Boehringer Ingelheim

Clinical Trial Protocol

	Document Number: **c38933360-01**
EudraCT No.	2022-003119-27
BI Trial No.	1305-0030
BI Investigational Medicinal Product	BI 1015550
Title	Investigation of pharmacokinetics and absolute oral bioavailability of BI 1015550 administered as an oral dose with an intravenous microtracer dose of [^{14}C]-BI 1015550 in healthy male volunteers
Lay Title	A study in healthy men to test how BI 1015550 is taken up and handled by the body
Clinical Phase	I
Clinical Trial Leader	[redacted] On behalf of: [redacted] Phone: Fax:
[redacted] **Investigator**	[redacted] Phone:
Current Version, Date	Version 1.0, 12 Dec 2022
Original Protocol Date	12 Dec 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	12 December 2022
Revision date	Not applicable
BI trial number	1305-0030
Title of trial	Investigation of pharmacokinetics and absolute oral bioavailability of BI 1015550 administered as an oral dose with an intravenous microtracer dose of [^{14}C]-BI 1015550 in healthy male volunteers
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	This trial is intended to examine the absolute oral bioavailability of BI 1015550 as tablet formulation for oral administration, using an intravenous microtracer approach with [^{14}C]-labelled BI 1015550. These data are considered necessary to further support the understanding of the pharmacokinetics of BI 1015550
Trial objective	To determine the absolute oral bioavailability of BI 1015550
Trial endpoints	*Primary endpoints:* $AUC_{0-\infty}$ of [^{14}C]-BI 1015550 i.v. $AUC_{0-\infty}$ of BI 1015550 p.o. *Secondary endpoint:* Oral route: C_{max} of BI 1015550 p.o.
Trial design	Non-randomised, open-label, single period, single arm
Number of subjects **total entered** **on each treatment**	 8 8
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product	BI 1015550 as film-coated tablet (Treatment Test (T))
dose	[redacted]
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h
Reference product	BI 1015550 (C-14) as intravenous solution (Treatment Reference (R))
dose	[redacted] BI 1015550 consisting of [redacted] unlabelled BI 1015550 mixed with [redacted] labelled [^{14}C]-BI 1015550 in [redacted] intravenous solution ([redacted] BI 1015550 (C-14)/mL) The radioactive dose per infusion will be ~40 kBq
mode of admin.	Intravenous infusion of [redacted] mg tablet after an overnight fast of at least 10 h
Duration of treatment	<u>Oral dose (Treatment T):</u> [redacted] oral dose, Day 1 <u>Intravenous dose (Treatment R):</u> [redacted] intravenous infusion of microtracer over [redacted], Day 1
Statistical methods	Absolute bioavailability (F) will be estimated by the ratios of the geometric means (test/reference) for the primary endpoints $AUC_{0-\infty}$ (dose normalized). Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [12, 13]	PK plasma BI 1015550 [9]	PK plasma [14C]-BI 1015550 [9]	12-lead ECG [7, 13]	Vital signs (BP, PR) [10, 13]	Questioning for AEs and concomitant therapy [6]
1	-21 to -2			Screening (SCR)[1]	x[A]			x	x	
2	-1	[redacted]	[redacted]	Admission to trial site	x[B,5,12]					x
		[redacted]	[redacted]	Dinner						
		[redacted]	[redacted]	Snack (voluntary)						
	1	[redacted]	[redacted]			x[2]	x[2]	x[2]	x[2]	x[2]
		[redacted]	[redacted]	**Drug administration (BI 1015550, [redacted] tablet, oral)**						
		[redacted]	[redacted]			x				
		[redacted]	[redacted]			x				
		[redacted]	[redacted]			x		x		
		[redacted]	[redacted]	**Start of i.v. infusion of BI 1015550 (C-14)**		x[11]				x
		[redacted]	[redacted]				x			
		[redacted]	[redacted]				x			
		[redacted]	[redacted]	**Stop of i.v. infusion of BI 1015550 (C-14)**		x[11]	x[11]			x
		[redacted]	[redacted]	240 mL fluid intake		x	x	x		
		[redacted]	[redacted]				x			
		[redacted]	[redacted]			x	x			x
		[redacted]	[redacted]	240 mL fluid intake, thereafter lunch[3]		x	x			
		[redacted]	[redacted]				x			
		[redacted]	[redacted]			x	x			
		[redacted]	[redacted]	240 mL fluid intake			x			
		[redacted]	[redacted]	Snack (voluntary)[3]		x	x	x	x	x
		[redacted]	[redacted]	Dinner						
		[redacted]	[redacted]			x	x			x
	2	[redacted]	[redacted]			x	x			
		[redacted]	[redacted]		x[B,12]	x	x	x	x	x
		[redacted]	[redacted]			x	x			x
	3	[redacted]	[redacted]			x	x			x
	4	[redacted]	[redacted]			x	x	x	x	x
		[redacted]	[redacted]	Breakfast (voluntary)[3], discharge from trial site						
	6	[redacted]	[redacted]	Ambulatory visit	x[B]	x	x			x
	8	[redacted]	[redacted]	Ambulatory visit		x	x			x
	10	[redacted]	[redacted]	Ambulatory visit			x			x
3	11-21			End of study (EoS) examination[4]	X[A]			x	x	x

A, B Letters A and B describe different sets of safety laboratory examinations (see Table 5.2.3: 1).

