:00 | 00:00 | | | x | | | x |
| | | | 18:00 | 02:00 | | | x | | | |
| | | | 20:00 | 04:00 | | | x | | | |
| | | | 22:00 | 06:00 | | | x | | | |
| | | | 24:00 | 08:00 | Breakfast (voluntary)[3] | B | x | x | x | x |
| | | | 28:00 | 12:00 | Lunch (voluntary) | | | | | |
| | | | 31:00 | 15:00 | Snack (voluntary) | | | | | |
| | | | 34:00 | 18:00 | Dinner (voluntary)[3] | | x | | | x |
| | | 3 | 48:00 | 08:00 | Breakfast (voluntary)[3] | | x | | | x |
| | | | 52:00 | 12:00 | Lunch (voluntary) | | | | | |
| | | | 55:00 | 15:00 | Snack (voluntary) | | | | | |
| | | | 58:00 | 18:00 | Dinner (voluntary)[3] | | x | | | x |
| | | 4 | 72:00 | 08:00 | Breakfast (voluntary)[3] **Discharge from trial site** | B | x | x | x | x |
| EoT | 5 | 15 to 22 | | | End of trial (EoT) examination[4] | A | | x | x | x |

*Visit 4 only applicable for trial parts 1 and 2

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs (BP, PR), ECG, safety laboratory (including drug screening and virology), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. At the end of trial visit the EoT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Letter A and B define different sets of safety laboratory examinations (for details refer to Table 5.2.3: 1)
8. Blood sampling within 5 minutes before drug administration (for trough estimation)

# FLOW CHART - TEST TREATMENT NINTEDANIB MR1-4

| Period | Visit | Day | Planned time (relative to drug administration) [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory [7] | PK blood | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|
| SCR | 1 | -28 to -1 | | | Screening (SCR)[1] | A | | x | x | |
| 1/2/3 (2 or 3 periods separated by a wash-out of at least 14 days) | 2 or 3 or 4* | -1 | -12:00 | 20:00 | **Admission to trial site** | x[5] | | | | x |
| | | | -11:30 | 20:30 | Snack (voluntary) | | | | | |
| | | 1 | -1:30 | 06:30 | Allocation to treatment[2] (visit 2 only) | B[2] | x[2] | x[2] | x[2] | x[2] |
| | | | -0:30 | 07:30 | Light breakfast | | | | | |
| | | | **0:00** | **08:00** | **Drug administration (with 240 mL fluid intake)** | | | | | |
| | | | 1:00 | 09:00 | | | x | | | |
| | | | 2:00 | 10:00 | 240 mL fluid intake | | x | x | x | x |
| | | | 3:00 | 11:00 | | | x | | | |
| | | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | | x | x | x | x |
| | | | 6:00 | 14:00 | | | x | | | |
| | | | 8:00 | 16:00 | Snack (voluntary)[3] | | x | | | |
| | | | 10:00 | 18:00 | | | x | | | |
| | | | 11:30 | 19:30 | Dinner | | | | | |
| | | | 12:00 | 20:00 | | | x | | | x |
| | | | 14:00 | 22:00 | | | x | | | x |
| | | | 15:00 | 23:00 | | | x | | | |
| | | 2 | 16:00 | 00:00 | | | x | | | x |
| | | | 17:00 | 01:00 | | | x | | | |
| | | | 18:00 | 02:00 | | | x | | | |
| | | | 20:00 | 04:00 | | | x | | | |
| | | | 22:00 | 06:00 | | | x | | | |
| | | | 24:00 | 08:00 | Breakfast (voluntary)[3] | B | x | x | x | x |
| | | | 28:00 | 12:00 | Lunch (voluntary) | | | | | |
| | | | 31:00 | 15:00 | Snack (voluntary) | | | | | |
| | | | 34:00 | 18:00 | Dinner (voluntary)[3] | | x | | | x |
| | | 3 | 48:00 | 08:00 | Breakfast (voluntary)[3] | | x | | | x |
| | | | 52:00 | 12:00 | Lunch (voluntary) | | | | | |
| | | | 55:00 | 15:00 | Snack (voluntary) | | | | | |
| | | | 58:00 | 18:00 | Dinner (voluntary)[3] | | x | | | x |
| | | 4 | 72:00 | 08:00 | Breakfast (voluntary)[3] **Discharge from trial site** | B | x | x | x | x |
| EoT | 5 | 15 to 22 | | | End of trial (EoT) examination[4] | A | | x | x | x |

*Visit 4 only applicable for trial parts 1 and 2

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs (BP, PR), ECG, safety laboratory (including drug screening and virology), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. At the end of trial visit the EoT examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Letter A and B define different sets of safety laboratory examinations (for details refer to Table 5.2.3: 1)

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# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| AST | Aspartate transaminase |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $AUC_{0-24}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours |
| $AUC_{0-24,ss}$ | Area under the concentration-time curve of the analyte in plasma at steady state over the time interval from 0 to 24 hours |
| [redacted] | [redacted] |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| BA | Bioavailability |
| BI | Boehringer Ingelheim |
| BMI | Body mass index (weight divided by height squared) |
| BP | Blood pressure |
| $C_{24}$ | Measured concentration of the analyte in plasma at 24 h post dose |
| CA | Competent authority |
| CI | Confidence interval |
| CL | Total clearance of the analyte in plasma after intravascular administration |
| CL/F | Apparent clearance of the analyte in plasma after extravascular administration |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| $C_{min}$ | Minimum measured concentration of the analyte in plasma |
| COVID-19 | SARS-CoV-2 induced disease |
| CRF | Case Report Form, paper or electronic (sometimes referred to as 'eCRF') |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| DILI | Drug induced liver injury |
| DLT | Dose limiting toxicity |
| DNA | Deoxyribonucleic acid |
| DV | Decision value |

| | |
|---|---|
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDTA | Ethylenediaminetetraacetic acid |
| EoT | End of trial |
| EudraCT | European Clinical Trials Database |
| F | Absolute bioavailability factor |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| gCV | Geometric coefficient of variation |
| GGT | Gamma-GT |
| gMean | Geometric mean |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator's brochure |
| ILD | Interstitial lung disease |
| IEC | Independent Ethics Committee |
| IMPD | Investigational Medicinal Product Dossier |
| IPD | Important protocol deviation |
| IPF | Idiopathic pulmonary fibrosis |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| [redacted] | [redacted] |
| MDA | Methylenedioxyamphetamine |
| MDMA | Methylenedioxymethamphetamine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MR | Modified release |
| [redacted] | [redacted] |
| MTD | Maximum tolerated dose |
| NSCLC | Non-small cell lung cancer |
| PCR | Polymerase chain reaction |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic parameter analysis set |
| PR | Pulse rate |
| QT | Time between start of the Q-wave and the end of the T-wave in an electrocardiogram |
| QTc | QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB) |
| R | Reference treatment |

| | |
|---|---|
| REP | Residual effect period |
| RNA | Ribonucleic acid |
| RP | Reference product |
| SAC | Safety advisory committee |
| SAE | Serious adverse event |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SCR | Screening |
| SmPC | Summary of Product Characteristics |
| SOP | Standard operating procedure |
| ss | (at) steady state |
| T | Test treatment |
| $t_{1/2}$ | Terminal half-life of the analyte in plasma |
| $t_{max}$ | Time from (last) dosing to the maximum measured concentration of the analyte in plasma |
| TP | Test product |
| TSAP | Trial statistical analysis plan |
| ULN | Upper limit of normal |
| $V_{ss}$ | Apparent volume of distribution at steady state after intravascular administration |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extravascular administration |
| XTC | Ecstasy |

# 1. INTRODUCTION

Nintedanib is approved for 4 indications in 2 different therapeutic areas: IPF, progressive fibrosing ILD, and SSc-ILD in the respiratory therapeutic area as Ofev® and NSCLC for oncology as Vargatef®. In most countries, nintedanib is marketed under the trade name Ofev® for the respiratory indications and as Vargatef® for oncology (NSCLC). Ofev® has been approved for treatment of idiopathic pulmonary fibrosis (IPF) since 2015 with a standard therapeutic dose of [redacted] mg twice daily. Each treatment includes one [redacted] mg Nintedanib soft capsule with an immediate release (IR) profile, which releases the total drug amount at once in the gut. Since the rapid local drug exposure is associated with increased gut toxicity and adverse drug reactions, dose reduction to [redacted] mg twice daily is often necessary. Alteration in the capsule's composition can lead to a modified release (MR) profile with a preferable steadier increase of local drug exposure. This is postulated to reduce local toxicity and increase overall tolerability of Nintedanib. Therefore, several MR formulations for Nintedanib have been developed and are planned to be tested in this clinical trial in healthy volunteers.

