Clinical Trial Protocol

	Document Number: **c41830059-03**
EUCT No. **Universal Trial No.**	2023-505522-34-00 U1111-1292-0376
BI Trial No.	1305-0034
BI Investigational Medicinal Product	BI 1015550
Title	The effect of multiple oral doses of BI 1015550 on the pharmacokinetics of nintedanib and pirfenidone administered single dose to healthy male subjects (open-label, two-period, fixed-sequence crossover trial)
Lay Title	A study in healthy men to test whether BI 1015550 influences the amount of nintedanib and pirfenidone in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: +[redacted] Fax: +[redacted]
[redacted] **Investigator**	[redacted] Phone: +[redacted] Fax: [redacted]
Current Version, Date	Version 3.0, 05 October 2023
Original Protocol Date	31 May 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	31 May 2023
Revision date	05 October 2023
BI trial number	1305-0034
Title of trial	The effect of multiple oral doses of BI 1015550 on the pharmacokinetics of nintedanib and pirfenidone administered single dose to healthy male subjects (open-label, two-period, fixed-sequence crossover trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	Nintedanib (NIN) and pirfenidone (PIR) are the only drugs registered for the treatment of idiopathic pulmonary fibrosis (IPF). Nintedanib is also registered for systemic sclerosis interstitial lung disease (SSc-ILD) and progressive fibrosing ILDs. As BI 1015550 is developed for treatment of IPF and other forms of progressive pulmonary fibrosis, it is very likely that it may be used on top of NIN or PIR in clinical practice. Therefore, it is crucial to investigate if there is any effect of BI 1015550 on the kinetics of and NIN or PIR when administered together.
Trial objective	The main objective is to investigate the effect of multiple oral doses of 18 mg of BI 1015550 bid on the pharmacokinetics of single oral doses of NIN or PIR.
Trial endpoints	Primary endpoints: AUC_{0-tz} , $AUC_{0-\infty}$ and C_{max} of nintedanib AUC_{0-tz} , $AUC_{0-\infty}$ and C_{max} of pirfenidone
Trial design	Open-label, two-period fixed sequence crossover design trial
Number of subjects **total entered** **in each treatment**	 14 14
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m2 (inclusive)
Trial product 1 **dose** **mode of admin.**	BI 1015550, 18 mg film-coated tablets 2 x 1 tablet (= 36 mg BI 1015550 daily) Oral with 240 mL of water

Trial product 2 **dose** **mode of admin.**	Nintedanib (Ofev®) 100 mg soft capsules 1 capsule (= 100 mg nintedanib), single dose Oral with 240 mL of water, after a standardised breakfast
Trial product 3 **dose** **mode of admin.**	Pirfenidone (Esbriet®) 267 mg film-coated tablets 1 tablet (= 267 mg pirfenidone), single dose Oral with 240 mL of water, after a standardised breakfast
Duration of treatment	Treatment Period Reference (R): 1 x 1 tablet Esbriet® (single dose) on Day 1 of Period 1 and 1 x 1 capsule Ofev® (single dose) on Day 2 of Period 1 Treatment Period Test (T): 1 tablet BI 1015550 twice daily for 10 days (Day -6 to Day 4) together with 1 tablet Esbriet® (single dose) in the morning of Day 1 of Period 2 1 capsule Ofev® (single dose) in the morning of Day 2 of Period 2
Statistical methods	The effect of steady state BI 1015550 on the pharmacokinetics of nintedanib or pirfenidone will be estimated by the ratios of the geometric means (T/R) for the primary 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 ‘subject’ and ‘treatment’, with ‘subject’ as random and ‘treatment’ as fixed effect. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART - REFERENCE

Period	Visit	Day	Planned time (relative to the first drug intake [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK $_{blood}$ BI 1015550	PK $_{blood}$ pirfenidone	PK $_{blood}$ nintedanib	Suicidality assessment	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	-14 to -2			Screening (SCR)[1]	A				x	x	
1 (Treatment Reference)	2	-1	-12:00	20:00	Admission[9]	x[5]						x
		1	-1:00	07:00	treatment allocation[2]						x[2]	x[2]
			-0:30	07:30	Standard breakfast							
			0:00	08:00	Pirfenidone administration		x[8]	x[8]				x[8]
			0:30	08:30				x				
			1:00	09:00				x				
			1:30	09:30				x				
			2:00	10:00	240 mL fluid intake			x				x
			3:00	11:00				x				
			4:00	12:00	240 mL fluid intake, Lunch[3]			x				x
			6:00	14:00				x				
			8:00	16:00	Snack (voluntary)[3]			x				
			10:00	18:00				x				
			11:00	19:00	Dinner, all subjects together							
			12:00	20:00				x				x
		2	23:30	07:30	Standard breakfast[3]						x[2]	x[2]
			24:00	08:00	Nintedanib administration		x[8]	x[8]	x[8]			x[8]
			24:30	08:30					x			
			25:00	09:00					x			
			25:30	09:30					x			
			26:00	10:00	240 mL fluid intake				x			x
			27:00	11:00					x			
			28:00	12:00	240 mL fluid intake, Lunch[3]				x			x
			30:00	14:00					x			
			32:00	16:00	Snack (voluntary)[3]				x			
			34:00	18:00					x			
			35:00	19:00	Dinner, all subjects together							
			36:00	20:00					x			x
		3	48:00	08:00	Breakfast (voluntary) [3] and discharge				x			x
			60:00	20:00	Ambulatory visit				x[10]			x[10]
		4	72:00	08:00	Ambulatory visit				x[10]			x[10]
		5	96:00	08:00	Ambulatory visit	B[10] C[10]			x[10]			x[10]

FLOW CHART – TEST

Period	Visit	Day	Planned time (relative to the first drug intake [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood BI 1015550	PK blood pirfenidone	PK blood nintedanib	Suicidality assessment	ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
		Wash-out of at least 72 h to last study drug administration in period 1											
2 (Treatment Test)	3	-6	-144:00	08:00	BI 1015550 administration[11]						x[2]	x[2]	x[2]
			-132:00	20:00	BI 1015550 administration[11]								x[2]
		-5	-120:00	08:00	BI 1015550 administration[11]								x[2]
			-108:00	20:00	BI 1015550 administration[11]								x[2]
		-4	-96:00	08:00	BI 1015550 administration[11]								x[2]
			-84:00	20:00	BI 1015550 administration[11]								x[2]
		-3	-72:00	08:00	BI 1015550 administration[11]	B[2]							x[2]
			-60:00	20:00	BI 1015550 administration[11]								x[2]
		-2	-48:00	08:00	BI 1015550 administration[11]								x[2]
			-36:00	20:00	BI 1015550 administration[11]								x[2]
		-1	-24:00	08:00	BI 1015550 administration[11]								x[2]
			-14:00	18:00	Admission[9]	x[5]							
			-12:00	20:00	BI 1015550 administr.								x[2]
		1	-0:30	07:30	Standard breakfast[3]	B[2]						x[2]	x[2]
			0:00	08:00	BI 1015550 + pirfenidone		x[8]	x[8]					x[8]
			0:30	08:30				x					
			1:00	09:00				x		x			
			1:30	09:30				x					
			2:00	10:00	240 mL fluid intake			x					x
			3:00	11:00				x					
			4:00	12:00	240 mL fluid intake, lunch[3]			x					x
			6:00	14:00				x					
			8:00	16:00	Snack (voluntary)[3]			x					
			10:00	18:00				x					
			11:00	19:00	Dinner, all subjects together								
			12:00	20:00	BI 1015550 administr. (after PK)			x					x
		2	23:30	07:30	Standard breakfast[3]						x[2]	x[2]	x[2]
			24:00	08:00	BI 1015550 + nintedanib		x[8]	x[8]	x[8]				x[8]
			24:30	08:30					x				
			25:00	09:00					x		x		
			25:30	09:30					x				
			26:00	10:00	240 mL fluid intake				x		x		x
			27:00	11:00					x		x		
			28:00	12:00	240 mL fluid intake, lunch[3]				x		x		x
			30:00	14:00					x				
			32:00	16:00	Snack (voluntary)[3]				x				
			34:00	18:00					x				
			35:00	19:00	Dinner, all subjects together								
			36:00	20:00	BI 1015550 administr. (after PK)				x				x
		3	48:00	08:00	BI 1015550 administr. (after PK), breakfast (voluntary)[3] , discharge		x		x		x[2]		x[2]
			60:00	20:00	Ambulatory visit, BI 1015550 administration (after PK) [10]				x[10]				x[10]

FLOW CHART – TEST, (CONT.)