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, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed between waking up and (still prior to) drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. [redacted]
5. Drug and alcohol screening will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the times indicated in the Flow Chart above. If no particular time is indicated, AEs and concomitant therapies will be checked twice daily (morning and evening) until discharge.
7. 12-lead ECG for clinical evaluation by the investigator only. For details of 12-lead ECG, refer to Section 5.2.4. If several assessments are planned at the same time, ECG should be performed before vital signs, which will be followed by blood samples.
8. Time window for ambulatory visits is [redacted]
9. For details of PK blood sampling (including samples for the quantification of BI 1015550 concentrations in plasma, [^{14}C]-BI 1015550, and total radioactivity in plasma), refer to Section 5.3.2. Up to 2.5 h following the administration of BI 1015550 tablets, samples should be taken within [redacted] from the scheduled time; from [redacted] until discharge, samples should be taken within +/- 5% of the elapsed time since BI 1015550 tablets were taken. After discharge, samples should be taken in line within the time window for ambulatory visits (cf. footnote 8).
10. For details of vital signs evaluation, refer to Section 5.2.2.
11. PK samples will be taken before the start of infusion and after the end of infusion, respectively.
12. PCR testing for SARS-CoV-2 will be performed on Day -1 prior to admission, and on Day 2. PCR testing for SARS-CoV-2 may be performed additionally as needed based on the current status of the pandemic. SARS-CoV-2 testing on Day 2 may take place at any time during this day.
13. Up to [redacted] following the administration of BI 1015550 tablets, all safety assessments should be done within [redacted] of the planned time; from [redacted] until discharge, all safety assessments should be done within +/- 10% of the elapsed time since BI 1015550 tablets were taken. After discharge, samples should be taken in line within the time window for ambulatory visits (cf. footnote 8).

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

^{14}C (also C-14)	Carbon 14 (radiolabelled)
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALAT	Latin American Thoracic Association
ALT	Alanine aminotransferase
AMS	Accelerator Mass Spectrometry
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
AUC_{0-24}	Area under the concentration-time curve (zero to 24 h)
$AUC_{0-24,ss}$	Area under the concentration-time curve (zero to 24 h) at steady state
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
cAMP	Cyclic adenosine monophosphate
[redacted]	[redacted]
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
COVID-19	SARS-CoV-2 induced disease
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P
DILI	Drug induced liver injury

ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EoS	End of Study (synonym for End of Trial)
ERS	European Respiratory Society
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
iCF	Intended commercial formulation
ICF	Informed consent form
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
INR	International Normalized Ratio
IPF	Idiopathic pulmonary fibrosis
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
JRS	Japanese respiratory society
KMed	Knowledge Management Medicine
K2-EDTA	Dipotassium ethylenediaminetetraacetic acid
[redacted]	[redacted]
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
[redacted]	[redacted]
[redacted]	[redacted]
PDE	Phosphodiesterases
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PPF	Progressive pulmonary fibrosis

PR	Pulse rate
QTc	Corrected QT interval
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
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SCR	Screening
SOP	Standard operating procedure
ss	(at) steady state
SUSARS	Suspected unexpected serious adverse reactions
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
[redacted]	[redacted]
TSAP	Trial statistical analysis plan
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
UIP	Usual interstitial pneumonia
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
WHO	World Health Organisation

1. INTRODUCTION

BI 1015550 is a selective inhibitor of the phosphodiesterase 4B (PDE4B) isoenzyme which hydrolyses and inactivates cyclic adenosine monophosphate (cAMP) and shows broad anti-inflammatory and anti-fibrotic activities. It is under development for the treatment of idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis (PPF). This trial is intended to examine the absolute oral bioavailability of BI 1015550 as tablet formulation for oral administration. These data are considered necessary to further support the understanding of the pharmacokinetics of BI 1015550.

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) [P22-03204]. Apart from IPF, 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 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, P20-01299, P22-03204, R19-0854].

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].
Preclinical experiments have shown that BI 1015550 affects the fibrotic pathway and the effects may be complementary and/or synergistic to those of nintedanib. PDE4 inhibition is expected to inhibit pro-fibrotic growth factors, to decrease fibroblast proliferation, transformation of fibroblast to myofibroblast, and fibroblast motility, as well as to promote cell death of fibroblasts, and to decrease synthesis, release, and function of extra-cellular matrix components [R12-5544, R12-5545, R12-5546]. Interference with pro-fibrotic factors/ inflammatory cascades may translate in clinical improvement of lung function, symptoms, and quality of life in patients with IPF.

Based on this, it is postulated that BI 1015550 may provide therapeutic benefit to patients with IPF or other forms of progressive pulmonary fibrosis.

1.2 DRUG [redacted]

BI 1015550 is a potent inhibitor of human PDE4 B, showing mean half-maximal inhibition (IC50) at [redacted] with a nine-fold selectivity over phosphodiesterase 4D (PDE4 D) (mean IC50 [redacted]) without relevant known interaction with other targets (78 receptors and 42

enzymes tested at the very high concentration of [redacted]). In-vitro anti-inflammatory activity has been confirmed for TNF-α (IC50: [redacted]) and IL-2 release (IC50: [redacted]) from purified human peripheral blood mononuclear cells respectively.

Drug drug interactions
BI 1015550 is mainly metabolized by CYP3A with minor contributions from Uridine Diphosphoglucuronosyl Transferase. Administration of BI 1015550 together with a strong CYP3A4 inhibitor increased AUC of BI1015550 [redacted] and Cmax [redacted] [c24902949]. Based on in-vitro evaluation, BI 1015550 has the potential to induce CYP3A4.

Data from non-clinical studies
The toxicity profile for BI 1015550

The toxicity profile for BI 1015550 has been assessed in safety pharmacology studies, genetic toxicology studies, and repeat dose studies in the rat, minipig, and monkeys of up to 26, 39, and 13 weeks, respectively.

Vasculopathy and mortality secondary to vasculopathy are the primary findings defining the no adverse effect level (NOAEL) and lowest observed adverse effect Level (LOAEL) in the rat and minipig, respectively. In contrast, vascular changes were not observed in a 13-week monkey study at [redacted], supporting the decreased sensitivity of primates to PDE4i-induced vascular changes. Vasculopathy is a well characterized class-effect pathology associated with PDE4 inhibitors [R10-1559] and has not been demonstrated in humans administered marketed PDE4i apremilast and roflumilast.

In addition, a fertility and early embryonic development (rat) and embryo-fetal development toxicity studies (rat and rabbit) were conducted. Decreased mating, fertility, and pregnancy indices were observed in male and female rats at a dose level that also level caused evidence of severe toxicity in both sexes. In rats but not in rabbits foetal loss was increased.

Teratogenicity and fetotoxicity was not observed. In long-term toxicity studies in rats (26-weeks), minipig and monkeys (13-weeks) there was no microscopic evidence of changes in female reproductive organs or on male spermatogenesis.