## 1.1 MEDICAL BACKGROUND

The major abnormality in fibrosing interstitial lung diseases (ILDs) is the disruption of the distal lung parenchyma. Although the pathogenesis, especially of the interstitial idiopathic pneumonias (including IPF), remains unknown, it is generally agreed that some form of injury of the alveolar epithelial cells initiates an inflammatory response coupled with inappropriate repair mechanisms. The initiating injury can be introduced via the airways (e.g. inhalation of mineral fibres or dust as in occupational diseases or sensitisation to inhaled allergens as in hypersensitivity pneumonitis) or via the circulation (e.g. connective tissue disease and drug-induced ILDs). The injury-repair process is reflected pathologically as inflammation, fibrosis or a combination of both. Fibrosing ILD, including IPF, is characterised by alveolar epithelial cell injury and subsequent dysregulated repair, characterised by excessive deposition of extracellular matrix and loss of normal parenchymal architecture and lung function. In IPF fibroblasts exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis. Several growth factors are implicated in the proliferation, migration and transdifferentiation of the fibroblast and myofibroblast pool in pulmonary fibrosis.

For details on medical background refer to the current version of the Investigator's Brochure (IB) [c01783972].

## 1.2 DRUG PROFILE

Nintedanib is an oral small molecule triple receptor tyrosine kinase inhibitor that potently blocks vascular endothelial growth factor receptor 1-3, fibroblast growth factor receptor 1 and 3, platelet derived growth factor receptor α/β, lymphocyte-specific tyrosine-protein kinase, tyrosine-protein kinase lyn, proto-oncogene tyrosine-protein kinase src, and colony stimulating factor 1 receptor. Nintedanib imparts its therapeutic effects through receptor

engagement and blockage of intracellular signal transmission, which reduces fibrogenesis in interstitial lung tissue of IPF and interstitial lung disease patients.

For a detailed description of the non-clinical pharmacology, pharmacokinetics (in animals) and toxicology of Nintedanib please refer to the current IB [c01783972] and to the Summary of Product Characteristics (SmPC) of Ofev® [R21-3511].

### 1.2.1 Human pharmacokinetic profile in healthy volunteers

Table 1.2.1: 1 shows human PK parameters and Tables 1.2.1: 2 and 1.2.1: 3 show drug exposure after single dose in healthy volunteers for Ofev® in fed state [R21-3511], [c01783972], [U06-1411] and Vargatef® [c08883821].

Table 1.2.1: 1 Human pharmacokinetic parameters for [redacted] mg Ofev® in healthy volunteers (SmPC and IB Ofev®)

| Parameter | Value |
|---|---|
| F [%] | 4.69 (+ 20% when fed) |
| $V_{ss}$ [L] | 1,050 |
| CL [mL/min] | 1,390 |
| $t_{max}$ [h] | 2.0 (fasted) - 4.0 (fed) |
| $t_{1/2,eff}$ [h] | 10 – 15 (> 90% recovery after 4 d) |

[redacted]

### 1.2.2 Clinical experience with Nintedanib in healthy volunteers

Nintedanib has been given as single doses of up to [redacted] mg (immediate release as marketed) to healthy volunteers in 9 Phase I trials. In addition to the studies listed in the IB for fibrotic lung diseases [c01783972], one clinical bioequivalence trial (1199-0237; [c08883821]) was performed with oncologic Vargatef® (Nintedanib). In that trial, 70 healthy male volunteers were administered 2 single doses of [redacted] mg Nintedanib in fed state. Over all 9 trials, Nintedanib was given to approximately 240 healthy volunteers (including also study 1199-0237 [c08883821]; excluding liver-impaired subjects in trial 1199-0200 [c03149997]). Single doses of Nintedanib were generally safe and well tolerated in healthy subjects. All

investigator-defined drug-related adverse events (AEs) after treatment with single doses of Nintedanib were mild or moderate and fully reversible. Headache and gastro-intestinal side effects (e.g. diarrhea, abdominal discomfort, nausea or vomiting) were the most common drug-related AEs.

Table 1.2.2: 1 Completed phase I trials with Nintedanib in healthy volunteers and subjects with investigator-reported drug-related AEs.

| Indication | Study No. / Doc No. | Doses of Nintedanib [mg] | Healthy subjects treated with Nintedanib [N] | Drug-related AEs[1] [number of subjects] |
|---|---|---|---|---|
| Food effect | 1199-0017 [c01787137] | [redacted] mg, 1 single dose, p.o. | 15 | Diarrhea (7), abdominal discomfort (3), nausea (1) |
| ADME | 1199-0020 [c01787114] | [redacted] mg, 1 single dose, p.o. | 8 | Nausea (1), asthenia (1) |
| Relative BA | 1199-0021 [c01798932] | [redacted] mg, 2 or 3 single doses, p.o. | 36 | Diarrhea (14), headache (8), nausea (2), vomiting (1), dizziness (1), fatigue (1), dry mouth (1) |
| Absolute BA | 1199-0075 [c01789568] | [redacted], [redacted], or [redacted] mg (i.v.), single dose; [redacted] mg (p.o.), single dose | 24 | Diarrhea (1) |
| DDI with ketoconazole | 1199-0161 [c02036462] | [redacted] mg, 2 single doses, p.o. | 31 | Headache (4), back pain (2), fatigue (1) |
| DDI with rifampin | 1199-0162 [c01801263] | [redacted] mg, 2 single doses, p.o. | 26 | Diarrhea (7), headache (2) |
| Liver impairment | 1199-0200 [c03149997] | [redacted] mg, 2 single doses, p.o. | 17[2] | Nausea (2), vomiting (1), headache (1) |
| BE[3] | 1199-0237 [c08883821] | [redacted] mg, 2 single doses, p.o. | 70 | Diarrhea (24), nausea (7), abdominal discomfort (3), abdominal pain upper (1), headache (9), dizziness (3), fatigue (1) |
| DDI with bosentan | 1199-0239 [c09412738] | [redacted] mg, 2 single doses, p.o. | 13 | Headache (2), diarrhea (1) |

[1] In treatment periods with Nintedanib; drug-relatedness assessed by the investigator

[2] Only healthy controls shown here.

[3] With oncologic IMP Vargatef® (Nintedanib); not included in fibrosis IB

### 1.2.3 Human pharmacokinetic profile in NSCLC patients

Tables 1.2.3: 1 and 1.2.3: 2 show human PK parameters and drug exposure after single dose of [redacted], [redacted] and [redacted] mg Nintedanib in NSCLC patients for the respective trials 1199.0001 [U05-2191] and 1199.0003 [U06-1697].