Period	Visit	Day	Planned time (relative to the first drug intake [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood BI 1015550	PK blood pirfenidone	PK blood nintedanib	Suicidality assessment	ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
		4	72:00	08:00	Ambulatory visit, BI 1015550 administration (after PK) [10]				x[10]				x[10]
			84:00	20:00	Ambulatory visit, BI 1015550 administration[10]								x[10]
		5	96:00	08:00	Ambulatory visit				x[10]				x[10]
FU	4	11-25			End of study (EoS) examination[4]	D				x		x	x

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, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, suicidality assessment, concomitant therapy, review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within 3 h prior to next 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 study (synonym for end of trial), the EoS examination includes physical examination, suicidality assessment, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Urine drug screening and alcohol breath test.
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. Letters A, B C and D define different sets of safety laboratory examinations (for details refer to Section 5.2.3).
8. To be done within 15 min prior to study drug dosing.
9. The time is approximate. Procedures are to be performed no later than 10 h prior to the next drug administration in period 1 and within 2 hours prior to next study drug administration in period 2.
10. After discharge from [redacted] in the morning of Day 3 the tolerance time for all subsequent procedures is ± 60 min.
11. The tolerance time for ambulatory dosing on Day -6 to Day -1 in Treatment Test is ± 2 hours.

For details of suicidality assessment, refer to Section 5.2.5.1.

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
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
bid	Twice a day
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
C-SSRS	Columbia Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DDI	Drug Drug Interaction
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid

EoS	End of Study (synonym for End of Trial)
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FEED	Fertility and early embryonic development
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
HR	Heart rate
IB	Investigator's brochure
ICH	International Council for Harmonisation
IGRA	Interferon Gamma Release Assays
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IPD	Important protocol deviation
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NIN	Nintedanib
PD	Pharmacodynamic(s)
PDE	Phosphodiesterases
PIR	Pirfenidone
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Peak-trough swing
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment

REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
ss	(at) steady state
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
TB	Tuberculosis
TBA	Trial Bioanalyst
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

BI 1015550, an oral preferential inhibitor of the phosphodiesterase 4B (PDE4B) isoenzyme which hydrolyses and inactivates cyclic adenosine monophosphate (cAMP), is being developed by Boehringer Ingelheim (BI) for the treatment of idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis.

1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) [P11-07084].

While IPF is considered a prototypical form of progressive pulmonary fibrosis, there is a group of patients with different underlying clinical interstitial lung disease (ILD) diagnoses who develop a phenotype similar to patients with IPF during the course of their disease [P17-10582, P18-04729, P19-01738, R19-0854, P20-01299], which is characterised by increasing extent of pulmonary fibrosis on imaging, declining lung function, worsening respiratory symptoms and quality of life despite disease management considered appropriate in clinical practice, and, ultimately, early mortality [P17-10582, P18-04729, P19-01738, R19-0854, P20-01299].

Nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and both treatments are recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of Idiopathic Pulmonary Fibrosis [P15-07539]. Nintedanib is also registered for the treatment of adults with other chronic fibrosing ILDs with a progressive phenotype and Systemic Sclerosis-associated ILD. However, despite existing treatment, there remains a high unmet need for new treatments for IPF and other fibrosing ILDs that have greater efficacy and fewer side effects than existing therapies [P18-06345].

BI 1015550 is an oral preferential inhibitor of the PDE4B with broad anti-inflammatory and antifibrotic activities. Based on its mode of action, as well as available pre-clinical and clinical data, BI 1015550 is hypothesised to have complementary activity to current therapies in IPF and other forms of progressive pulmonary fibrosis.

1.2 DRUG PROFILE

1.2.1 BI 1015550

1.2.1.1 Pharmacokinetic properties

Absorption

[redacted] BI 1015550 plasma exposure had a dose proportional increase following both single- and multiple-dose administration. Following multiple-dose administration of BI 1015550 [redacted] under fed conditions over 14 days in

healthy male subjects, [c22991937].

Administration of BI 1015550 together with standard high-fat and high caloric meal did not have noticeable impact on BI 1015550 exposure (9% increase in AUC and 11% reduction in Cmax) compared with the fasted state study (1305-0028, c40013550).

Distribution

[n00201897].
BI 1015550
[n00201905]. The apparent volume of distribution appeared to [c25085412]).

Metabolism

BI 1015550 is mainly

However, following a [n00261666]

Elimination

Drug-drug interaction potential of BI 1015550

[redacted]

Based on the current knowledge of BI 1015550's non-clinical evaluation and nintedanib and pirfenidone's labelled ADME characteristics, neither a relevant DDI between BI 1015550 and nintedanib, nor between BI 1015550 and pirfenidone is expected. [redacted]

1.2.1.2 Clinical safety in healthy subjects

In clinical studies BI 1015550 has been administered to about 190 healthy subjects. Overall, BI 1015550 has shown an acceptable safety and tolerability, [redacted] Headache, abdominal pain, nausea and diarrhoea were the most commonly reported events.

In the [redacted] AEs related to the intake of BI 1015550 were reported by 5 subjects and comprise abdominal pain / lower abdominal pain (3x), diarrhea, constipation, headache, aphthous stomatitis, oral herpes and increased CRP (1x each). [redacted]

[redacted] The most frequent drug related AE was headache reported by 3 subjects. Further drug related AEs comprise diarrhoea, abdominal distension, upper abdominal pain, constipation, and nausea. [redacted] The most frequent drug related AE was headache reported by 5 subjects. Further drug related AEs comprise diarrhoea, abdominal distension, nausea, and oral hypoaesthesia. These AEs were of mild or moderate intensity and resolved by end of the trial. Three isolated cases of positive FOB test were reported (thereof 1 on placebo). There were no relevant changes to other lab values (including fecal calprotectin), vital signs and ECG parameters. [redacted] Drug related AEs were reported by 9 of 15 subjects and diarrhoea (2x), headache (2x), flatulence (2x) and hyperaesthesia (1x). All these AEs were of mild intensity. No relevant changes of lab values, vital signs and ECG parameters have been reported [c40607236, draft report].

For a more detailed description of the BI 1015550 profile, please refer to the current Investigator's Brochure (IB) [c02094779].

1.2.2 Nintedanib (NIN)

Nintedanib is a tyrosine kinase inhibitor used for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype and systemic sclerosis associated interstitial lung disease (SSc-ILD) in adults.

1.2.2.1 Pharmacokinetic properties

After oral administration, nintedanib is absorbed moderately fast. Maximum plasma concentrations (C_{max}) occurred 2 to 4 hours after oral intake. Nintedanib exposure increases dose proportionally. The absolute bioavailability of nintedanib administered as capsule was slightly below 5%. After food intake nintedanib exposure is slightly increased (15-20%).