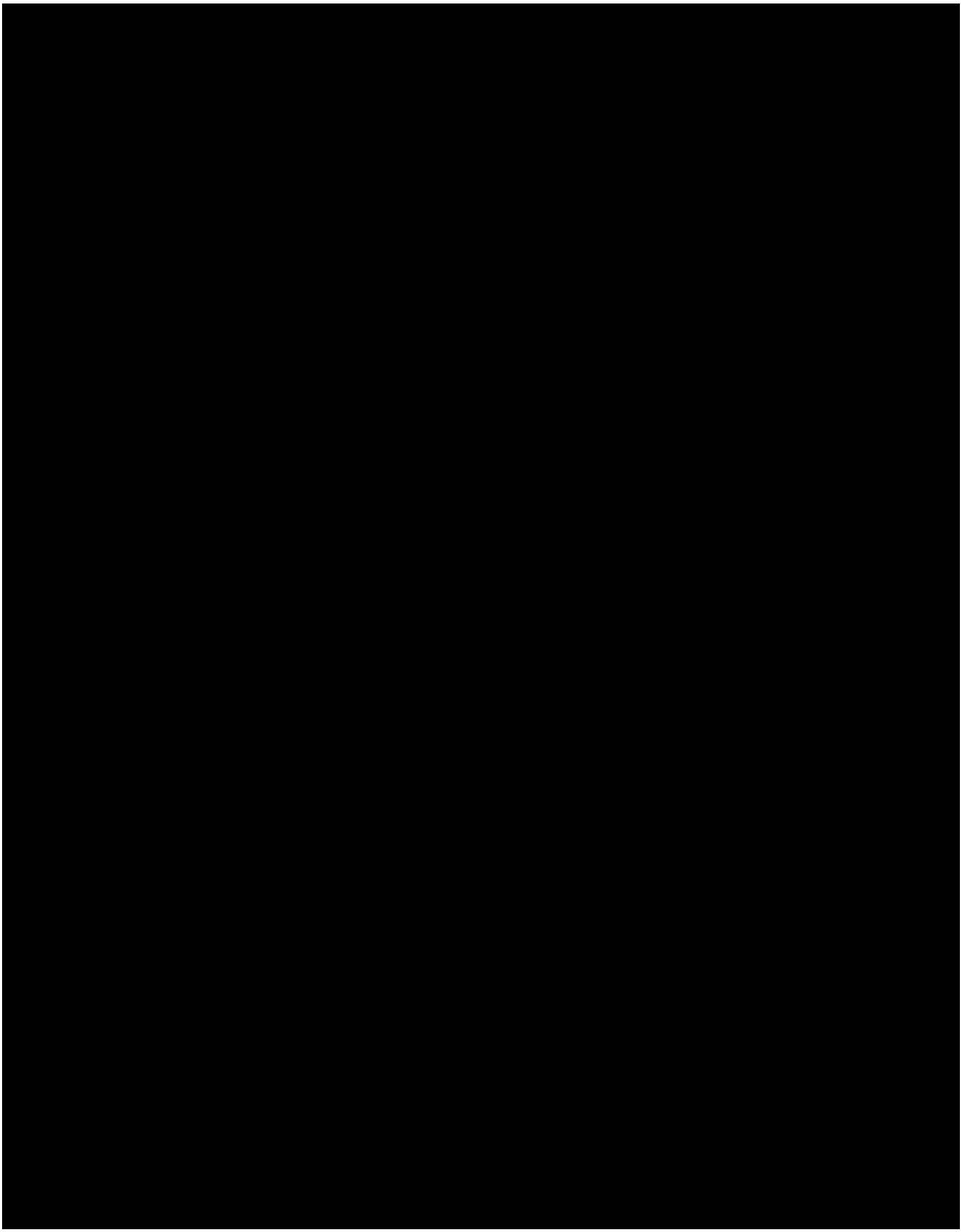
For a more detailed description, please refer to the current Investigator's Brochure (IB) [c02094779].

[redacted]

1.2.2 Clinical safety and efficacy

BI 1015550 has been investigated in a total of nine clinical studies: eight Phase I trials (seven trials in healthy subjects and one in patients with IPF), and a proof-of-clinical principle Phase II trial in patients with IPF. Overall, 146 healthy volunteers and 107 patients with IPF have been exposed to BI 1015550.

BI 1015550 was well tolerated following single dose administration up to [redacted] in healthy volunteers and following multiple administrations [redacted] over a treatment period of up to 12 weeks in patients.



Clinical efficacy

In the proof-of-clinical principle Phase II trial, a relevant treatment effect in favour of BI 1015550 [redacted] was observed on the primary efficacy endpoint, the change from baseline in forced vital capacity (FVC) at 12 weeks. Treatment with BI 1015550 prevented a decline in FVC in patients with IPF, irrespective of background antifibrotic treatment, in contrast to the placebo groups in which a marked decline in FVC was observed. Thus, treatment with BI 1015550 [redacted] preserved lung function in patients with IPF over 12 weeks.

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the absolute oral bioavailability of BI 1015550 as tablet formulation for oral administration, using an intravenous microtracer approach with [^{14}C]-labelled BI 1015550. These data are considered necessary to further support the understanding of the pharmacokinetics of BI 1015550.

1.3.1 Nomenclature

In this clinical trial protocol, the following nomenclature is used:

- [^{14}C]-radioactivity: Radioactivity measured by means of isotope ^{14}C
- [^{14}C]-BI 1015550: BI 1015550 compound labelled with ^{14}C (“hot” drug substance)
- BI 1015550: non-radioactive compound (“cold” drug substance)
- BI 1015550 (C-14): Final drug product containing radioactive microtracer, mixture of “hot” and “cold” drug substance

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, and thus is expected to be of benefit for future patients receiving this drug.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.
There are no identified risks for BI 1015550, based on the toxicology program or any clinical trials conducted for this product to date. Vasculitis and foetal loss are considered as important potential risk based only on non-clinical findings (see Section 1.2).

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs and from preclinical and clinical data of compounds with a comparable mode of action. For adverse events reported during clinical trials with BI 1015550 please refer to Section 1.2.2.