[redacted]

### 1.2.4 Clinical experience with Nintedanib in NSCLC patients

A wide range of Nintedanib monotherapy doses was investigated in phase I and II trials in NSCLC (non-small cell lung cancer) patients (clinical trials 1199.0001 [U05-2191], 1199.0002 [c01787114], and 1199.0003 [U06-1697]), from [redacted] to [redacted] mg *q.d.* and from [redacted] to [redacted] mg *b.i.d.*. [redacted]

In the clinical trial 1199.0001 [U05-2191], Nintedanib showed an acceptable safety profile at doses up to 250 mg/day as once daily and 500 mg/day as twice daily administration. All patients who had received at least 1 dose of Nintedanib were included into the safety analysis (n=61). The most frequent adverse events over all treatment courses were gastrointestinal disorders with nausea (80.3%), vomiting (60.7%), diarrhoea (55.7%), fatigue (47.5%), malignant neoplasm progression (44.3%), constipation (31.1%), abdominal pain (27.9%), nasopharyngitis (23.0%), anorexia (21.3%), dizziness (19.7%), cough (18.0%), pyrexia (18.0%), dyspnoea (16.4%), headache (16.4%), pleural effusion (14.8%), CD4 lymphocyte decreased (13.1%), cancer pain (13.1%), dyspepsia (13.1%), hyperhidrosis (13.1%), pruritus (13.1%) and ascites (11.5%). The most frequently reported drug–related adverse events were nausea (68.9%), vomiting (45.9%), diarrhoea (44.3%), fatigue (19.7%), CD4 lymphocytes decreased (9.8%), increased hepatic enzymes (9.8%), dizziness (9.8%), pruritus (8.2%), abdominal pain (6.6%), anorexia (6.6%), dyspepsia (6.6%), headache (6.6%), hypertension (4.9%) and constipation (3.3%). The frequencies of these adverse events and laboratory abnormalities were dose-dependent and increased strongly in doses above the MTD. The vast majority of these adverse events and substantial changes in laboratory parameters were already observed during the first 28-day treatment course with Nintedanib, suggesting that the safety profile does not deteriorate with prolonged application of Nintedanib [U05-2191].

In the clinical trial 1199.0003 [U06-1697], 40 patients were treated at doses of 100 mg (n=6), 200 mg (n=6), 300 mg (n=7), 400 mg (n=16) and 450 mg (n=5) given once a day. To confirm the MTD of twice daily dosing (observed in 1199.0001 [U05-2191]), a further 11 patients were treated at a dose of 250 mg *b.i.d.* following a protocol amendment. Nine patients developed dose limiting toxicity (DLT). The most common DLT was an elevation in liver function tests (8/9 patients). In the 450 mg/day cohort 2/5 patients experienced DLT; hence the MTD of Nintedanib was determined to be 400 mg given once a day. The rate of DLTs decreased by splitting the daily dose of the drug. In the 250mg *b.i.d.* cohort 2/11 patients developed DLTs, reaffirming this dose as the MTD for twice daily dosing. The incidence and severity of Adverse Events appeared to be dose dependent. Most of the reported Adverse Events were of CTC grade 1 or 2. Gastrointestinal disorders (diarrhoea, nausea and vomiting) in 49.3% of patients and increases in liver enzymes in 53.0% of patients were the most frequently reported Adverse Events associated with Nintedanib treatment. The number of reported drug related haemorrhagic events and hypertension was very low (2 and 1 respectively). No treatment-related deaths were reported. Results of the 1199.0003 study indicate that the MTD for Nintedanib is 400 mg *q.d.* or 250 mg *b.i.d.*. At doses ranging from 100 mg to 400 mg *q.d.* or 250 mg *b.i.d.* the drug is generally well tolerated. The dose limiting toxicity in the vast majority of patients is elevation in serum liver enzymes. [U06-1697].

### 1.2.5 Residual Effect Period

The Residual Effect Period (REP) is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

For this trial using 1 day treatment of [redacted] to (potentially) [redacted] mg Nintedanib in healthy male volunteers, a REP of 14 days is used, i.e. the individual subject's end of trial is on day 15 following dosing at the earliest and the washout between periods is at least 2 weeks (see Flow Chart).

## 1.3 RATIONALE FOR PERFORMING THE TRIAL

Ofev® soft capsules dissolve instantly within the gut environment and thus show an IR profile. However, the rapid increase of local drug exposure is associated with increased gut wall toxicity and gastro-intestinal adverse drug reactions such as diarrhoea. In contrast, a constant drug release over a longer period of time is hypothesized to improve gastro-intestinal tolerability. Alteration in the shell's composition may lead to such release profiles of Nintedanib and improve tolerability. Hence, several different tablets are to be manufactured to accomplish a MR of Nintedanib over 24 hours and match the equivalent drug exposures to that of the standard Ofev® treatment. Equivalent drug exposure can be presumed, if the MR formulation is within the same exposure corridor as Ofev®, i.e. equal total drug exposure ($AUC_{0\text{-}24,ss}$), non-inferior minimum drug concentration ($C_{min,ss}$) and non-superior ($C_{max,ss}$) peak drug concentration at steady state. Consequently, sufficient efficacy for the MR formulation can be assumed without explicit testing. Since only single dose administration is planned for the MR formulations, the concentration after 24 hours post dose will be measured ($C_{24}$), while $C_{min,ss}$ as well as $C_{max,ss}$ for steady state may be simulated in a respective model at the end of trial (e.g. after database lock).

## 1.4 BENEFIT – RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to improve overall tolerability and treatment success of patients with IPF and ILD. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

The total volume of blood withdrawn per subject during the entire study will not exceed a volume of 550 mL in a 4-week period. No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

Electrocardiogram (ECG) stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

Drug-related risks and safety measures

Nintedanib, as tyrosine kinase inhibitor with an anti-angiogenic mechanism of action, has been administered only short term to healthy volunteers. Nintedanib has been given in single doses to 240 healthy volunteers (see Section 1.2.2) and has been generally safe and well tolerated. The most common drug-related adverse events were gastrointestinal effects (mainly diarrhoea, nausea and vomiting) and headache. All drug-related adverse events were mild or moderate and fully reversible. The highest dose given so far to healthy volunteers was [redacted] mg (after at least 10 h overnight fasting followed by standardised continental breakfast 30 min. before drug administration); this was given (two single doses of [redacted] mg each separated by a wash-out phase) to 70 healthy male volunteers in trial 1199-0237 [c08883821]. Results of the trials 1199.0001 and 1199.0003 in cancer patients indicate a maximum tolerated dose (MTD) for Nintedanib IR of [redacted] mg *q.d.* or [redacted] mg *b.i.d.* Nintedanib IR was generally well tolerated within a dose range of [redacted] mg to [redacted] mg *q.d.* or [redacted] mg *b.i.d.,* while dose limiting toxicity in most patients was elevation in serum liver enzymes [U06-1697]; [U05-2191].

Adverse events as described above can be handled under conditions of a clinical trial. The starting dose of Nintedanib MR is within a supposably safe and well tolerable dose level, based on experience with healthy volunteers as well as patients. Further dose escalation is not expected to ultimately exceed exposure of tested [redacted] mg Nintedanib IR *q.d.* and will only be conducted if previous dose level is considered safe (e.g. by clinical and laboratory assessment) (also see Section 3.1 and 4.1.2). Therefore, no undue risk is expected from trial participation to healthy volunteers with short term administration of Nintedanib.

Intake with food is known to improve tolerability of Nintedanib in patients [U06-1411]. Therefore, in this study Nintedanib will be administered after a standardized continental breakfast and dinner (for reference treatment only). Subjects must consume 100% of the pre-dose breakfast in order to eligible for dosing. The start and stop time and percentage of the breakfast consumed must be recorded in the source.

Subject selection criteria and pre-dose measurements are suitable to select the appropriate healthy population for this trial. Post-dose safety laboratory includes parameters to assess potential side effects reported after multiple-dose treatment in patient populations.

As Ofev®, a marketed product which contains Nintedanib, has no requirement for precautions with regard to exposure to ultraviolet light, precautions with regard to exposure to ultraviolet light are not considered necessary for subjects enrolled in this study.

Drug-induced liver injury surveillance

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.4, adverse events of special interest.