Nintedanib is mainly metabolized by esterases. The by far most frequent metabolites in the human ADME study were BIBF 1202 resulting from ester cleavage of nintedanib, and BIBF 1202-glucuronide formed by subsequent glucuronidation.

The terminal half-life of nintedanib is between 10 and 15 h. In humans, 93.4% of total [^{14}C]-nintedanib was excreted in the faeces within 120 hours after oral administration of nintedanib. Only 0.7% of total [^{14}C]-nintedanib was eliminated via the urine.

Nintedanib a substrate of P-gp. Coadministration with the P-gp inhibitor ketoconazole increased AUC and C_{max} of NIN by 61% and 83%. Nintedanib and its main metabolites BIBF 1202 and BIBF 1202-glucuronide do not cause induction or inhibition of CYP enzymes.

Combined administration of NIN and PIR in IPF patients did not provide any signal of a relevant PK-interaction between both drugs [R23-1847].

1.2.2.2 Clinical safety in healthy subjects

Up to the present nintedanib has been administered to more than 200 healthy subjects. In clinical trials single oral doses of up to 200 mg nintedanib were well tolerated. Gastro-intestinal side effects and headache were the most common drug related adverse events.

In 1199.17, single doses of 150 mg nintedanib were administered to 15 healthy subjects. Drug related AEs were diarrhoea (reported in 7 cases), abdominal discomfort (reported in 3 cases) and nausea (reported by 1 subject) [U06-1411-02].

In 1199.20, a single oral dose of 100 mg nintedanib was administered to 8 healthy subjects. Two drug related adverse events have been reported – nausea (N= 1) and asthenia (N=1) [U06-1724].

In 1199.21, two single oral doses of 150 nintedanib were given to 36 healthy volunteers. Drug related AEs comprised diarrhoea (N=14), headache (N=8), nausea (N=2), vomiting (N=1), dizziness (N=1), fatigue (N=1) and dry mouth (N=1) [U07-1736-02].

In 1199.75, thirty subjects were treated with single doses of intravenous (1, 3 or 6 mg) or oral (100 mg) NIN or placebo. The only drug-related AE was diarrhoea (1x) [U10-1400-02].

In 1199.161, a single dose of 50 mg nintedanib was given alone and in combination with steady state ketoconazole to 34 healthy subjects. Drug related AEs (referring to the intake of NIN alone or in combination with ketoconazole) were headache (reported by 5 subjects), upper abdominal pain and fatigue (each reported by 1 subject) [U13-1925-01].

In 1199.162, a single dose of 150 mg nintedanib was given alone and in combination with steady state rifampin to 26 healthy subjects. Drug related AEs (referring to nintedanib alone or in combination with rifampin) were diarrhoea (8x) and headache (2x) [U13-1478-01].

In 1199.237 single doses of 200 mg NIN were given in three trial periods to 70 healthy male subjects. Drug related AEs were reported by 33 subjects and comprise loose stool (24x), nausea (7x), abdominal discomfort (3x), upper abdominal pain (1x), headache (9x), dizziness (3x) and fatigue (1x). All drug related AEs were of mild or moderate intensity and resolved without treatment. NIN had no relevant effects on safety lab and vital signs [c08883821-01].

For a more detailed description of the nintedanib profile, please refer to the current SmPC [R23-1847].

1.2.3 Pirfenidone (PIR)

Pirfenidone is used for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF) in adults. The mechanism of action of pirfenidone in the treatment of IPF has not been established.

1.2.3.1 Pharmacokinetic properties

After single oral-dose administration of a 801 mg pirfenidone tablet to healthy subjects, mean t_{max} was achieved after 1 h and 2 h under fasted and fed conditions. Food decreased the rate and extent of absorption by about 40% and 20%. The elimination half-life was about 2.77 and 2.74 hours in fasted and fed state [R17-3055].

Pirfenidone is mainly metabolised (70-80%) by cytochrome P450 1A2 and to a minor extent by CYP2C9, 2C19, 2D6 and 2E1. Pirfenidone is excreted predominantly (about 80% of an oral dose) in the urine.

Co-administration with the strong CYP1A2 inhibitor fluvoxamine increased exposure to pirfenidone by approximately 4-fold in non-smokers and 7-fold in smokers. Co-administration with ciprofloxacin (moderate inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%.

1.2.3.2 Clinical safety in healthy subjects

In clinical trials, the most frequent adverse events reported by healthy subjects were gastrointestinal disorders (e.g. nausea, abdominal pain, vomiting) and dizziness. To reduce the incidence of nausea and dizziness a fed intake is recommended.

In a dose-escalation study single doses of 200, 400 and 600 mg pirfenidone (fasted intake) and multiple doses of 400 mg tid (for 5 days, fed intake) have been tested in healthy male and female Chinese subjects. Adverse events were reported by 8 of 48 subjects and comprise dizziness (7 cases), nausea (4 cases), vomiting, stomach upset and cold sweat (each in 1 case). AEs generally occurred 0.5 h to 2 h after pirfenidone intake. Incidence of adverse events was higher in the highest dose group (5 cases) and in females (7 of 8 cases). No AEs were reported in the low dose group and in the multiple dose part[R23-1844].

In another trial single doses of 200 mg and 600 mg pirfenidone (randomised cross-over design, fasted intake, cohort 1 with N=10) and 400 mg pirfenidone (single dose followed by tid dosing for 6 days, fed intake, group 2 with N=10) have been tested in healthy male and female Chinese subjects. Drug related adverse events have been reported by 6 subjects and comprise dizziness (3 cases), stomach discomfort (2 cases), intermittent headache, nausea, belching, drowsiness and decreased haemoglobin (1 case each). Incidence of AEs was higher in females (5 subjects) and in the multiple dose group (5 subjects). All Adverse events were of mild intensity and recovered without treatment. No AEs were reported after single dose administration of 200 mg and 400 mg pirfenidone. There were no significant changes from baseline regarding ECG and vital signs and [R23-1846].

In a four-period cross-over trial the bioequivalence of an 801 mg tablet versus 3 capsules containing 267 mg pirfenidone have been investigated under fasted and fed conditions in 44 healthy subjects. Adverse events have been reported by 22 subjects, predominantly in fasted treatments. Most frequent AEs comprise nausea (13x), dizziness (8x), constipation (4x), headache (4x), vomiting (2x) and dyspepsia (2x). All adverse events were of mild intensity [R17-3055].

Rubino et al investigated the effect of antacids on single dose kinetics of 801 mg pirfenidone under fasted and fed conditions in 16 healthy elderlies. AEs were reported by 12 subjects.

Most commonly reported AEs comprise nausea (7x) and dizziness (6x), which more frequently occurred in the fasted state. All AEs were of mild or moderate intensity. There were no significant ECG changes or laboratory abnormalities [R23-1845].

For a more detailed description of the pirfenidone profile, please refer to the current SmPC [R23-1848].

1.2.4 Residual Effect Period

[redacted] This is the period after the last dose during which measurable drug levels are still likely to be present.

The REP of nintedanib for single dose is 3 days.

The REP of pirfenidone is 12 hours.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Nintedanib and pirfenidone are the only drugs registered for the treatment of idiopathic pulmonary fibrosis (IPF). Nintedanib is also registered for SSc-ILD and progressive fibrosing ILDs. As BI 1015550 is developed for treatment of IPF and other forms of progressive pulmonary fibrosis, it is very likely that it may be used on top of nintedanib or pirfenidone in clinical practice.