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
Investigational Medicinal Product: BI 1015550 as film-coated tablet		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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
Investigational Medicinal Product: BI 1015550 as film-coated tablet		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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
Investigational Medicinal Product: BI 1015550 as film-coated tablet		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Reference Product: BI 1015550 (C-14) as intravenous solution		
[redacted]	[redacted]	[redacted]
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, or by indwelling venous catheter for the purpose of intravenous infusion and/or blood sampling; acceptable in the framework of trial participation.	Medical expertise of the trial site.
Loss of blood due to blood samples	The total volume of blood withdrawn during the entire study per subject will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.	Close monitoring and follow-up of trial subjects for any adverse events.

Considerations on male contraception requirements:

The exposure through seminal fluid to sexual partners of males receiving BI 1015550 is expected to be minimal. At a plasma BI 1015550 Cmax of [redacted] dose, the worst-case seminal fluid level is anticipated to be [redacted]. Assuming a seminal fluid volume of 5 mL, a worst-case 100% absorption from the vagina, and a plasma volume of 3.5 L, the resultant plasma concentration in the woman would be [redacted]. This concentration is approximately [redacted] fold below the most conservative maximum plasma level of [redacted] at the NOAEL in rats in a fertility and early embryonic development study [n00290709], and in EFD studies in rats and rabbits. This large safety margin, the absence of dysmorphogenesis in two species, and lack of genotoxicity suggest that barrier methods of contraception should not be required for a male administered BI 1015550 [c39775503].

Considerations on COVID-19:

Generally, in a healthy volunteers' population, the risk of severe COVID-19 infection is not higher, and study participation would not increase the risk of becoming infected with SARS-CoV-2 beyond the potential risk associated with any need for the study participant to leave their home for study-related activities. The appropriate risk minimisation measures will be taken in accordance with the public health precautions if needed due to the current status of the pandemic.

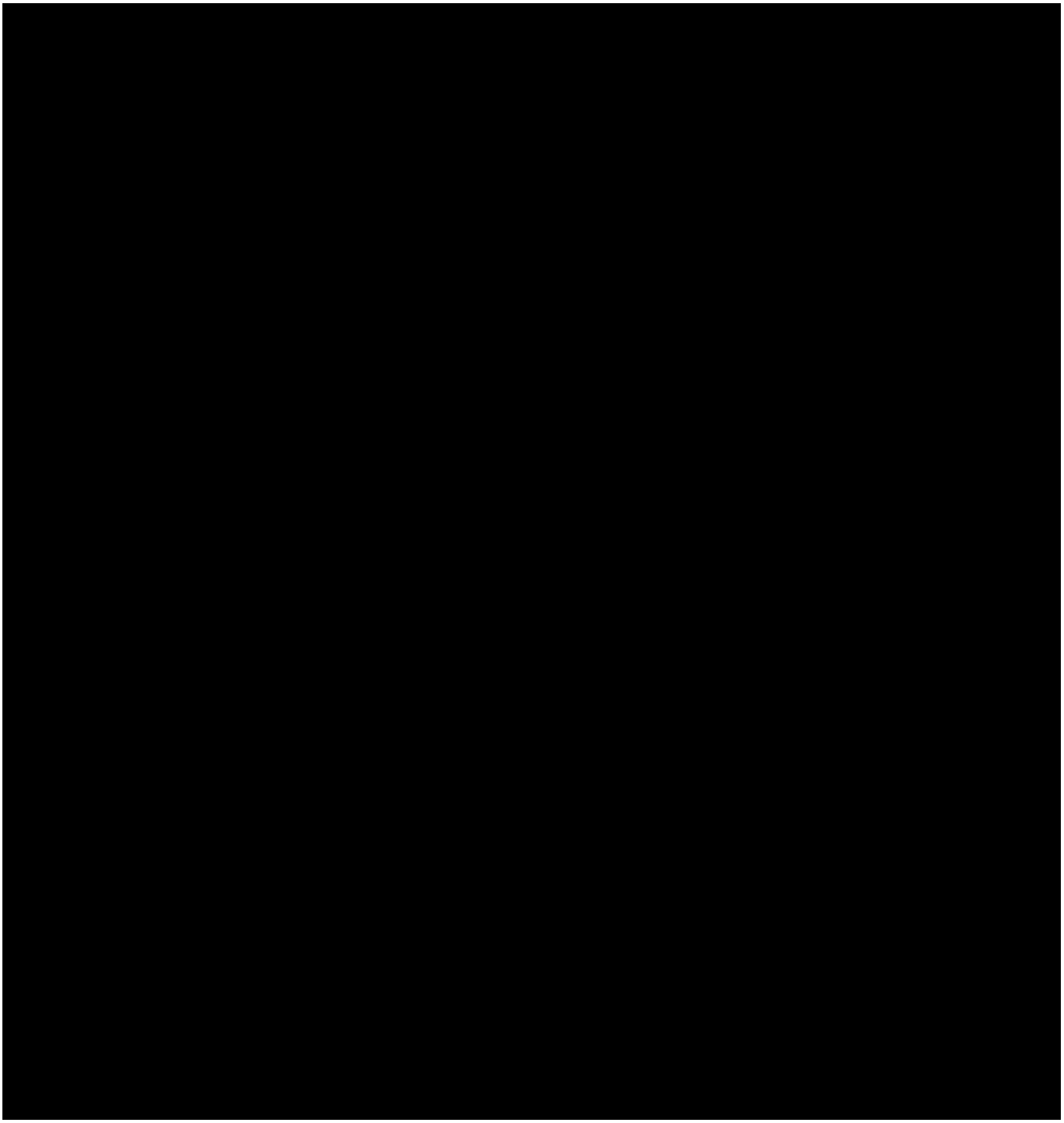
Based on the pharmacological mechanism and existing non-clinical and clinical data, there is no indication that treatment with BI 1015550 may increase the risk of infection including SARS-CoV-2 infection. Even though an increased risk of SARS-CoV-2 infection or of a more severe COVID-19 disease in case of such an infection appears unlikely, subjects with active or recent (i.e., within the 4 weeks prior to screening) SARS-CoV-2 infection should not be included in the trial (cf. exclusion criterion No. 25) which also applies to any other relevant acute infection.