COVID-19 pandemic

Based on the pharmacological mechanism and existing non-clinical, clinical and post-marketing data there is no indication that treatment with Nintedanib may increase the risk of infection with or progression of SARS-CoV-2 infection. Participation in this trial may increase the risk of COVID-19 exposure due to travels to the study site and completion of protocol-defined procedures at the site. A risk management plan has been set up at the clinical site that details precautionary measures (e.g., hygiene rules, wearing of face masks, physical distancing) and screening for SARS-CoV-2 infection.

General risk mitigation against COVID-19 will be implemented in accordance with [redacted] monitoring and prevention control measures.

COVID-19 testing may be performed based on current infection rates and availability of tests. If required, testing will comprise an antibody blood test performed at screening, and an antigen polymerase chain reaction (PCR) test or other antigen test performed at screening, the day before admission to each treatment period, and discharge or the day before discharge from each treatment period. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points will be agreed by the study team and documented in the Investigator Site File (ISF) via the Clinical Kick-Off Meeting minutes. The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

COVID-19 Vaccine-Related Risk

Approved (including health authority conditional marketing optimization) COVID-19 vaccines eg killed, inactivated, peptide DNA and RNA vaccines may be permitted according to the investigator's discretion and as per local guidance. Based on the mechanism of action of Nintedanib, as a tyrosine kinase inhibitor, there is no perceived impact on the safety of the study subjects or on the study objectives for subjects who may receive these vaccines (either first or second doses). It is also very unlikely that administration of Nintedanib would interfere with COVID-19 vaccination response; however, no specific preclinical or clinical investigations have been conducted at this point with Nintedanib.

The emerging safety and efficacy data from millions of vaccinated people, many of whom are elderly and with underlying health conditions and taking multiple concomitant medications, indicate that these vaccines have an excellent safety and efficacy record. In the broader interests of society and to limit the extent of the global pandemic, it is important that subjects should receive a vaccine when it is offered to them.

Summary of benefit-risk assessment

Taking into account the safety profile of Nintedanib, the safety measures in this trial, and the need for effective treatment of fibrosing interstitial lung diseases, the expected benefit of this trial outweighs the potential risks and justifies exposure of healthy human subjects.

# 2. TRIAL OBJECTIVES AND ENDPOINTS

## 2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

### 2.1.1 Main objectives

The main objective of this trial is to assess single dose drug exposure of several newly developed MR formulations of Nintedanib (MR1 and MR2 prototypes) compared to [redacted] mg of Ofev® IR, twice daily (Reference, R) following oral administration.

In trial part 1, four MR prototypes of Nintedanib (prototypes 1 and 2, each with a fast and slow in-vitro dissolution rate) will be tested. Based on pharmacokinetic results, one MR formulation may be selected for subsequent optimisation in dissolution and dose rate to ultimately match exposure corridor of Ofev® IR. The optimised MR formulation will then be evaluated in optional trial part 2. If the pre-selected MR formulation is still not matching the Ofev® IR exposure corridor, an optional trial part 3 is conducted after further optimisation of dissolution profile and dose.
Plasma drug exposure and PK parameters will be assessed after each trial part and MR formulations adjusted accordingly (e.g. coating compositions, drug dose) for the following trial part.

### 2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for Nintedanib:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 [first dose] extrapolated to infinity which includes also the second Nintedanib dose of the day)

### 2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for Nintedanib:

- $AUC_{0-tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- $C_{max}$ (maximum measured concentration of the analyte in plasma within the 24h dosing interval)
- $C_{24}$ (concentration of the analyte in plasma 24 h after the (first) dose)

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of Nintedanib will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed in healthy male subjects as an open-label, randomised, single-dose study in up to three trial parts in order to compare each of the test treatments (MR1, MR2, MRX) to the respective reference treatment R. The subjects will be randomly allocated to three treatment sequences in trial part 1 and 2 (Latin square design). There will be a washout period of at least 14 days between the treatments, i.e. the morning dose in the preceding treatment period and the morning dose in the following treatment period are separated by at least 14 days.
For illustration of the overall study design, refer to Figure 3.1: 1. An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

Trial part 1

Trial part 1 (n=30) will be performed with two parallel groups (cohort 1 and 2, each n=15), each in a randomised three-period crossover design in order to compare MR1 test treatments to the reference treatment R (for trial part 1A) as well as MR2 test.

These treatments will be administered after light fed conditions (light breakfast, additionally light dinner in Reference) and in one of the following three sequences for each group:

For Trial part 1A:

R → MR1-1 → MR1-2
MR1-2 → R → MR1-1
MR1-1 → MR1-2 → R

For Trial part 1B:

R → MR2-1 → MR2-2
MR2-2 → R → MR2-1
MR2-1 → MR-2 → R

A single dose (test treatments) and a *b.i.d.* dose for one day (reference treatments), respectively will be administered as depicted in Figure 3.1: 1 above and Table 4.1.4: 1.

*Decision point:* either (a) stop here or (b) proceed to trial part 2 with one selected formulation MR1 or MR2 and release profile in order to optimise dose.
In-study decisions will be made by the safety advisory committee (SAC), which will always comprise the investigator, the sponsor's representative medical monitor or the sponsor's medically qualified designee who is familiar with the study protocol and IB, and a PK expert where appropriate. Formulation and dose selection will only be made after a complete review of all data collected from the previous dose group.

The following in-study decisions will be made:

- Formulation selection
- Dose selection (please see Section 4.1.2)

*Decision rules:* The decision will be based on data of all evaluable subjects (see Section 7.3 PKS definition) in each of trial parts 1A as well as 1B and will include the assessment of (i) safety parameters (e.g., AE, ECG, vital signs and safety laboratory data) up to 72 h post-dose, (ii) preliminary pharmacokinetic analysis up to 72 h post-dose.
Criteria to stop particular MR formulation after trial part 1 will be in case one of the below points holds true:

- MR formulation is considered not to be safe (see Section 3.3.4.3 for stopping criteria)
- the 90% confidence interval (CI) of the $AUC_{0-\infty}$ gMean ratio between a MR formulation and Ofev® IR lies completely outside of 95-105% and further optimisation of the formulation with regards to dose and dissolution rate is not expected to improve pharmacokinetic properties, accordingly
- the lower 90% CI of the $C_{max}$ gMean ratio between a MR formulation and Ofev® IR is >105% and further optimisation of the formulation with regards to dose and dissolution rate is not expected to improve pharmacokinetic properties, accordingly
- the upper 90% CI of the $C_{24}$ gMean ratio between a MR formulation and Ofev® IR is <95% and further optimisation of the formulation with regards to dose and dissolution rate is not expected to improve pharmacokinetic properties, accordingly

In case no MR formulation fulfils the criteria above the following rule will help in deciding which MR formulation to develop further:

- for $AUC_{0-\infty}$, $C_{max}$ and $C_{24}$ the adjusted gMean ratios for each MR formulation as well as the gSE of the difference will be calculated coming from the defined ANOVA model in Section 7.3.1.
- for an adjusted gMean ratio >1 the decision value (DV) is defined by gMean ratio*gSE

- for an adjusted gMean ratio ≤1 the decision value (DV) is defined by gMean ratio/gSE
- the MR formulation with DV values for $AUC_{0-\infty}$, $C_{max}$ and $C_{24}$ closest to 1 will be chosen for further development

*Decision outcome:* If optimisation is considered possible for at least one of the two MR formulations, further optimisation will be done on the selected formulation(s) and tested in trial part 2.

Trial part 2 (optional)

Trial part 2 (cohort 3, n=15) will be performed as a randomised three-period crossover design in order to compare further prototypes to the reference treatment R.

These treatments will be administered after light fed conditions (light breakfast, additionally light dinner in Reference) and in one of the following three sequences:

R → MRX-3 → MRX-4

MRX-4 → R → MRX-3

MRX-3 → MRX-4 → R

A single dose (test treatments) and a *b.i.d.* dose for one day (reference treatment), respectively will be administered as depicted in Figure 3.1: 1 above and Table 4.1.4: 1.