This trial investigates the potential impact BI 1015550 on the pharmacokinetics of nintedanib or pirfenidone. The results will provide further rationale for development of the drug label with regards to restriction of concomitant medication.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1015550, which may help to treat patients suffering from idiopathic pulmonary fibrosis.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication.

Potential side effects of BI 1015550 will be under continuous evaluation during clinical development. Vasculitis and foetal loss are considered as important potential risks based on nonclinical findings. The risks shown in the table 1.4.2:1 below are hypothetical in nature; these are not limited to data from BI 1015550 but also derived from general safety considerations of immunomodulatory drugs and from preclinical and clinical data of compounds with a comparable mode of action.

In addition to the data from trials in healthy volunteers as described above (sections 1.2.2, 1.2.3), the safety profile as summarized in the current SmPCs of nintedanib and pirfenidone is based on a substantial number of clinical trials in patients and post-marketing experience, mainly after long-term treatment. Overall, the most frequently reported adverse reactions

associated with the use of nintedanib included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased. The most frequently reported adverse reactions during clinical study experience with pirfenidone were nausea, diarrhoea, dyspepsia, anorexia, headache, and photosensitivity reaction.

In the evaluation of risks, it is of note that only single doses of nintedanib and pirfenidone will be administered in the current trial to healthy male subjects.

An overview of trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
<u>Investigational Medicinal Product</u>: BI 1015550		
[redacted]		
Vasculitis	• Vasculopathy is an established preclinical toxicity of PDE4 inhibitors [redacted]	• Close clinical monitoring (AE questioning, lab values) in order to early detect potential signs of vasculitis. • Treatment of a subject is discontinued in case of any suspected vasculitis event.
Major Adverse Cardiovascular Events (MACE) and tachyarrhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast. • In clinical trials with BI 1015550 no relevant findings were observed.	• These risks will be addressed by careful safety monitoring (AE-questioning) and safety measures (vital signs, ECG)

Table 1.4.2: 1 Overview of trial-related risks for this trial, (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		
Psychiatric disorders: depression and suicidality	• For the marketed PDE4 inhibitors depression is listed as side effect and they are associated with increased risk of depression with some patients reporting suicidal ideation and attempts and also reported cases of completed suicide. [redacted]	• The risk of depression and suicidality within the planned dosing period of 10 days is considered low • Subjects will be proactively screened and monitored for SIB in accordance with regulatory guidance (use of C-SSRS questionnaire) • Exclusion of subjects with any suicidal ideation in the past 12 months or any lifetime history of suicidal behaviour
Severe infections including, serious, opportunistic and mycobacterium tuberculosis infections	• Inhibition of the immune response due to the anti-inflammatory mode of action of BI 1015550 potentially increases the risk of severe and serious infections. • Serious infections were balanced between placebo and BI 1015550 in Phase II trial. [redacted]	• Screening procedures for infections are defined for this trial. Subjects with any relevant chronic or acute infections are excluded from the trial • Treatment of infections should be initiated promptly according to standards of care • In case of severe acute infection treatment with BI 1015550 will be stopped

Table 1.4.2: 1 Overview of trial-related risks for this trial, (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Malignancies	• Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus, theoretically decrease immune defence against malignancies.	• Subjects with active or suspected malignancy or history of malignancy within 5 years prior to screening will be excluded from participation in this trial
Gastrointestinal disorders (e.g., diarrhoea, nausea, vomiting, abdominal pain)	• Vomiting and diarrhea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. • In phase I trials gastrointestinal disorders are frequently reported side effects	• Subjects are regularly asked for adverse events • Gastrointestinal side effects can be managed in the setting of a phase I trial (e.g. hydration of subjects with diarrhoea)
Drug-induced liver injury (DILI)	• Rare but severe event, thus under constant surveillance by sponsors and regulators	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety • Increased awareness and expedited reporting (AESI).

Table 1.4.2: 1 Overview of trial-related risks for this trial, (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
<u>Nintedanib (NIN)</u>		
Reproductive toxicity	• NIN caused embryofetal letality in rats and rabbits.	• Female subjects are not included in this trial.
Tolerability in healthy subjects	• Gastro-intestinal side effects and headache were the most common drug related adverse events reported from healthy subjects	• A single low dose of 100 mg NIN is administered in this trial • side effects described by healthy subjects so far can be managed in the setting of a phase I trial
Hepatic function	• Liver enzyme elevation has been very commonly observed with nintedanib treatment, in the majority of cases reversible upon dose reduction or interruption. • Cases of drug-induced liver injury have been observed with nintedanib treatment including severe liver injury with fatal outcome.	• Single doses will be administered in this trial rendering the risk of liver injury very low. • Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety • Increased awareness and expedited reporting (AESI)
Hypersensitivity to peanut or soya	• Each Ofev® 100 mg soft capsule contains 1.2 mg of soya lecithin • Dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. • Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.	• Subjects with hypersensitivity to peanut or soya will be excluded.

Table 1.4.2: 1 Overview of trial-related risks for this trial, (cont.)

bleeding	• Listed side effect in the SmPC of Ofev®	• The risk of bleeding is considered minimal based on the single applications in this study. • Nevertheless, subjects with a hereditary bleeding disorder and subjects with an out-of-range value at screening indicating a bleeding risk will be excluded from participation
proteinuria	• Listed side effect in the SmPC of Ofev®	• The risk of proteinuria is considered minimal based on the single applications in this study. • Patients with proteinuria at screening will be excluded from participation.

Table 1.4.2: 1 Overview of trial-related risks for this trial, (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
<u>Pirfenidone (PIR)</u>		
Tolerability in healthy subjects	• Gastrointestinal disorders and dizziness were the most frequent drug related adverse events reported from healthy subjects	• A breakfast will be served prior to PIR intake to reduce the incidence of nausea and dizziness • A single low dose of 267 mg PIR is administered in this trial • side effects described by healthy subjects can be managed in the setting of a phase I trial • subjects will be discharged only after confirmation of their fitness
Photosensitivity reaction and rash	• listed as Special warnings and precautions for use in the SmPC of pirfenidone	• a low single dose of pirfenidone will be given • after PIR dosing subject will be kept inhouse for 48 hours (during this time direct exposure to sunlight should be avoided) • half-life of PIR is about 2.8 h
angioedema	• listed as Special warnings and precautions for use in the SmPC of pirfenidone	• healthy subjects with a history of angioedema are excluded (exclusion 33)

Table 1.4.2: 1 Overview of trial-related risks for this trial, (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Drug-induced liver injury (DILI) and increased transaminases	• listed as Special warnings and precautions for use in the SmPC of pirfenidone • Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe drug-induced liver injury, including isolated cases with fatal outcome, have been reported post-marketing	• a low single dose of pirfenidone will be given • half-life of PIR is about 2.8 h • measurement of liver function tests should be performed in subjects who report symptoms that may indicate liver injury, including right upper abdominal discomfort, dark urine, or jaundice.
<u>Trial procedures</u>		
Inflammation of the wall of the vein. Injuring of a nerve while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.	General risk by venepuncture for blood sampling, acceptable in the framework of trial participation.	Evaluation of the medical expertise of the trial sites is part of site feasibility assessment. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.
Skin irritation, redness, itching	General risk by ECG electrodes, acceptable in the framework of trial participation.	Exclusion of subjects from trial participation with known clinically relevant hypersensitivity reactions to adhesive tapes

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

1.4.3.1 Risks of drug-drug-interaction

1.4.3.2 Overall assessment

BI 1015550 is developed for the treatment of idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis. So far NIN and PIR are the only drugs registered for the treatment of IPF. This trial investigates the effect of BI 1015550 on the kinetics of NIN and PIR to give recommendations on the safe use of BI 1015550 if administered together with NIN and PIR in the clinical practice.