In case of severe COVID-19 infection during the conduct of the trial, treatment with BI 1015550 will not be given which also applies to any other relevant acute infection (cf. criterion of withdrawal from trial treatment No. 4).

Of note, depending on the current status of the COVID-19 pandemic, all subjects with confirmed SARS CoV-2 infection will be handled in accordance with local guidance and SOPs, i.e., any confirmed SARS-CoV-2 infection during the conduct of the trial will lead to withdrawal of the affected subject from further trial procedures to avoid undue risks to other subjects at the trial site and the site personnel. Appropriate diagnostic and treatment measures will be taken in accordance with the public health precautions. If feasible, the EoS examination should be performed as early as possible after the SARS-CoV-2 infection has resolved.

1.4.3 Discussion

Seven clinical studies in healthy subjects have been completed with BI 1015550 so far. Overall, BI 1015550, [redacted] appeared to



2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the absolute oral bioavailability [redacted] of BI 1015550 administered as film-coated tablet (Test, T) compared with [redacted] [^{14}C]-BI 1015550 administered as intravenous microtracer (the total dose administered intravenously is a mixture of [redacted] unlabelled BI 1015550 and [redacted] labelled [^{14}C]-BI 1015550) (Reference, R) following oral administration.

2.1.2 Primary endpoint(s)

The following pharmacokinetic parameters will be determined for [^{14}C]-BI 1015550 in plasma after intravenous (i.v.) administration as well as for BI 1015550 after oral (p.o.) administration:

- $AUC_{0-\infty}$ of [^{14}C]-BI 1015550 i.v.
- $AUC_{0-\infty}$ of BI 1015550 p.o.

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 1015550 after oral administration:

- C_{max} (maximum measured concentration of the analyte in plasma) of BI 1015550 p.o.

[redacted]

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)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)
- Local tolerability assessed by investigator (based on swelling, induration, heat, redness, pain, and other clinically relevant findings reported as AE after intravenous infusion)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

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

To investigate the absolute bioavailability a single arm, single period trial design using a microtracer approach was considered favourable as compared to the traditional cross-over design used for absolute bioavailability studies. In this context 'microtracer' is defined as an intravenous dose of an isotopically labelled drug in an absolute bioavailability study administered as 1% of the pharmacologic dose or 0.1 mg, whichever is lower [R17-1799]. Reasons favouring the microtracer approach:

- Like in a traditional cross-over design each subject serves as their own control removing inter-subject variability. However, additionally day to day variability within a subject is also eliminated as potential confounding variable as each subject is exposed to the two treatments in parallel, i.e., treatment R will be administered at T_{max} of treatment T

- Expected favourable safety due to very low radioactive exposure after an intravenous microdose

- The radioactive dose per infusion has been calculated to be 40 kBq, thereby not exceeding the ICRP 1 limit for administration of [^{14}C]-BI 1015550, i.e., trivial level of risk [R18-1836, R18-2184].

- Reduced duration of the clinical trial

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 8 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

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 65 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (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 40 to 100 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
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 (including but not limited to major depressive disorder or history of suicide attempts)
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 or squamous cell carcinoma in situ 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 (or 5 half-lives, whichever is longer) of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation, potent CYP3A4 inhibitors, selective and non-selective PDE inhibitors, based on investigator judgement, as well as vaccination of any kind with or without re-vaccination required during the course of the trial)
13. Intake of an investigational drug in another clinical trial within 60 days (or 5 half-lives, 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 (more than 5 cigarettes or 1 cigar or 1 pipe per day)
15. Inability to refrain from smoking on specified trial days
16. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits)
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 4 days prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site and life-style restrictions of the clinical trial protocol
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) 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

In addition, subjects will not be allowed to participate, if any of the following trial-specific criteria apply:

24. A medical history of vasculitis
25. Persistent symptoms of known prior COVID-19 infection and/or laboratory test indicative of an ongoing SARS-CoV-2 infection within 4 weeks prior to the administration of trial medication

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 1.2.3), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 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 the subject 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, adverse events (AEs), or diseases)
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

6. In addition to these criteria, the investigator may discontinue subjects at any time based on their clinical judgment.

Even if trial treatment is discontinued, the subject will remain in the trial and, given their agreement, will undergo the end of study procedures outlined in the Flow Chart and Section 6.2.3.

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, or the contract with BI 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 more than two subjects have drug-related severe non-serious adverse events, or if at least one drug-related serious adverse event is reported

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

3.3.5 Replacement of subjects

If data from fewer subjects than the required number of subjects are considered evaluable (including subjects non-evaluable for PK), enrolment of additional subjects (replacement subjects) will be considered if deemed necessary in order to reach the objective of the trial. For subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event, no additional subjects will be enrolled. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide if and how

many subjects will be enrolled additionally. A replacement subject will be assigned a unique trial subject number and will receive all treatments of this single arm. Note that data from the subjects to be replaced and data from subjects who withdraw or are withdrawn (after trial drug intake) will be included in the safety analysis.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product (test product) BI 1015550 (film-coated tablets for oral administration) has been manufactured by BI Pharma GmbH & Co. KG.

Radiolabelled BI 1015550 (C-14) solution for intravenous administration (reference product) consists of [redacted] [^{14}C]-labelled BI 1015550 and [redacted] unlabelled BI 1015550, manufactured by BI Pharma GmbH & Co. KG. The final solution for infusion from both components is manufactured by the pharmacy of the trial site ([redacted]).

Refer to Section 1.3.1 for nomenclature.

[redacted]

4.1.2 Selection of doses in the trial

The dose selected for this trial is one single oral dose of [redacted] BI 1015550, which is below the highest single dose of BI 1015550 already tested in previous single-dose trials ([redacted], see Section 1.2) and in line with the currently planned therapeutic dose [redacted].

A dose of [redacted] 1015550 [redacted] has been tested over 12 weeks in patients in phase II study 1305-0013. In healthy volunteers, a single dose [redacted] was safe and well-tolerated (see Section 1.2) and is considered adequate for the objectives of this trial.

Using the microtracer approach to investigate the absolute bioavailability the intravenously administered dose is not expected to significantly add to the systemic drug concentrations arising from the oral administration [R17-1799]. The oral dose ([redacted] BI 1015550) is [redacted] higher than the intravenously infused dose ([redacted] BI 1015550 (C-14)).