*Decision point*: either (a) stop here or (b) proceed to trial part 3 with the optimised formulation in order to optimise release rate and dose.
In-study decisions will be made by the SAC.
*Decision rules:* The decision will be based on data of all evaluable subjects and will include the assessment of (i) safety parameters (e.g. AE, ECG, vital signs and safety laboratory data) up to 72 h post-dose, (ii) preliminary pharmacokinetic analysis up to 72 h post-dose.

Criteria to stop or to continue particular MR formulation after trial part 2 will be the same as for Part 1 (see above).

*Decision outcome:* If further optimisation is considered necessary and possible for the selected MR formulation(s) tested in part 2, another prototype will be developed and further tested in trial part 3.

Trial part 3 (optional)

Trial part 3 (cohort 4, n=14) will be performed as a randomised two-period crossover design in order to compare test treatment to the reference treatment R.

These treatments will be administered after light fed conditions (light breakfast, additionally light dinner in Reference) and in one of the following two sequences:

R → MRX-5

MRX-5 → R

A single dose (test treatment) and a *b.i.d.* dose for one day (reference treatment), respectively will be administered as depicted in Figure 3.1: 1 and Table 4.1.4: 1.

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

### 3.2.1 Discussion of study design

The Clinical Trial Authorisation (CTA) application for this study describes a flexible protocol design using the concept of formulation design space to allow decision-making in response to interim pharmacokinetic (PK) observations. The principles of a flexible protocol were discussed and agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) at a Scientific Advice Meeting between the MHRA and [redacted] formerly Pharmaceutical Profiles).

Based upon the concept of formulation design space/a bracketed dose approach, specific IMPs are not detailed within the Investigational Medicinal Product Dossier (IMPD) but rather a defined dose range of formulation inputs and corresponding performance outputs are described and justified based on in vitro studies. The chosen formulation from within the approved design space for the first prototype to be dosed will be documented in a decision document and approved by the sponsor and a [redacted] representative ahead of manufacture.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte.

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations [R94-1529].

### 3.2.2 Rationale for decision rules

The rationale for performing this trial is to identify an MR formulation that still results in Nintedanib exposure within the corridor of standard Ofev® IR treatment.

Rules, described in Section 3.1, allow to make a decision whether one of the tested formulations meets the requirements after trial part 1, or whether it can be improved within this trial in part 2 and/ or part 3. Rules would also guide the termination of the process, either after trial part 1 or trial part 2, if no successful formulation was to be achieved.

## 3.3 SELECTION OF TRIAL POPULATION

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not. It is planned that 30 or 59 (optional) healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

[redacted] must have a full medical history from each subject's general practitioner (GP) within the last 24 months, prior to enrolment in the study. Before subjects are admitted to the clinical unit, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a study at another site within at least 90 days of the dosing date.
As this is a Phase I study assessing the PK, relative bioavailability and safety of Nintedanib, the most relevant population is healthy volunteers. Subjects who are non-smokers without a history of alcohol or drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and to avoid non-compliance.

Considering the teratogenic potential of Nintedanib, only male subjects will be included. (refer also to [R21-3511]).

### 3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

### 3.3.2 Inclusion criteria

Subjects will only be included in the trial if they meet the following criteria:

1. Healthy male subjects (Caucasian and Black only) according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG and clinical laboratory tests

2. Age of 18 to 55 years (inclusive)

3. BMI of 18.5 to 29.9 kg/m$^2$ (inclusive) and absolute body weight of at least 65 kg

4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation

5. Non-smokers for at least 6 months

6. Subjects who are sexually active must use with their partner, highly effective contraception from the time of administration of trial medication until 30 days after administration of trial medication. Adequate methods are:

    - Condoms plus use of hormonal contraception by the female partner that started at least 2 months prior to administration of trial medication (e.g., implants, injectables, combined oral or vaginal contraceptives, intrauterine device) or

    - Condoms plus surgical sterilization (vasectomy at least 1 year prior to enrolment) or

    - Condoms plus surgically sterilised partner (including hysterectomy) or

    - Condoms plus intrauterine device or

    - Condoms plus partner of non-childbearing potential (including homosexual men)

Subjects are required to use condoms to prevent unintended exposure of the partner (both, male and female) to the study drug via seminal fluid. Male subjects should use a condom throughout the study and for 30 days after last IMP administration. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active with their partner, they must comply with the contraceptive requirements detailed above.

Male subjects should not donate sperm for the duration of the study and for at least 30 days after last IMP administration.

Male subjects with pregnant or lactating partners are allowed.

### 3.3.3 Exclusion criteria

Subjects will not be allowed to participate, if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator

2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm

3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance

4. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) antibody results

5. Liver enzymes (AST and ALT) above upper limit of normal at the screening examination

6. Any evidence of a concomitant disease assessed as clinically relevant by the investigator

7. Clinically significant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, dermatological or hormonal disorders. Subjects with Gilbert's syndrome are not permitted.

8. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)

9. Significant diseases of the central nervous system (including but not limited to any kind of seizures [febrile seizures are acceptable] or stroke), and other relevant neurological or psychiatric disorders

10. History of relevant orthostatic hypotension, fainting spells, or blackouts

11. Relevant chronic or relevant acute infections

12. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)

13. Use of drugs (excluding Covid-19 vaccination, within 7 days) within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation). Ibuprofen up to 1200 mg per day is allowed.

14. Intake of an investigational drug in another clinical trial within 90 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered

15. Alcohol abuse (consumption of more than 21 units per week)

16. Drug abuse or positive drug screening

17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

18. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening

19. Intention to perform unaccustomed excessive physical activities within one week prior to the administration of trial medication or during the trial

20. Inability to comply with the dietary regimen of the trial site

21. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

22. Increased bleeding risk, including known genetic predisposition to bleeding, use of medication that could relevantly increase bleeding risk (e.g. low-molecular weight heparin; recent use of non-steroidal anti-inflammatory drugs is allowed), history of haemorrhagic central nervous system event within 12 months of planned first study medication, or any of the following within 3 months of planned first study medication: Haemoptysis or macrohaematuria, active gastro-intestinal bleeding or gastro-intestinal ulcers, or major injury or surgery (investigator judgement)

23. During Covid-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection

24. Subjects who have previously been administered IMP in this study. Subjects who have taken part in one trial part are not permitted to attend to any following trial part.

### 3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

#### 3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

- The subject wants to discontinue trial treatment, without the need to justify the decision
- The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The subject has a concurrent illness [redacted] or needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
- The subject experiences a serious or severe AE including but not limited to:
    - an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
    - corrected QT interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation, please see Section 3.3.4.1 above

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall

2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated or halted if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported, or if severe non-serious adverse reactions (i.e. severe non-serious AE considered as at least possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system organ class. Relatedness to IMP will be determined by the investigator.

3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial

4. The sponsor decides to discontinue the further development of the investigational product

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

### 3.3.5 Replacement of subjects

In case more than 3 subjects in one of the parallel groups of trial part 1 or in trial parts 2 and 3 do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be

replaced. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment as the subject he replaces.

It is planned to have at least 12 evaluable subjects per crossover part. Up to 3 replacement subjects may be used per cohort. The maximum number of subjects that may be dosed is 18, the cohort size of 15 plus 3 replacements.