The safety profile of BI 1015550 has been characterized in several clinical trials including administration to about 190 healthy subjects so far. The observed adverse events can be handled in the setting of a phase I trial. There is no undue risk from the administration of BI 1015550 to healthy subjects in this trial.

NIN and PIR are marketed compounds that have been well tolerated by healthy subjects at doses that exceed the doses given in this trial thus providing a safety margin for a potential DDI.

In this trial adequate safety monitoring including safety laboratory, ECG, suicidality assessment and adverse events monitoring has been implemented. Taking into account these safety measures and considering the chosen low doses of the PIR and NIN the potential risks to healthy participants are considered to be low and outweighed by the benefit of a successful clinical development of BI 1015550 for the treatment of IPF.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVE AND PRIMARY ENDPOINTS

2.1.1 Main objective

The main objective of this trial is to investigate the induction effect of multiple oral doses of 18 mg bid of BI 1015550 on the pharmacokinetics of nintedanib or pirfenidone.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for nintedanib:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

The following pharmacokinetic parameters will be determined for pirfenidone:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 1015550 will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, two-period fixed sequence crossover design trial in order to compare the test treatment (T) to the reference treatment (R) using the fixed sequence R-T. An overview of both treatments is given below, for details refer to Section 4.1.

Reference Treatment (R):

- 267 mg pirfenidone (single dose) given orally alone on Day 1 of period 1
- 100 mg nintedanib (single dose) given orally alone on Day 2 of period 1

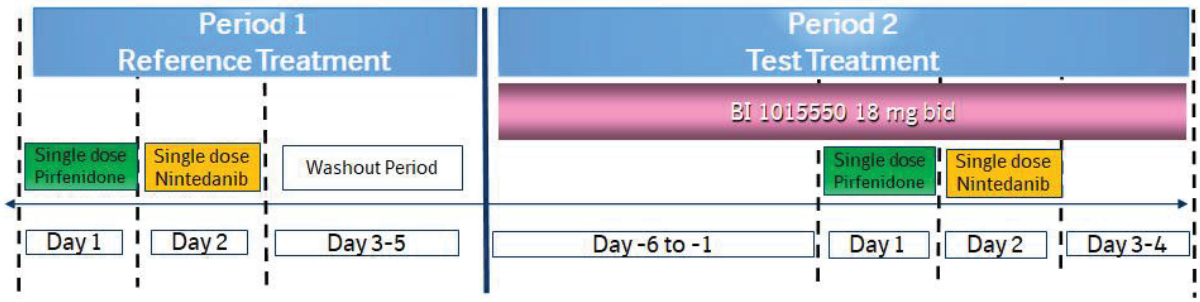
Test Treatment (T)

- 18 mg BI 1015550 given twice daily for 10 days (Day -6 to Day 4) together with
- 267 mg pirfenidone (single dose) in the morning of Day 1 of Period 2
- 100 mg nintedanib (single dose) in the morning of Day 2 of Period 2

For details on drug administration, refer to Section 4.1.

There will be a washout period of at least 72 hours between the nintedanib treatment (R) and the first BI 1015550 administration in the test treatment period (T).

Figure 3.1: Study Design



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.

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

For this one-sided DDI-trial (investigates the effect of the offender drug on 2 victim drugs), the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94 1529].

Because of the [redacted] different treatment schedules and in order to avoid overlapping effects, a fixed-sequence design is selected, in which the offender (BI 1015550) will be administered in the second study period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration.

[redacted]

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte, that are not influenced by the subject`s knowledge of the treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 14 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

Female subjects will not be recruited due to the teratogenic potential of nintedanib.

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.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as 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/m2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

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. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders (including severe renal or hepatic impairment)
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs 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). This includes any kind of vaccination.
13. Intake of an investigational drug in another clinical trial within 60 days or within 5 half-lifes of the investigational drug or its metabolites (whichever is longer) of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 24 g per day for males)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform 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. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for Torsade de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)

23. 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
24. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of administration of trial medication until 90 days thereafter
25. According to C-SSRS questionnaire at screening: any suicidal ideation in the past 12 months or any lifetime history of suicidal behaviour
26. History of depressive disorders
27. History of vasculitis
28. Subjects with active tuberculosis
29. Liver enzymes (ALT, AST, GGT) or serum creatinine above upper limit of normal range at screening examination, confirmed by a repeat test
30. Known hypersensitivity to peanut or soya
31. Concomitant intake of fluvoxamine
32. No intake of prescription medicine within 2 months prior to the planned administration of investigational drug in the current trial
33. History of angioedema
34. Thyroid dysfunction based on TSH outside the normal range confirmed by repeat test
35. History of hereditary bleeding disorder
36. Proteinuria at screening, if confirmed by a repeat test

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may 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, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.4, 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 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery or diseases) or in case of occurrence of one AE of severe intensity or one SAE.
5. The subject has 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

   If any of the following adverse events is reported, the treatment has to be discontinued:

   - Severe or serious infections, opportunistic or mycobacterium tuberculosis infections
   - Vasculitis

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

   If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

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 (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site

2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported

3.3.5 Replacement of subjects

In case more than 2 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. 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 group as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of trial product 1 are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	18 mg
Posology:	1 – 0 – 1
Mode of administration:	Oral
Duration of use:	10 days (from Day – 6 to Day 4 in Period 2)

The characteristics of trial product 2 are given below:

Name:	Ofev®
Substance:	Nintedanib
Pharmaceutical formulation:	Soft capsules
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	1 – 0 – 0
Mode of administration:	Oral
Duration of use:	Single dose on Day 2 of Period 1 and Period 2

The characteristics of trial product 3 are given below:

Name:	Esbriet®
Substance:	Pirfenidone
Pharmaceutical formulation:	Film-coated tablets
Source:	[redacted]
Unit strength:	267 mg
Posology:	1 – 0 – 0
Mode of administration:	Oral
Duration of use:	Single dose on Day 1 of Period 1 and Period 2

4.1.2 Selection of doses in the trial

BI 1015550:

18 mg bid of BI 1015550 is the therapeutic dose that is currently used in clinical trials. In this trial BI 1015550 is the perpetrator drug that has to be used in the maximum dose [R20-2271].

Nintedanib:

100 mg of nintedanib is the lowest therapeutic dose which is used for safety reasons.

Pirfenidone:

267 mg of pirfenidone is the lowest therapeutic dose which is used for safety reasons.

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a trial subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2.

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

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable (for discussion of trial-associated risks and safety measures, see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

This is a one-way crossover trial. All subjects will receive the 2 treatments in a fixed order. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage
R (Reference)	Pirfenidone	Film coated tablets	267 mg	1 x 1 tablet on Day 1 of visit 2
	Nintedanib	Soft capsule	100 mg	1 x 1 capsule on Day 2 of visit 2
T (Test)	BI 1015550	Film coated tablets	18 mg	2 x 1 tablet (from Day -6 to Day 4) of visit 3, together with
	Pirfenidone	Film coated tablets	267 mg	1 x 1 tablet on Day 1 of visit 3
	Nintedanib	Soft capsule	100 mg	1 x 1 capsule on Day 2 of visit 3

On Day 1 and 2 of both trial periods (PK-profile days) NIN and PIR will be administered after a standardised breakfast. The breakfast has to be consumed within 30 min prior to study drug administration. In period 2 NIN and PIR will be given together with BI 1015550. 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. During the first 4 h after 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).