Therefore, the exposure to the radiolabelled compound [^{14}C]-BI 1015550 originating from the infused microtracer is considered negligible (refer to Section 1.4).

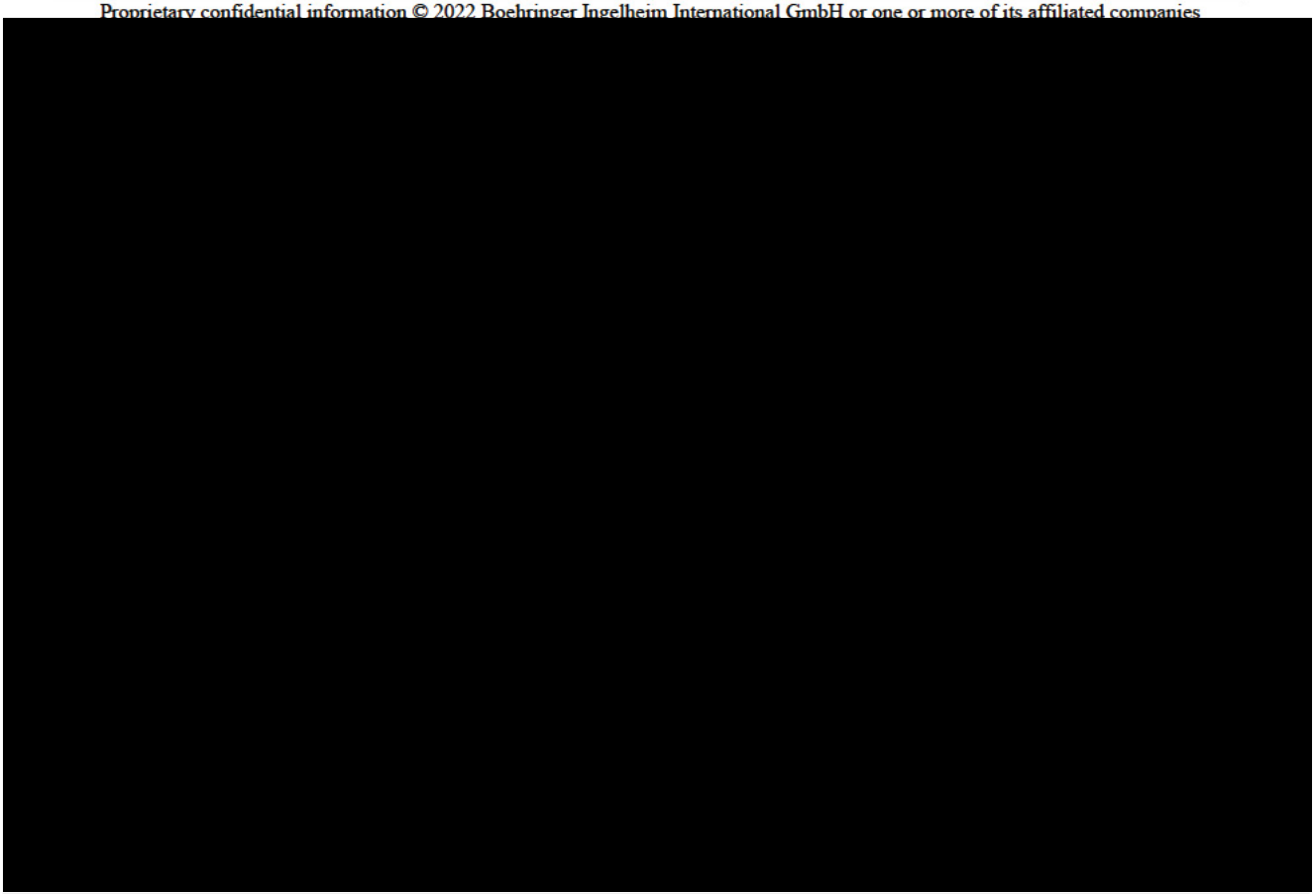
4.1.3 Method of assigning subjects to treatment groups

This is an open-label, phase I, [redacted]-dose study. All subjects receive the same treatment and same dose. There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (T-R). At screening, subjects will receive a screening number. Eligible subjects will be allocated to a trial subject number prior to the administration of trial medication in the morning of [redacted] of [redacted].

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. For discussion of trial-associated risks and safety measures, see Section 1.4.

[redacted]



4.1.5 Blinding and procedures for unblinding

This non-randomised open-label 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 investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany will provide film-coated tablets of BI 1015550 (treatment T) (in blisters of 8 tablets per blister with 2 blisters per carton) to the trial site's pharmacy.

[redacted] will provide radiolabelled [^{14}C]-BI 1015550 as well as non-radioactive BI 1015550 to the pharmacy at [redacted]. [redacted] is responsible for drug product manufacturing under GMP and preparation of the solution for i.v. infusion of BI 1015550 (C-14) (treatment R) under GCP.

Trial medication will be labelled according to GMP Annex 13 / EU GMP guideline and local drug law.

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

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

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 site's pharmacy will prepare the dosing units for infusion of BI 1015550 (C-14) (for treatment R) and will receive the film-coated tablets of BI 1015550 (for treatment T) from the sponsor once the below mentioned requirements are fulfilled. The pharmacy will deliver both the film-coated tablets (treatment T) and the solution for infusion (treatment R) to the investigator upon availability of a valid prescription from the investigator.

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- Approval/notification of the regulatory authority, e.g., competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol
- Availability of licence for clinical research using radioactive isotopes

Only authorised personnel documented on 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. If necessary, short-term use of paracetamol is acceptable for symptomatic treatment of AEs. In case of adverse events necessitating treatment, the required concomitant therapy and medical treatment will be permitted. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

CYP3A4 is regarded as the major enzyme responsible for the metabolism of BI 1015550. Therefore, potent CYP3A4 inhibitors are specifically restricted in this trial. Refer to Appendix 10.2 for a list of potent CYP3A4 inhibitors.

4.2.2.2 Restrictions on diet and lifestyle

While admitted to the trial site, subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least [redacted] after the administration of BI 1015550 tablet.

From [redacted] before the administration of BI 1015550 tablet until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at [redacted] post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages are not allowed 48 hours before the administration of BI 1015550 tablet and during in-house confinement at the site. During the ambulatory phase alcohol consumption is restricted to a maximum of 2 units per day (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits).

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 [redacted] before the administration of BI 1015550 tablets until after the last PK sample is collected. Consumption of poppy-seed containing products is not permitted within [redacted] prior to drug screening (at Screening visit and on Day -1).

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from [redacted] before until [redacted] after the administration of BI 1015550 tablet.

Smoking is not allowed during in-house confinement.

Excessive physical activity (such as competitive sports) should be avoided from [redacted] before the administration of trial medication until the end of study examination.

4.2.2.3 Contraception requirements

Not applicable

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, and a physical examination. At the end of study (end of trial) examination, assessments will include the review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of body weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by an automated blood pressure monitor 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 safety laboratory evaluation at the Screening visit, Day -1 and End of Study visit, a 4 h fast is sufficient, respectively. 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.

SARS-CoV-2 testing will be conducted as specified in the Flow Chart.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	Reticulocytes, absol.	X	X
	Reticulocytes/Erythrocyte	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leucocytes; Eosinophils/Leucocytes; Basophils/Leucocytes; Monocytes/Leucocytes; Lymphocytes/Leucocytes	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 and according to [redacted]'s lab standards)	Neutr. Poly (segs)/Leucocytes [%]; Eosinophils/Leucocytes [%]; Basophils/Leucocytes [%]; Monocytes/Leucocytes [%]; Lymphocytes/Leucocytes [%]		
Manual differential red blood cell count (if there is an abnormality in the blood cell count in accordance with Clinical laboratory [redacted] standard procedures)	Only positive findings will be reported (for instance the presence of microcytes)		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time – INR (International Normalized Ratio)	X	X
	Fibrinogen	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
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Serum)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglycerides	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
Urine sediment (examinations will only be performed if there is an abnormality in urinalysis in accordance with Clinical Laboratory, standard procedure)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

A: parameters to be determined at Visit 1 (screening examination) and Visit 3 (end of trial examination)
B: parameters to be determined at Visit 2 on Day -1, Day 2 and Day 6 (for time refer to Flow Chart)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and on Day -1, prior to the treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Alcohol Amphetamine/MDA[1] including Ecstasy Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA[2] Opiates Phencyclidine
Drug screening (blood)	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV[3]-1 and HIV[3]-2 antibody (qualitative)

1: Methylenedioxyamphetamine
2: Methylenedioxymethamphetamine
3: Human Immunodeficiency Virus

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the laboratory of [redacted]

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 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.

All ECGs will be stored electronically.

ECG printouts will be provided. All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (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 Local tolerability

Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings. Local findings assessed as clinically relevant by the investigator must be recorded as AE.

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, 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 eDC. 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.
- Vasculitis
  In this trial protocol vasculitis is defined as any adverse event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels. 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 (suspected) event of vasculitis, further work-up and management as outlined has to be followed, including biopsy, appropriate imaging/angiography, laboratory measures (e.g., ESR, additional lab sample for immunological and further inflammation markers).
- Severe infections, serious infections, opportunistic or mycobacterium tuberculosis infections (refer to Appendix 10.1 for a list of severe infections considered as AESI)

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.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

Upon enrolment into a trial, 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 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 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 investigator must report any drug exposure during pregnancy immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form for Clinical Studies to the sponsor's unique entry point.

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

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

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

For quantification of BI 1015550 concentrations in plasma, 2.7 mL of blood will be required. Blood will be drawn from an antecubital or forearm vein into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

For quantification of [^{14}C]-BI 1015550 concentrations in plasma, an additional 2 mL of blood needs to be collected in a K_2-EDTA tube at the times indicated in the Flow Chart.

For quantification of total radioactivity in plasma, 9 mL of blood needs to be collected at pre-dose and 2 mL of blood needs to be collected in a K_2-EDTA tube at all other 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.

Details about blood sample collection, plasma preparation, required tubes, labelling of tubes, storage, and shipment (addresses) will be provided in the Laboratory Manual. At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

After analysis, the plasma samples 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.

[redacted]

[redacted]

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 the administration of trial medication. Safety assessments are standard, are accepted for the evaluation of safety and tolerability of an orally and intravenously administered drug and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments for drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The acceptable time windows for screening visit and the end-of-study examination are provided in the Flow Chart. Exact times of measurements outside of the permitted time windows will be documented.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed between waking up and (still prior to) trial drug administration.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be [redacted] until [redacted] after trial drug administration and ± 10% of the time window of elapsed time since last medication dosing thereafter.

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

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.

For logistical reasons, ambulatory visits may take place within [redacted] of the scheduled time.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

From obtaining the subject's informed consent onwards, AEs and AESIs will be collected unless a subject discontinues from the trial due to screening failure prior to the 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. Please refer to Section 5.2.6.2.1.

[redacted]

6.2.3 Follow-up period and trial completion

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

Subjects who discontinue treatment or study procedures before the planned end of trial should undergo the EoS Visit.

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The main objective of this trial is to investigate the absolute oral bioavailability of [redacted] BI 1015550 administered as tablet (Test, T) compared to [redacted] [^{14}C]-BI 1015550 administered as intravenous microtracer (mixed with [redacted] unlabelled BI 1015550) (Reference, R) on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and Section 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model for logarithmically transformed PK endpoints.

[redacted]

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

7.1 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this trial.

The absolute bioavailability of [redacted] orally administered BI 1015550 (Test, T) compared to [redacted] [^{14}C]-BI 1015550 administered as intravenous microtracer (mixed with [redacted] unlabelled BI 1015550) (Reference, R) will be estimated by the ratios of the geometric means (test/reference) for the dose normalized primary PK endpoints. Additionally, their 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.

Confidence intervals and p-values will be computed, but have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects, while p-values are considered as an exploratory measure of evidence for effects in the present data.

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 not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in Section 7.2.1.2). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value 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 drug BI 1015550 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
- Incorrect duration of infusion
- 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
- The subject did not receive the complete assigned infusion volume

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 'formulation'. The effect 'subjects' will be considered as random, whereas the 'formulation' effect 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 (dose normalized) measured on subject m receiving formulation k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 12

τ_k = the k^{th} formulation effect (either tablet or i.v.), k = 1, 2,

e_{km} = the random error associated with the m^{th} subject who received formulation 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

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

7.2.5 Safety analyses

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

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the assigned 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 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 (test treatment) will be assigned to the screening period, those between first trial medication intake and beginning of reference treatment will be assigned to test treatment period. Those between the start of infusion until the end of REP (see Section 1.2.3) will be assigned to the combined test/reference treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to ’follow-up’. 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 database lock of 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.

In general, unless otherwise specified in the TSAP, the last non-missing measurement prior to study treatment will be used as baseline for safety variables.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values 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.

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

7.4 RANDOMISATION

This is a non-randomised trial. All subjects will receive the same treatments in the same order.

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory trial, no prospective calculations of statistical precision or power have been made. The planned sample size of 8 subjects is considered sufficient to get reliable results regarding the trial objectives. This sample size accounts for up to 2 dropouts or non-evaluable subjects in order to have at least 6 subjects who completed the trial as per protocol.

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 directive 2001/20/EC, 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 webpage: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to 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 (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan 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.

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.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 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 form (ICF)
- 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 the 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, 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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted] under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g., their curricula vitae) will be filed in the ISF. 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 Manager (CT Manager), Clinical Research Associate (CRA), and investigators of participating trial site

In the participating country the trial will be supported by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs.

The trial medication will partly be provided by the [redacted], and partly by the CRO ([redacted] Non-radiolabelled BI 1015550 (film-coated tablets for oral administration) will be manufactured and provided by BI Pharma GmbH & Co. KG. The non-radiolabelled and [^{14}C]-labelled BI 1015550 compound for intravenous administration will be manufactured and provided by BI Pharma GmbH & Co. KG. The final solution for infusion from both components is manufactured by [redacted]. Refer to Section 4.1 for further details on trial medication.

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

Analyses of (non-radiolabelled) BI 1015550 concentrations in plasma will be performed at [redacted]

Analyses of [^{14}C]-labelled BI 1015550 via [redacted] will be conducted at [redacted].

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

Data management and statistical evaluation will be done by BI and/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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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P17-10582 [redacted]

P18-04729 [redacted]

P18-06345 [redacted]

P19-01738 [redacted]

P20-01299 [redacted]

P22-03204 [redacted]

R10-1559 [redacted]

R12-5544 [redacted]

R12-5545 [redacted]

R12-5546 [redacted]

R17-1799 [redacted]

R17-2617 [redacted]

R18-1836 [redacted]

R18-2184 International Commission on Radiological Protection (ICRP). Radiological protection in biomedical research: a report of Committee 3 adopted by the International Commission on Radiological Protection (adopted by the Commission in November 1992) (ICRP publication 62). Ann ICRP;1992;22(3);1-28.

R19-0854 [redacted]

9.2 UNPUBLISHED REFERENCES

c02094779 [redacted] Investigator's Brochure BI 1015550 for 1305.P3, current version.

c02191718 Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 1015550 powder for oral solution in healthy male volunteers q.d. or bid for 14 days (a randomised, double-blind, placebo-controlled within dose groups Phase I trial). 1305.2.

c20307414 Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects. 1305-0020.

c22991937 Safety, tolerability and pharmacokinetics of single and multiple rising oral doses of BI 1015550 in healthy subjects. 1305-0011.

c24902949 Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects. 1305-0015.

c25085412 Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy. 1305-0012.

c36151567 A Phase I, open-label, non-randomized, single-dose, single-arm, single-period study to investigate the metabolism and pharmacokinetics of [C-14]-labelled BI 1015550 after oral administration in healthy male subjects. 1305-0016.

c37065416 A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally. 1305-0013.

c39775503 [redacted] Assessment of requirement for male contraception. Memo. 09 June 2022

n00201897 In vitro determination of BI 1015550 protein binding in human and animal plasma and in human serum albumin and α1-acid glycoprotein solutions. (DM-11-1046).

n00201905 In vitro blood cell partitioning of 14C-BI 1015550 in rat, Göttingen minipig, and human blood. (DM-11-1045).

n00261666 BI 1015550: Metabolite profiling in plasma after multiple oral administration to healthy volunteers and metabolite exposure determination in human and the relevant toxicity species.

n00290709 A fertility and early embryonic development to implantation study of BI 1015550 by oral gavage in male and female rats. CRL study no. 9001829, BI no. 21R070.

10. APPENDICES

10.1 APPENDIX 1: SEVERE INFECTIONS CONSIDERED AS AESI

The opportunistic infections to be considered as AESI include (R17-2617):

pneumocystis jirovecii,
Human Polyoma-1 virus disease including polyomavirus-associated nephropathy,
Cytomegalie Virus,
posttransplant lymphoproliferative disorder (Epstein-Barr-Virus),
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),
Hepatitis C progression.

10.2 APPENDIX 2: STRONG CYP3A4 INHIBITORS

Strong CYP 3A4 inhibitors:

- boceprevir
- ceritinib
- clarithromycin
- cobicistat
- conivaptan
- diltiazem
- idelalisib
- indinavir
- itraconazole
- ketoconazole oral administration
- LCL161
- mifepristone
- mibefradil
- nefazodone
- nelfinafir
- posaconazole
- ribociclib
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- troleandomycin
- VIEKIRA PAK2
- voriconazole

Combinations of CYP 3A4 inhibitors:

- danoprevir/ritonavir
- elvitegravir/ritonavir
- indinavir/ritonavir
- lopinavir/ritonavir
- paritaprevir/ritonavir/ombitasvir/dasbuvir
- saquinavir/ritonavir
- tipranavir/ritonavir

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		
EudraCT number		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☐
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

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Title: Investigation of pharmacokinetics and absolute oral bioavailability of BI 1015550 administered as an oral dose with an intravenous microtracer dose of [14C]-BI 1015550 in healthy male volunteers.

Signatures (obtained electronically)

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