# 4. TREATMENTS

## 4.1 INVESTIGATIONAL TREATMENTS

The investigational products are manufactured by two different manufacturers:

- Ofev® IR: BI Pharma GmbH & Co. KG., Ingelheim, Germany.
- MR tablets: [redacted]

### 4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

| | |
|---|---|
| **Name:** | [redacted] |
| Substance: | Nintedanib |
| Pharmaceutical formulation: | Tablet |
| Source: | [redacted] |
| Unit strength: | |
| Posology: | 1-0-0 |
| Route of administration: | oral |
| Duration of use: | One day (single dose) in trial part 1A (MR1-1, MR1-2), part 2 (optional, MRX-3, MRX-4) and part 3 (optional, MRX-5) |

| | |
|---|---|
| **Name:** | [redacted] |
| Substance: | Nintedanib |
| Pharmaceutical formulation: | Tablet |
| Source: | [redacted] |
| Unit strength: | |
| Posology: | 1-0-0 |
| Route of administration: | oral |
| Duration of use: | One day (single dose) in trial part 1B (MR2-1, MR2-2), part 2 (optional, MRX-3, MRX-4) and part 3 (optional, MRX-5) |

The characteristics of the reference product are given below:

| | |
|---|---|
| **Name:** | **Ofev® 150 mg soft capsules** |
| Substance: | Nintedanib |
| Pharmaceutical formulation: | Capsule |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 150 mg |
| Posology: | 1-0-1 |
| Route of administration: | oral |
| Duration of use: | One day (*b.i.d.*) in all trial parts |

### 4.1.2 Selection of doses in the trial and dose modifications

The doses selected for the MR tablets are expected to result ultimately in clinically relevant Nintedanib exposures comparable to twice daily intake of the marketed [redacted] mg Ofev® IR. Dose modification within a defined range would become necessary, if the absorption from MR formulation differs notably from that of Ofev® IR (see Section 1.2.2).

The proposed starting dose of Nintedanib for the MR tablet formulation is [redacted] mg, since [redacted] mg Nintedanib IR *q.d.* (Ofev®) was already tested in healthy volunteers [c08883821] while up to [redacted] mg Nintedanib IR *q.d.* was tested in patients. The MTD for patients was determined at [redacted] mg *q.d.* and [redacted] mg *b.i.d.* [U13-1506], so the suggested maximum dose of [redacted] mg for trial part 2 or 3 will not exceed the MTD nor the highest tested dose in patients beforehand. Additionally, any dose escalation and adjustment of release profile is depending on tolerability, safety, and clinical PK profile of the previous trial part (see Section 3.1). The administered dose may be modified within a dose range of [redacted] to [redacted] mg, based on emerging safety and clinical PK data.

If individual $C_{max}$ and AUC levels of any tested dose levels reach safe and well-tolerated exposures seen from [redacted] mg Nintedanib IR *q.d.* in patients fed state ($C_{max}$ 80.9 ng/mL + 75.5% gCV (=141.98 ng/mL), $AUC_{0-\infty}$ 601 ng*h/mL +73.6% gCV (=1043.34 ng*h/mL) [U06-1697]), no further dose escalation will be performed.

Administration in the fed state is considered better tolerable than fasted in patients [U06-1697]. Food effect studies showed no clinically relevant impact on drug exposure in fed vs. fasted state (1199-0017 [c01787137]).

### 4.1.3 Method of assigning subjects to treatment groups

The randomisation list will be provided to the trial site in advance.

According to the planned sample size of trial part 1 (n=30), two groups of 15 subjects each are planned. Each subject participating in either parts 1A or 1B will be allocated to one of three treatment sequences. For details, refer to Section 3.1 and 7.6.

According to the planned sample size of trial part 2 (n=15), each subject will be allocated to one of three treatment sequence. For details, refer to Section 3.1 and 7.6.

According to the planned sample size of trial part 3 (n=14), each subject will be allocated to one of two treatment sequence. For details, refer to Section 3.1 and 7.6.

Prior to the start of the study, subjects willing to participate will be recruited to trial parts (1A, 1B, 2, 3) according to their temporal availability. In the morning of Day 1 (Visit 2 for all trial parts), subjects will be allocated to treatment sequences prior to the first administration of trial medication. For this purpose, numbers of the randomisation list will be allocated to the subjects sequentially just prior to first dosing by using the method 'first come, first served'. Subjects are then assigned to a treatment sequence according to the randomisation list. Hence, no bias is introduced when providing the randomization list in advance to the site.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

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

This trial is an open-label, randomised, single-dose study in three parts.

All 30 subjects of trial part 1 will receive three treatments in randomised order as a three-period crossover design.

All 15 subjects of trial part 2 will receive three treatments in randomised order as three-period crossover design.

All 14 subjects of trial part 3 will receive two treatments in a randomised order as two-period crossover design.

Trial part 1

Trial part 1 consists of two parallel groups each with a three-way crossover study. All subjects of each group will receive the three treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1.

Table 4.1.4: 1 Dosage and treatment schedule for trial part 1

| Trial Part | Treatment | Substance | Formulation | Unit strength | Dosage | Total dose |
|---|---|---|---|---|---|---|
| [redacted] | | | | | | |

Trial part 2 (optional)

Trial part 2 consists of a three-way crossover study. All subjects will receive the three treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 2.

Table 4.1.4: 2 Dosage and treatment schedule for trial part 2

| Trial Part | Treatment | Substance | Formulation | Unit strength | Dosage | Total dose |
|---|---|---|---|---|---|---|
| [redacted] | | | | | | |

Trial part 3 (optional)

Trial part 3 consists of a two-way crossover study. All subjects will receive the two treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 3.

Table 4.1.4: 3 Dosage and treatment schedule for trial part 3

| Trial Part | Treatment | Substance | Formulation | Unit strength | Dosage | Total dose |
|---|---|---|---|---|---|---|
| [redacted] | | | | | | |

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication.

A standardised light-fat, light-calorie meal (e.g., Corn Flakes 50 g, 1 Butter Croissant, Jam 20 g and 240 ml skimmed milk, also see Section 10 Appendices) will be served 30 min before each Nintedanib administration in the morning. The standardized breakfast meals must be completely consumed prior to drug administration. In the evening,

For restrictions with regard to diet, see Section 4.2.2.2.

Subjects will be kept under close medical surveillance until at least 72 h after morning drug administration. During the first 2 h after each drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The treatments will be separated by a wash-out phase of at least 14 days.

### 4.1.5 Blinding and procedures for unblinding

This Phase I trial will be handled in an open fashion throughout. This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations. Emergency envelopes will not be provided, because the medication and its dose is known to investigators and subjects.

The table below summarizes the blinding level of individual functions involved in the trial.

Table 4.1.5: 1 Blinding level of individual functions

| Role/function | Timing of unblinding / receiving access to the treatment information |
|---|---|
| Trial subject | After treatment allocation has been completed. |
| Investigator/Site staff | As requested to prepare study site prior to first subject entered. |
| Unblinded pharmacy staff members | Prior to first subject entered |
| Sponsor trial team and database | As requested during trial conduct for subjects, who are already randomised. |
| Bioanalytical staff | Persons directly involved in bioanalyses of PK samples cannot be blinded to trial treatments since test and reference have different sampling schedules. |

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

The reference medicinal products (Ofev®) will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice and shipped to [redacted].

The investigational medicinal products will be provided by [redacted]. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice and used at trial site [redacted]. All development of tablet composition takes place at [redacted].

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

The telephone number of the of the trial site is provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

### 4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be contacted immediately.

### 4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor following requirements are fulfilled:

- Approval of the clinical trial protocol by the ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and 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

Only authorised personnel documented in the form 'delegation log' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the 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 medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the

investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the trial clinical monitor. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

## 4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

### 4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

Drugs with a known hepatotoxicity profile (e.g., paracetamol or diclofenac) or medication with an increased risk for bleeding (e.g. acetylsalicylic acid) should be avoided during the entire study; if necessary, short term use of ibuprofen is acceptable.

Known inhibitors or inducers of P-gp and CYP3A activity should be avoided during the entire study due to drug-drug interaction potential with Nintedanib. Drugs that cause QT/QTc interval prolongation should also be avoided.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake in the morning.

From 1 h before drug intake in the morning until lunch, fluid intake is restricted one cup of water without sugar served with breakfast (see Section 4.1.4), the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Poppy-seeds containing foods should not be consumed starting 3 days before screening and admission to each treatment period to avoid false-positive results in the drug screen.