Dosing of BI 1015550 is done in an ambulatory fashion on Days -6 to -1 and on Days 3-4 in period 2. For ambulatory dosing BI 1015550 will be administered with 240 ml water to subjects who are in a standing position. On ambulatory dosing days no specific restrictions regarding food intake have to be followed. Start of BI 1015550 dosing in period 2 should be separated by a wash-out phase of at least 72 hours after NIN dosing in period 1.

For all 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, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 48 hours after PIR intake and until 24 h after NIN intake.

4.1.5 Blinding and procedures for unblinding

This non-randomised Phase I trial will be handled in an open fashion throughout. The treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The BI 1015550 tablets will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). For details of packing and the description of the label, refer to the ISF.

The labels will be prepared according to Regulation (EU) No 536/2014, Annex 6 omitting certain particulars with the following justifications:

- The visit number is not relevant for the label because the product will remain at the clinical site.
- The investigator name was omitted from the label because it is included on the Trial Identification Card, which will be issued to each trial participant.
- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.

Pirfenidone and nintedanib will be obtained by the clinical trial site from a public pharmacy. The drugs will be dispensed out of the original, unmodified packages.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EUCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

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 Clinical Research Associate (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 when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- 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 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

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 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 Clinical Trial Leader. 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 trial days) on the appropriate pages of the CRF.

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. On PK-profile days no food is allowed for at least 4 h after drug intake.

On PK-profile days from 1 h before drug intake until lunch, fluid intake is restricted to the water provided at breakfast, to 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 12 h post-dose, total fluid intake is restricted to 2000 mL (thereafter subjects may drink ad libidum).

Green tea, 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 sampling of the trial.

Alcoholic beverages are not permitted starting 48 h before first trial drug administration until last PK sampling.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during in-house confinement at the trial site.

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.

Direct exposure to sun should be avoided during inhouse confinement.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial 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 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history 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 in all subjects), a physical examination, and assessment of suicidal ideation and behavior using the C-SSRS ('baseline/screening scale').

At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination, assessment of suicidal ideation and behavior using C-SSRS ('since last visit scale').

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 (Dinamap Pro 100, [redacted] 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.

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 lab panel A and D; for panel B and C no specific fasting period is required). For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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	C	D
Haematology	Haematocrit	X	X		X
	Haemoglobin	X	X		X
	Red Blood Cell Count/Erythrocytes	X	X		X
	Reticulocytes, absol.	X	X		X
	Reticulocytes/Erythrocyte	X	X		X
	White Blood Cells/Leucocytes	X	X		X
	Platelet Count/Thrombocytes (quant)	X	X		X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X			X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X			X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X			X
	Prothrombin time (Quick)	X			X
	Prothrombin time – INR (International Normalization Ratio)	X			X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X			X
	ALT [Alanine aminotransferase] /GPT, SGPT	X			X
	Alkaline Phosphatase	X			X
	Gamma-Glutamyl Transferase	X			X
Hormones	Thyroid Stimulating Hormone	X			
Substrates	Glucose (Plasma)	X			X
	Creatinine	X			X
	Bilirubin, Total	X			X
	Bilirubin, Direct	X			X
	C-Reactive Protein (Quant)	X	X		X
	Troponin T	X	X		X
Electrolytes	Sodium	X			X
	Potassium	X			X
	Calcium	X			X
Urinalysis (Stix)	Urine Nitrite (qual)	X		X	X
	Urine Protein (qual)	X		X	X
	Urine Glucose (qual)	X		X	X
	Urine Ketone (qual)	X		X	X
	Urobilinogen (qual)	X		X	X
	Urine Bilirubin (qual)	X		X	X
	Urine HGB (qual)	X		X	X
	Urine leucocyte esterase (qual)	X		X	X
	Urine pH	X		X	X
Urine sediment (microscopic examination)	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)
B: parameters to be determined at Visit 2 on Day 5 and Visit 3 on Days -3 and 1 (also refer to Flow Chart)
C: parameters to be determined at Visit 2 on Day 5 (also refer to Flow Chart)
D: parameters to be determined at Visit 4 (end of trial examination)

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 admission to the trial site.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) QuantiFERON®-TB Gold-Plus-Test (IGRA)

To encourage compliance with alcoholic restrictions, a breath alcohol test [redacted] will be performed prior to each admission to the trial during the trial 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. These tests will be performed at the trial site using [redacted] or comparable test systems.

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

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph [redacted] 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 trial procedures scheduled for the same time to avoid compromising ECG quality.

[redacted]Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

All locally printed ECGs will be evaluated by the investigator or a designee. For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcF (correction according to Fridericia's formula) values generated by the computerised ECG system will be used. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) 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.

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

Based on the FDA guidance on prospective assessment of suicidality [R12-4395] suicidal ideation and behaviour (SIB) will be proactively evaluated as part of the drug development. This also refers to clinical trials in healthy volunteers with multiple dose administration of the IMP.

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation [R08-1147].

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening / baseline' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The life time history of suicidal ideation and behavior

will also be recorded. The C-SSRS version used in this trial are filed in the ISF. For this trial, the paper version of the respective German translation will be used.

After the screening visit, the 'since last visit' version is used for the suicidality assessment at the time points indicated in the Flow Chart.

The investigator is to review all reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the report is confirmed, appropriate actions for the subject's safety have to be initiated.

There are following types of suicidal ideation and behaviour [R12-4395]:

Suicidal ideation

1. Passive
2. Active: nonspecific – no method, intent or plan
3. Active: method, but no intent or plan
4. Active: method and intent, but no plan
5. Active: method, intent, and plan

Suicidal behaviour

1. Completed suicide
2. Suicide attempt
3. Interrupted attempt
4. Aborted attempt
5. Preparatory actions toward imminent suicidal behaviours.

For details regarding AE reporting see Section 5.2.6.2.3

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 considered related or not.

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 (except hospitalisation for routine check-up, diagnostic purposes only or for a planned surgery), or 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’

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

The latest list of ‘Always Serious AEs’ can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of ‘Always Serious AEs’ will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

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

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:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  - 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.

- Serious infections, opportunistic or mycobacterium tuberculosis infections.

  These include Pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy (PVAN), Cytomegalovirus (CMV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), Scedosporium/Pseudallescheria boydii, fusarium), legionellosis, Listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, Penicillium marneffei, Sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), Trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617]

- Vasculitis

  The investigator should monitor for any signs and symptoms of vasculitis at all times and specifically as part of the AE questioning. In case of a suspected event of vasculitis an additional safety lab has to be performed (general parameters: ESR, CRP, erythrocytes, leukocytes [incl. differential], thrombocytes) and further blood samples will be taken to analyse the following immunological vasculitis markers:

- 2 container (serum) for MPO-ANCA, PR3-ANCA, IL-6, anti C1q antibodies, antiglomerular basement membrane (GBM) antibodies, rheumatoid factor, antinuclear antibodies, complement C3 and C4 to be sent to [redacted]
- 1 container (serum) for CH 50. Sample processing has to be done at site. Centrifugation at 2000 g for 10 min. 2 aliquots of at least 1 ml serum to be frozen within 60 min at about -70°C. One aliquot to be sent to [redacted] back-up aliquot to be stored at site until successful analysis of first aliquot has been confirmed by the lab.

Number and matrix of containers may change based on requirements of [redacted]
This can be implemented via non-substantial amendment.

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 whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, 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.

An adverse event for which a causal relationship to an investigational medicinal product cannot be ruled out has to be classified as related.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

Upon enrolment into a trial, 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. 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 (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs 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 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 new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event (the only exception to this rule are SAEs and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication), the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send 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. 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 characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

5.2.6.2.3 AE reporting from suicidality assessment

Any suicidal ideation or behaviour will be reported to the sponsor. Suicidal ideation of type 1, 2 or 3 can be reported as AE, at the discretion of the investigator. All reports should be

reviewed by the Investigator for clinical relevance and determination if an AE report is warranted.

All reports of suicidal ideation type 4 and 5 and all reports of suicidal behaviour (based on C-SSRS questionnaire during the trial, see section 5.2.5.1), must be reported as separate SAEs by the investigator.

Suicidal ideation is given in the list of Always Serious AEs (see 5.2.6.1.3).

5.2.6.2.4 Female partner pregnancy

Potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies.

5.2.6.2.5 SUSAR reporting by the sponsor

Expedited reporting of suspected unexpected serious adverse reactions (SUSARs) will be performed by the Sponsor according to applicable regulations.

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 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 of nintedanib

For quantification of Nintedanib concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediamine-tetraacetic 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 venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 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 within 2 hours with interim storage of blood samples and aliquots at room temperature. 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, barcode, subject number, visit, and planned sampling time.

The back-up samples in period 2 can be used to get a profile of BI 1015550 after confirmation of the TBA about the successful analysis of NIN in the 1st aliquots.

5.3.2.2 Blood sampling for pharmacokinetic analysis of pirfenidone

For quantification of Pirfenidone concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediamine-tetraacetic 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 venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 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 within 2 hours with interim storage of blood samples and aliquots at room temperature. 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, barcode, subject number, visit, and planned sampling time.

The back-up samples in period 2 can be used to get a profile of BI 1015550 after confirmation of the TBA about the successful analysis of PIR in the 1st aliquots.

5.3.2.3 Blood sampling for pharmacokinetic analysis of BI 1015550

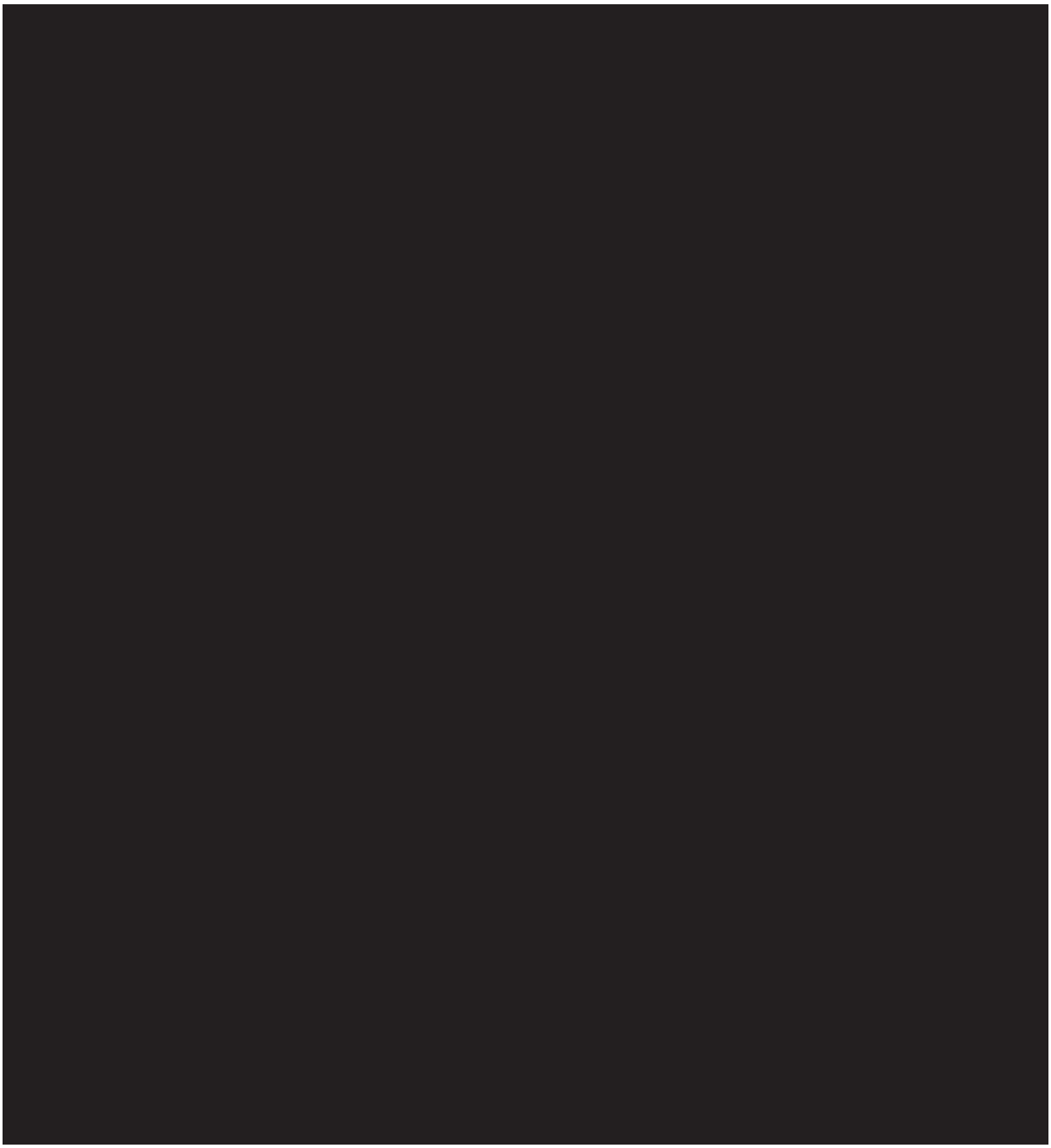
For quantification of BI 1015550 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediamine-tetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 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 within 2 hours with interim storage of blood samples and aliquots at room temperature. 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, barcode, subject number, visit, and planned sampling time.

After analysis, the plasma samples (NIN, PIR, BI 1015055) may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. 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 trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.



5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination or during Visit 2 from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

5.7 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 and the end of trial examination are provided in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, laboratory tests, ECG and for suicidality assessment will be ± 1 hour.

If scheduled in the Flow Chart at the same time as a meal, blood sampling and vital signs recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture 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

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 trial.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.6).

6.2.2 Treatment period

Each subject is expected to participate in 2 treatment periods: Period 1 (Reference Treatment, visit 2) and Period 2 (Test Treatment, visit 3) in the fixed order R-T. At least 72 hours will separate the last drug administration in period 1 and the first drug administration in period 2.

Period 1: In the evening of Day -1 trial participants will be admitted to the trial site and kept under close medical surveillance for at least 48 h. On Day 1 a single dose of PIR will be administered, on Day 2 a single dose of NIN. In the morning of Day 3 the subjects will then

be allowed to leave the trial site after formal assessment and confirmation of their fitness. Blood sampling until Day 5 will be performed in an ambulatory fashion.

Period 2: In period 2 subjects will be dosed with BI 1015550 twice daily for 10 days (from Day -6 until Day 4). Dosing is performed in an ambulatory fashion from Day -6 to Day -1. In the evening of Day -1 trial participants will be admitted to the trial site and kept under close medical surveillance for at least 48 h. On Day 1 a single dose of PIR will be administered, on Day 2 a single dose of NIN. In the morning of Day 3 the subjects will be dosed with BI 1015550 and thereafter they will be allowed to leave the trial site after formal assessment and confirmation of their fitness. Further dosing of BI 1015550 until the evening of Day 4 and further blood sampling until Day 5 will be performed in an ambulatory fashion.

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. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, suicidality assessment and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

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 EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of PIR and NIN given alone and together with BI 1015550 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.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial 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 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.