Alcoholic beverages are not permitted from 3 days before first drug administration until the end of trial examination.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of the study is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during inhouse stays.

Smoking is not allowed during in-house confinement.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before the first administration of trial medication until the end of trial examination.

## 4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

# 5. ASSESSMENTS

## 5.1 ASSESSMENT OF EFFICACY

Not applicable.

## 5.2 ASSESSMENTS OF SAFETY

### 5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests (including drug screening), and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of weight.

### 5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g., DASH 4000) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible. If required, vital signs assessment can be repeated.

In addition, oral body temperature may be measured at any time at the discretion of the investigator. These measurements will not be recorded in the eCRF.

### 5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

| Functional lab group | BI test name [comment/abbreviation] | A | B |
|---|---|---|---|
| Haematology | Haematocrit | X | X |
| | Haemoglobin | X | X |
| | Red Blood Cell Count/Erythrocytes | X | X |
| | White Blood Cells/Leucocytes | X | X |
| | Platelet Count/Thrombocytes (quant) | X | X |
| Automatic WBC differential, relative | Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes | -- | -- |
| Automatic WBC differential, absolute | Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol. | X | X |
| Manual differential WBC (only if automatic differential WBC is abnormal) | Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol. | X | X |
| Coagulation | Activated Partial Thromboplastin Time | X | X |
| | Prothrombin time | X | X |
| | INR (International Normalization Ratio) | X | X |
| Enzymes | AST [Aspartate transaminase] /GOT, SGOT | X | X |
| | ALT [Alanine transaminase] /GPT, SGPT | X | X |
| | Alkaline Phosphatase | X | X |
| | Gamma-Glutamyl Transferase | X | X |
| | Creatine Kinase [CK] | X | X |
| | Creatine Kinase Isoenzyme MB [only if CK is elevated] | X | X |
| Hormones | Thyroid Stimulating Hormone | X | -- |
| Substrates | Glucose (Plasma) | X | -- |
| | Creatinine | X | X |
| | Bilirubin, Total | X | X |
| | Bilirubin, Direct | X | X |
| | Protein, Total | X | X |
| | C-Reactive Protein (Quant) | X | X |
| Electrolytes | Sodium | X | X |
| | Potassium | X | X |
| | Chloride | X | X |
| Urinalysis (Stix) | Urine Nitrite (qual) | X | X |
| | Urine Protein (qual) | X | X |
| | Urine Glucose (qual) | X | X |
| | Urine Ketone (qual) | X | X |
| | Urobilinogen (qual) | X | X |
| | Urine Bilirubin (qual) | X | X |
| | Urine RBC/Erythrocytes (qual) | X | X |
| | Urine WBC/Leucocytes (qual) | X | X |
| | Urine pH | X | X |
| Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine) | Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes) | | |

A: parameters to be determined at Visit 1 (screening examination) and Visit 5 (EOT examination)
B: parameters to be determined at Visit 2, 3 and 4 (for time points refer to Flow Chart)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

| Functional lab group | Test name |
|---|---|
| Drug screening (urine) | Amphetamine/MDA<br>Barbiturates<br>Benzodiazepine<br>Cannabis<br>Cocaine<br>Methadone<br>Methamphetamines/MDMA/XTC<br>Opiates<br>Phencyclidine<br>Tricyclic antidepressants |
| Infectious serology (blood) | Hepatitis B surface antigen (qualitative)<br>Hepatitis B core antibody (qualitative)<br>Hepatitis C antibodies (qualitative)<br>HIV-1 and HIV-2 antibody (qualitative) |

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g., Lion Alcolmeter 500) will be performed prior to each treatment period and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of drug screening tests. These tests will be performed at the trial site using an Alere Drug Screen Test Cup, respectively, or comparable test systems. Urinalysis assessments also will be performed at the trial site using, e.g., Combi-Screen® Urine Test Strips. If urine microscopy is required, a sample will be shipped to [redacted]" for analysis.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

### 5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g., Mortara ELI 250c) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. All ECGs will be stored as paper copies.

### 5.2.5 Other safety parameters

Not applicable.

### 5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 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.

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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 defined above.

These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that 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.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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 reduced)

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 trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

Upon enrolment into a trial (written informed consent), the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious)
    - The only exception to this rule are AEs (serious and non-serious) in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for AEs but should only report any occurrence of cancer and related SAEs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

## 5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

### 5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

### 5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of Nintedanib concentrations in plasma, approximately 2.7 mL of blood will be drawn from an antecubital or forearm vein into an $K_2$-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle. The first 0.5 mL withdrawn by an indwelling cannula will be discarded.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 *g* to 4000 *g* and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min with interim storage of blood samples and aliquots in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At

the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

### 5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

## 5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

## 5.5 BIOBANKING

Not applicable.

## 5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, the end of trial examination, and measurements and assessments scheduled to occur 'before' trial medication administration in the morning of Day 1 are provided in the Flow Chart.

If not stated otherwise in the Flow Chart, the general acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.

The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- The pre-dose urine sample will be the first void of the day or a sample collected ≤3 h before dosing
- Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned blood sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

### 6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (part 1, optional part 2) or in 2 treatment periods (optional part 3) (Days -1, 1, 2, 3, and 4 in each period). At least 14 days will separate drug administrations in each treatment periods.

In the evening before drug administration, study participants will be admitted to the trial site and kept under close medical surveillance for at least 72 h following drug administration in the morning of Day 1. The subjects will then be allowed to leave the trial site after formal

assessment and confirmation of their fitness. No ambulatory appointments are planned during treatment periods.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

### 6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.6.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoT Visit.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoT Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

For definition of 'end of the trial' refer to Section 8.6.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the relative bioavailability of several MR formulations of Nintedanib (Test, T) compared to [redacted] mg of Ofev® IR, twice daily (Reference, R) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of each of the MR formulations compared with [redacted] mg of Ofev® IR will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

## 7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses for each crossover part will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomised and treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the DV domain sheet, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- The subject experiences emesis at any time during the labelled dosing interval.
- A predose concentration is >5% $C_{max}$ value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

### 7.3.1 Primary endpoint analyses

Each of the crossover parts will be analysed separately according to bellows description.

Primary analyses

The statistical model used for the analysis of the primary endpoint will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, where

$y_{ijkm}$ = logarithm of response measured on subject m in sequence i receiving treatment k in period j,

$\mu$ = the overall mean,

$\zeta_i$ = the $i^{th}$ sequence effect, i = 1, 2,(3),

$s_{im}$ = the effect associated with the $m^{th}$ subject in the $i^{th}$ sequence, m = 1, 2, ..., $n_i$

$\pi_j$ = the $j^{th}$ period effect, j = 1, 2, (3),

$\tau_k$ = the $k^{th}$ treatment effect, k = 1, 2, (3),

$e_{ijkm}$ = the random error associated with the $m^{th}$ subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and $s_{im}$, $e_{ijkm}$ are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoint (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoint but with all sources of variation ('sequence', 'subjects within sequences', 'period', 'treatment') considered as fixed effects.

In addition to the model based approach all parameters will be calculated and analysed descriptively.

### 7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the relevant internal BI procedures and will be assessed statistically using the same methods as described for the primary endpoint.

### 7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Blinded Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and follow-up intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

## 7.4 INTERIM ANALYSES

Prior to start of a next study part (Part II or III) a preliminary analysis on PK parameters ($AUC_{0-\infty}$, $C_{24}$ and $C_{max}$) will be performed as described in Section 3.1.

The pharmacokinetic parameters $AUC_{0-\infty}$, $C_{max}$ and $C_{24}$ for Nintedanib will be calculated according to relevant internal procedures. The non-compartmental analysis will be performed using a validated software program such as Phoenix WinNonlinTM software (version 6.3 or higher, [redacted] or SAS® Version 9.4 (or later version). A quality check of the preliminary data will be performed.

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results.

The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values. The preliminary results will be distributed to the investigator and the trial team.

Depending on the results of available preliminary PK analyses and the tolerability and safety of the compound, changes to the formulation and additional PK preliminary analysis may be performed if requested by the Clinical Trial Leader, the investigator, Trial Statistician or Trial Clinical Pharmacokineticist. Preliminary PK results will not be reported in the CTR.

## 7.5 HANDLING OF MISSING DATA

### 7.5.1 Safety

It is not planned to impute missing values for safety parameters.

### 7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

## 7.6 RANDOMISATION

For each of the three-way crossover part subjects will be randomised to one of the 3 treatment sequences in a 1:1:1 ratio. Within the two-way crossover part, subjects will be randomised to one of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation. The randomisation list will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

## 7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter 15 subjects in each of the three-way crossover parts (part 1A, part 1B, optional part 2) and 14 subjects in the optional part 3 with the two-way crossover , because this sample size is considered sufficient to achieve the aims of this exploratory trial. Thus, in total 30 (optional 59) subjects will enter this study.

With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for Nintedanib in previous trials [c08883821], [c09412738] was roughly 26.5% for $C_{max}$ and 12% for $AUC_{0\text{-}tz}$.

For various assumptions around the gCV of 26% Table 7.7: 1 and 7.7: 2 provide an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a **three-way crossover trial** (N=15).

| gCV [%] | Precision upper CL / relative BA estimate | Ratio [%]* | Lower CI limit [%] | Upper CI limit [%] |
|---|---|---|---|---|
| 20 | 1.163 | 80 | 68.80 | 93.02 |
| 20 | 1.163 | 90 | 77.40 | 104.65 |
| 20 | 1.163 | 95 | 81.70 | 110.47 |
| 20 | 1.163 | 105 | 90.30 | 122.10 |
| 20 | 1.163 | 110 | 94.60 | 127.91 |
| 20 | 1.163 | 125 | 107.50 | 145.35 |
| 26.5 | 1.215 | 80 | 65.6 | 97.56 |
| 26.5 | 1.215 | 90 | 73.8 | 109.75 |
| 26.5 | 1.215 | 95 | 77.9 | 115.85 |
| 26.5 | 1.215 | 105 | 86.1 | 128.05 |
| 26.5 | 1.215 | 110 | 90.2 | 134.14 |
| 26.5 | 1.215 | 125 | 102.5 | 152.43 |
| 30 | 1.251 | 80 | 63.97 | 100.04 |
| 30 | 1.251 | 90 | 71.97 | 112.55 |
| 30 | 1.251 | 95 | 75.97 | 118.80 |
| 30 | 1.251 | 105 | 83.96 | 131.31 |
| 30 | 1.251 | 110 | 87.96 | 137.56 |
| 30 | 1.251 | 125 | 99.96 | 156.32 |

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

Table 7.7: 2 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a **two-way crossover trial** (N=14).

| gCV [%] | Precision upper CL / relative BA estimate | Ratio [%]* | Lower CI limit [%] | Upper CI limit [%] |
|---|---|---|---|---|
| 20 | 1.193 | 80 | 67.05 | 95.45 |
| 20 | 1.193 | 90 | 75.43 | 107.38 |
| 20 | 1.193 | 95 | 79.62 | 113.35 |
| 20 | 1.193 | 105 | 88.00 | 125.28 |
| 20 | 1.193 | 110 | 92.19 | 131.25 |
| 20 | 1.193 | 125 | 104.77 | 149.14 |
| 26.5 | 1.256 | 80 | 63.42 | 100.92 |
| 26.5 | 1.256 | 90 | 71.34 | 113.54 |
| 26.5 | 1.256 | 95 | 75.31 | 119.84 |
| 26.5 | 1.256 | 105 | 83.23 | 132.46 |
| 26.5 | 1.256 | 110 | 87.2 | 138.77 |
| 26.5 | 1.256 | 125 | 99.09 | 157.69 |
| 30 | 1.299 | 80 | 61.58 | 103.94 |
| 30 | 1.299 | 90 | 69.27 | 116.93 |
| 30 | 1.299 | 95 | 73.12 | 123.43 |
| 30 | 1.299 | 105 | 80.82 | 136.42 |
| 30 | 1.299 | 110 | 84.67 | 142.91 |
| 30 | 1.299 | 125 | 96.21 | 162.40 |

*Ratio of geometric means (test/reference) for a PK endpoint is defined by exp(□T)/exp(□R).

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 4.0.2.

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

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 Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), The Medicines for Human Use (Clinical Trials) Regulations SI 2004, No 1031, as amended 2006 (SI No. 1928 and No. 2984), 2008 (SI No 941) and 2019 (SI No. 744) and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

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 general rule, no trial results should be published prior to archiving of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects, and are stored in the ISF.

## 8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by substantial amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject'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 subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate 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 risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

### 8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication

- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

### 8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

### 8.3.3 Storage period of records

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

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

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

## 8.5 URGENT SAFETY MEASURES

If [redacted] or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety

measures can be agreed. An urgent safety issue is defined as: • An immediate hazard to the health or safety of subjects participating in a clinical study • A serious risk to human health or potentially a serious risk to human health An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study subjects. In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, [redacted] may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved. The Sponsor is responsible for informing appropriate competent authorities, and the EC; the task of reporting will be delegated to [redacted]

## 8.6 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

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.

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site 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.

### 8.6.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

## 8.7 TRIAL MILESTONES

The start of the trial is defined as the date of the enrolment of the first subject in the trial.

The end of the trial is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed').

Early termination of the trial is defined as the premature termination of the trial for any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The EC/competent authority in each country will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

## 8.8 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Clinical Trial Leader, responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of Clinical Trial Managers (CTM), Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany (Reference product only) and [redacted] (test products only).

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]).

Analyses of Nintedanib concentrations in plasma will be performed at [redacted]

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Data management and statistical evaluation will be done by BI according to BI SOPs.

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

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

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## 9.2 UNPUBLISHED REFERENCES

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U13-1506 [redacted] Clinical Overview: Nintedanib (BIBF 1120) soft capsules, 100 mg, 150 mg. 02 September 2013.

U05-2191 [redacted] An open label dose escalation study of BIBF 1120 administered orally for four weeks in patients with advanced solid tumours with repeated administration in patients with clinical benefit. Clinical Trial Report 1199-0001. Nov 2009.

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U06-1411 [redacted] Safety and pharmacokinetics/bioavailability of a single dose of 150 mg BIBF 1120 administered as soft gelatine capsules with and without food to healthy male volunteers in an open, randomised, intra-individual crossover comparison design. Clinical Trial Report 1199-0017. Jun 2011.

# 10. APPENDICES

According to FDA Guidance for Industry, a low-fat meal contains total of 400-500 kcal, including 11-14 g fat (equals 100-125 kcal or 25 % of total calories). Table 10: 1 and 10: 2 show exemplary light (low-fat, low calorie) breakfast [R21-1406].

Table 10: 1 Exemplary composition of the low-fat, low-calorie meal

| Ingredients |
|---|
| 50 g Corn Flakes |
| One Butter Croissant |
| One portion Jam (20 g) |
| 240 ml Skimmed milk (0,1 % fat) |

This low-fat breakfast contains 545,8 kcal and has 14 grams of fat

Table 10: 2 Exemplary composition of the low-fat, low-calorie meal

| Ingredients |
|---|
| One bread roll |
| 15 g butter |
| One sliced cheese (40 g Gouda) |
| One sliced sausage (20 g turkey breast) |
| One cup of water or decaffeinated coffee without sugar |

This low-fat breakfast contains 430 kcal

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol

## 11.1 GLOBAL AMENDMENT 1

| | | |
|---|---|---|
| **Date of amendment** | | |
| **EudraCT number**<br>**EU number** | | |
| **BI Trial number** | | |
| **BI Investigational Medicinal Product(s)** | | |
| **Title of protocol** | | |
| | | |
| **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** | | |
| **Description of change** | | |
| **Rationale for change** | | |