Descriptions of additional analysis sets may be provided in the TSAP.

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for nintedanib or pirfenidone will be calculated according to the relevant BI internal procedures.

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 the 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.

Important protocol deviations 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 experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- 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 are 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).

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints 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: subjects and treatment. The effect 'subjects' will be considered as random, whereas the effect 'treatment' will be considered as fixed. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,
μ = the overall mean,
s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n,
τ_k = the k^{th} treatment effect, k = 1, 2,
e_{km} = the random error associated with the m^{th} subject who received treatment k

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

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (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.

[redacted]

7.2.3 Secondary endpoint analyses

Not applicable.

[redacted]

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 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 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 time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed 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 1.2.4) 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 unblinding the trial 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 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.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures. Concentration data identified as NOS (no sample available), NOR (no valid result) or NOA (not analysed) are not considered in the evaluation (graphs and calculations). However, they are listed in the respective tables of the CTR. PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

Subjects receive all treatments in the same order, thus no randomisation for the treatment assignment is performed.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 14 subjects in the trial with the aim of ≥ 12 evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means

(test/reference) 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 healthy subjects was roughly 30% for C_{max} and 18% for AUC [1199-0161, 1199-0162, 1199-0239]. For pirfenidone, the observed intra-individual gCV% in IPF patients was roughly 18% for C_{max} and 15% for AUC [1199-0229]. Given that the variability in patients is generally higher than those in healthy subjects, these estimates were considered to be sufficient.

For various assumptions around the gCV of 30%, Table 7.5: 1 provides 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 7.5: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2-period fixed sequence trial *(N=12)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
25	1.273	100	78.55	127.31
25	1.273	150	117.83	190.96
25	1.273	200	157.10	254.61
30	1.334	100	74.99	133.36
30	1.334	150	112.48	200.03
30	1.334	200	149.98	266.71
35	1.396	100	71.65	139.56
35	1.396	150	107.48	209.34
35	1.396	200	143.31	279.12

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

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 4.2.1.

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 EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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. As a general rule, no trial results should be published prior to finalisation 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 Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject 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.

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 or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, 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.

ClinBase™
In the [redacted] Phase I unit – the validated ClinBase system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as database. Instead of being entered into CRFs, selected data are directly entered into the ClinBase™ system.

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: gender, 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.

Data directly entered into ClinBase™ (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ are available for inspection at any time.

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 the local requirements valid at the time of the end of the trial.

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
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.

8.5.1 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 have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage 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 (e.g. 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

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first subject in the whole trial signs informed consent.

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

Early termination of the trial is defined as the premature termination of the trial due to 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 IEC / competent authority in each participating EU member state 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.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT 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 local Clinical Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

[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 or a contract research organisation appointed 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.

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U06-1411-02	[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. 1199.17. 15 Jun 2011
U06-1724	[redacted] Metabolism and pharmacokinetics of [14C]-BIBF 1120 after administration of single doses of 100 mg [14C]-BIBF 1120 oral solution in healthy male volunteers. 1199.20. 03 Aug 2006
U07-1736-02	[redacted] Safety and relative bioavailability of a single dose of 150 mg BIBF 1120 administered as soft gelatine capsules charge 1 compared to BIBF 1120 soft gelatine capsules charge 2 compared to BIBF 1120. 1199.21. 30 Mar 2009
U10-1400-02	[redacted] Safety and tolerability of single rising doses of 1 mg, 3 mg, 10 mg, and 20 mg of BIBF 1120 as intravenous infusion (single-blind, placebo-controlled at each dose group) and absolute bioavailability of 100 mg BIBF 1120. 1199.75. 11 Jan 2010

U13-1925-01 [redacted] Relative bioavailability of nintedanib given alone and in combination with ketoconazole at steady state in healthy male volunteers (an open-label, randomised, two-way cross-over clinical Phase I study). 1199.161. 04 Jul 2013

U13-1478-01 [redacted] Relative bioavailability of a single oral dose of nintedanib given alone and in combination with multiple oral doses of rifampicin in healthy male volunteers (an open-label, two-period, fixed-sequence Phase I trial). 1199.162. 08 Aug 2013

c08883821-01 [redacted] Bioequivalence of 1 soft gelatine capsule containing 200 mg nintedanib compared to 2 soft gelatine capsules containing 100 mg nintedanib following oral administration in healthy male subjects. 1199.237. 13 Jun 2016

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		07 August 2023
EU number		2023-505522-34-00
BI Trial number		1305-0034
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		The effect of multiple oral doses of BI 1015550 on the pharmacokinetics of nintedanib and pirfenidone administered single dose to healthy male subjects (open-label, two-period, fixed-sequence crossover trial)

Substantial Global Amendment due to urgent safety reasons	☐
Substantial Global Amendment	☒
Non-substantial Global Amendment	☐

Section to be changed		1.) Synopsis, 2.1.2, 2.) Synopsis, 2.1.3, 7.2.1, 7.2.3 3.) Flow Chart 4.) Table 1.4.2:1 5.) 3.3.3 6.) 3.3.4.1 7.) 5.2.3 8.) 5.2.4 9.) 5.2.6.1.6 10.) 5.2.6.2.4 11.) 5.2.6.2.5 12.) 7.3.2
Description of change		1.) AUC0-inf. added to primary endpoints 2.) AUC0-inf. removed from secondary endpoints (no secondary endpoints) 3.) Screening interval reduced to Day -14 to -2. Safety laboratory moved from Period 2 / Day -6 to Period 1 / Day 5. 4.) Bleeding and proteinuria added as drug related risks of nintedanib;

			angioedema added as drug related risk of pirfenidone 5.) Exclusion criteria 12 (vaccination added) and 13 (half-life of IMP), 24 (duration of male contraception) adapted and new exclusion criteria 32-36 added (intake of prescriptine medicine, history of angioedema, thyroid dysfunction, history of bleeding disorder, proteinuria at screening) 6.) withdrawal in case of severe AE or SAE 7.) inclusion of additional safety laboratory (urinalysis only) 8.) use of QTcF described 9.) assessment of causality of AEs 10.) handling of female partner pregnancy 11.) SUSAR reporting added 12.) Handling of missing PK-data added
Rationale for change		1.-12.)	regulatory request

11.2 GLOBAL AMENDMENT 2

Date of amendment		05 October 2023
EU number		2023-505522-34-00
BI Trial number		1305-0034
BI Investigational Medicinal Product(s)		BI 1015550
Title of protocol		The effect of multiple oral doses of BI 1015550 on the pharmacokinetics of nintedanib and pirfenidone administered single dose to healthy male subjects (open-label, two-period, fixed-sequence crossover trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		1) Synopsis 2) Flow chart 3) 5.2.3 4) table 5.2.3.1 5) 5.6.1 6) 6.1
Description of change		1) Change of Clinical Trial Leader 2) Tolerance for safety lab Visit 2, Day 5 was adjusted 3) Fed/fasted status of laboratory measurements was adjusted 4) Urin haemoglobin and leucocyte measurements were adjusted to reflect nomenclature of laboratory provider. Legend of table 5.2.3.1 was adjusted to reflect flow chart. 5) Visit 2 added to sampling 6) Tolerance for ECG was included
Rationale for change		1) Organisational change at Sponsor 2-6) Clarification

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	05 Oct 2023 19:06 CEST
Approval-Clinical Program [redacted]		05 Oct 2023 22:44 CEST
Author-Clinical Trial Leader		06 Oct 2023 09:08 CEST
Verification-Paper Signature Completion		06 Oct 2023 10:04 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed