Clinical Trial Protocol

	Document Number: **c42256721-01**
BI Trial No.	1305-0038
BI Investigational Medicinal Product	BI 1015550
Title	Pharmacokinetics of R-BI 1015550 after single oral doses of BI 1015550 in Japanese healthy male subjects (open-label, non-randomised, and parallel group design)
Lay Title	A study to test how different doses of BI 1015550 are taken up in the body of healthy Japanese men
Clinical Phase	I
Clinical Trial Leader	[redacted] Telephone: [redacted], Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 1.0, 05 Aug 2023
Original Protocol Date	05 Aug 2023

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	05 Aug 2023
Revision date	Not applicable
BI trial number	1305-0038
Title of trial	Pharmacokinetics of R-BI 1015550 after single oral doses of BI 1015550 in Japanese healthy male subjects (open-label, non-randomised, and parallel group design)
[redacted] **Investigator**	[redacted]
Trial site	[redacted] Phone: [redacted] Fax: [redacted]
Clinical phase	I
Trial rationale	BI 1015550 undergoes chiral inversion and forms inactive S-enantiomer. Pharmacokinetics of R-BI 1015550 after single oral doses of BI 1015550 will be assessed.
Trial objectives	To investigate pharmacokinetics of R-BI 1015550 after single doses of BI 1015550 in healthy Japanese male subjects
Trial endpoints	Primary endpoint: $AUC_{0-\infty}$ and C_{max} of R-BI 1015550
Trial design	Open-label, non-randomised, and parallel-group design
Number of subjects **total entered** **on each treatment**	 12 6 per dose group[DG] (6 receiving BI 1015550)
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive)
Test product **dose** **mode of administration**	BI 1015550 film-coated tablet (9 mg and 18 mg) 9 mg (DG 1), 18 mg (DG2) Oral approximately with 240 mL of water after an overnight fast of at least 10 h
Comparator product **dose** **mode of admin.**	Not applicable Not applicable Not applicable
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

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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[7]	PK blood	12-lead ECG	Vital signs (BP, PR,RR)	Questioning for AEs and concomitant therapy [8]
1	-28 to -1			Screening (SCR)[1]	x[A]		x	x	
2	-1	-12:00	20:00	Admission to trial site[2]	x[2, 3, C]				x[2]
	1	-3:00	6 :00	Allocation to study number[4]		x[4]	x[4]	x[4]	x[4]
		0:00	9:00	Drug administration					
		0:30	9:30			x			
		0:45	9:45			x			
		1:00	10:00			x			
		1:15	10:15			x			
		1:30	10:30			x			
		1:45	10:45			x			
		2:00	11:00	240 mL fluid intake[5]		x			
		3:00	12:00			x			
		4:00	13:00	240 mL fluid intake, Lunch[5]		x			
		6:00	15:00			x			
		8:00	17:00			x			x
		10:00	19:00	Dinner[5]					
		12:00	21:00			x			
	2	24:00	09:00	Breakfast[5]	x[B]	x	x	x	x
	3	48:00	09:00	Breakfast[5]		x			x
	4	72:00	09:00	Breakfast[5]		x			x
	5	96:00	09:00	Breakfast[5]		x			x
	6	120:00	09:00	Breakfast[5]	x[B]	x			x
	7	144:00	09:00	Breakfast[5]		x			x
3	8			Breakfast(voluntary)[5], End of study (EoS) examination,[6] discharge from trial site	x[C]		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening alcohol breath test, and infection screening except for SARS CoV2 / COVID-19), 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 an approximate. The procedure is to be completed no later than 12 hours prior to drug administration.
3. Drug screen and alcohol breath test will be performed on admission. Infection screening of SARS CoV2 / COVID-19 will be performed on admission or prior to admission.
4. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
5. If several actions are indicated at the same time, the intake of meals/fluid will be the last action.
6. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory recording of AEs and concomitant therapies, body weight.
7. Letters A, B, and C define different sets of safety laboratory examinations (see Section 5.2.3)
8. 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.

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALAT	Latin American Thoracic Society
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
cAMP	Cyclic adenosine monophosphate
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
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
DG	Dose group
DILI	Drug induced liver injury
ECG	Electrocardiogram
ECM	Extracellular matrix
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
ERS	European Respiratory Society
GCP	Good Clinical Practice
gMean	Geometric mean
HIV	Human immunodeficiency virus
HR	Heart rate

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IB	Investigator's brochure
IC_{50}	half maximal (50%) inhibitory concentration
IEC	Independent Ethics Committee
IFN	Interferon
ILD	Interstitial lung disease
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
JRS	Japanese Respiratory Society
LC-MS/MS	liquid chromatography tandem mass spectrometry
LOAEL	Lowest observed adverse effect Level
LPS	Lipopolysaccharide
[redacted]	
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NOAEL	no adverse effect level
PDE4B	phosphodiesterase 4B
PDE4D	phosphodiesterase 4D
PDE4i	phosphodiesterase 4 inhibitor
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PopPK	Population Pharmacokinetics
PP	Polypropylene
PPF	progressive pulmonary fibrosis
PR	Pulse rate
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)
REP	Residual effect period
RR	Respiratory rate
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single rising dose
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
TNF	Tumor Necrosis Factor
$t_{1/2}$	Terminal half-life of the analyte in plasma

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t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
[redacted]	
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
[redacted]	
WBC	white blood cell

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1. INTRODUCTION

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

1.1 MEDICAL BACKGROUND

IPF and other progressive fibrosing interstitial lung diseases share common pathophysiologic characteristics; alveolar epithelial cell injury and subsequent dysregulated repair, characterized by excessive deposition of extracellular matrix and loss of normal parenchymal architecture and lung function (P11-07084). In IPF, fibroblasts exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis (P12-03241). Several growth factors are implicated in the proliferation, migration and transdifferentiation of the fibroblast and myofibroblast pool in pulmonary fibrosis.

As of date, nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of Idiopathic Pulmonary Fibrosis [R18-2794]. Nintedanib is also approved in the U.S., the European Union and many other countries for the treatment of other fibrosing ILDs with progressive phenotype. Despite the availability of these drugs, the medical need remains high in these devastating diseases.

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[redacted]

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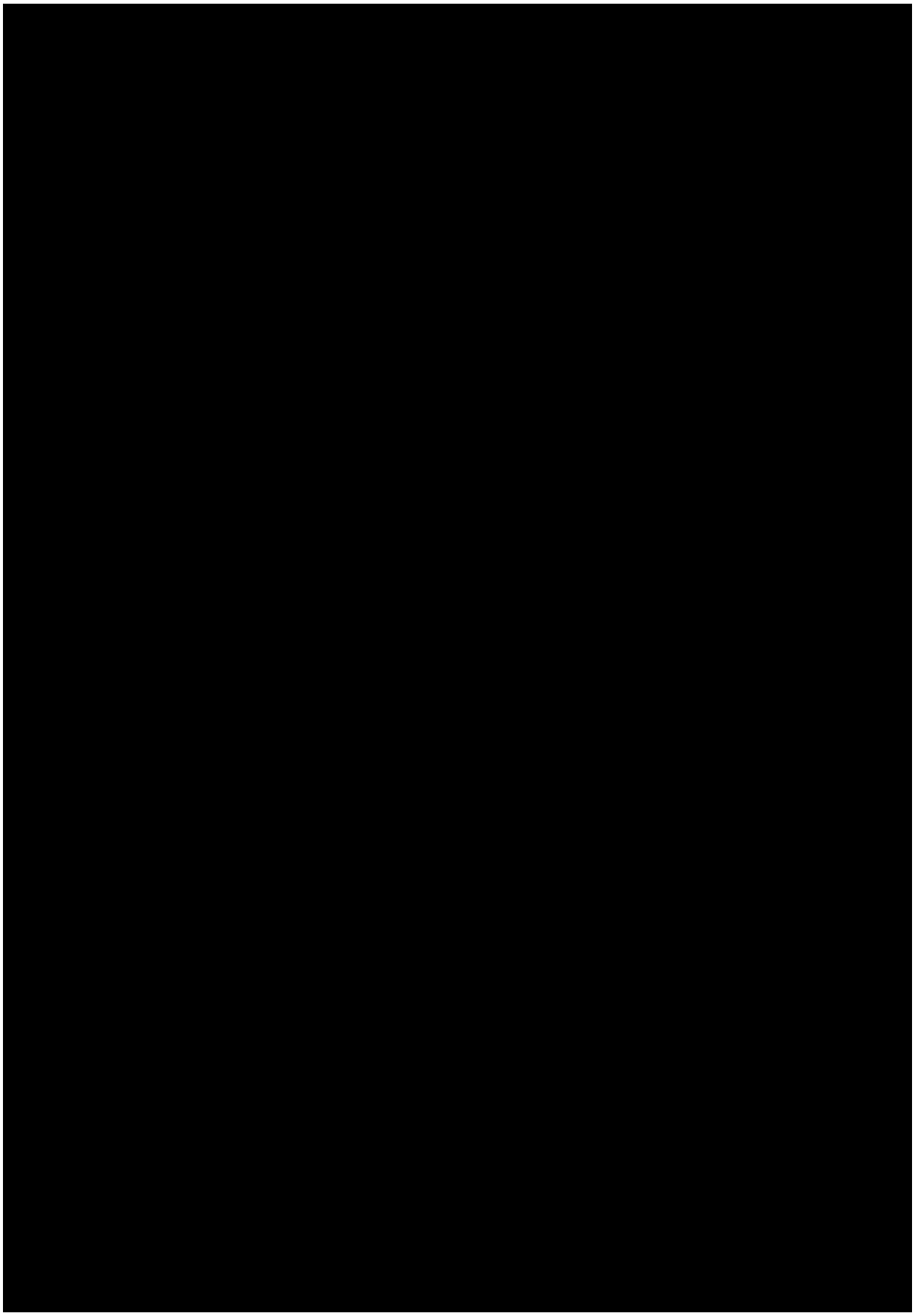

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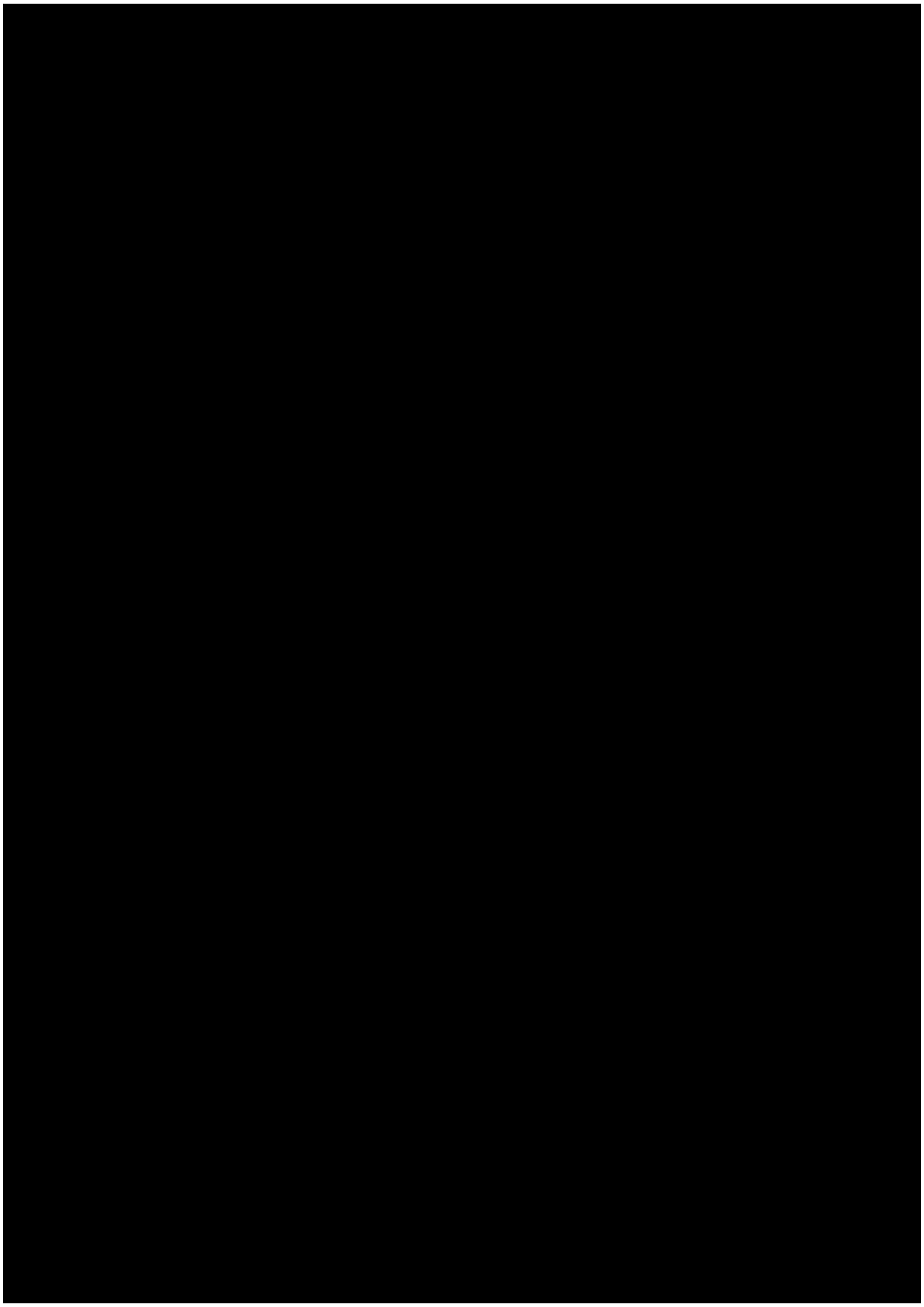

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1.3 RATIONALE FOR PERFORMING THE TRIAL

The rationale of this trial is to assess pharmacokinetics of R-BI 1015550 following single oral doses in Japanese healthy male subjects. The chosen population of healthy male subjects receiving single oral doses is considered adequate to provide the basis for the clinical development program of BI 1015550 in Japan.

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 its use in Japanese patients.

1.4.2 Risks

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

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trials conducted for this product to date. Vasculitis and foetal loss are considered as important potential risks based only on nonclinical findings (see section 1.2.1).

Apart from risks related to trial procedures, the risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs and from nonclinical and clinical data of compounds with a comparable mode of action. For clinical data including adverse events reported during clinical trials with BI 1015550 please refer to Section 1.2.

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product BI 1015550: compound/class specific (refer to Section 1.2)		
[redacted]		
Vasculitis	• Vasculopathy is an established nonclinical toxicity of PDE4 inhibitors. • Vasculitis has been shown in both the rats and minipigs following oral administration of BI 1015550 but not in 13- or 39-week studies in monkeys. • Vasculitis is listed as an important potential risk in the RMP for the marketed PDE4- inhibitor apremilast. • In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans	• History of vasculitis is an exclusion criterion. • Close clinical monitoring for AEs of vasculitis
Weight decrease in underweight patients (BMI <18.5 kg/m^2)	• For the marketed PDE4-inhibitors apremilast and roflumilast weight loss in underweight patients is an identified important risk. [redacted]	• Patients who have a BMI <18.5 kg/m^2 are excluded.
Psychiatric disorders: • Depression and anxiety • Suicidality	• For the marketed PDE4 inhibitors depression is listed as a side effect. They are associated with increased risk of depression with some patients reporting suicidal ideation and/or attempts, with some reported cases of completed suicide.	• The risk after single dose administration in Phase I (done on site) is considered low and will be addressed by careful close clinical monitoring for AEs and increased awareness by the investigator for signs and symptoms of depression

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Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	• High incidence of depression in the ILD population per se. • In IPF patients treated with 18 mg BI 1015550 bid for up to 12 weeks, no on-treatment events of suicidal ideation or behavior and no events of depression or anxiety were reported	and anxiety as well as for signs and symptoms of suicidal ideation and behaviour. Only healthy subjects with no relevant medical history including psychiatric disorders will be enrolled. • Any lifetime history of suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior) at screening will be excluded
Severe Infections including, serious, opportunistic and *Mycobacterium tuberculosis* infections	• Inhibition of the immune response due to the anti-inflammatory mode of action of BI 1015550 potentially increases the risk of infections, including COVID-19 • Serious infections were balanced between placebo and BI 1015550 in Phase II trial [redacted]	• Screening procedures for infections are defined for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or active tuberculosis are excluded from the trial. • Treatment of infections should be initiated promptly according to standards of care.
MACE and tachyarhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast • In nonclinical studies with BI 1015550 no adverse cardiovascular findings detected • In clinical trials with BI 1015550 no relevant findings were observed	• These risks will be addressed by careful safety monitoring and safety measures such as o close clinical monitoring for AEs; o regular monitoring of vital signs and ECG assessments.
Malignancies	• Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus theoretically decrease immune defense against malignancies.	• Patients with a recent history of malignancy within 5 years will be excluded from participation in this trial except patients with appropriately treated basal cell carcinoma or in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix

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Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, abdominal pain)	• Vomiting and diarrhea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. • Diarrhoea was the most frequently reported adverse event in Phase II with the majority of events being of mild intensity. • Gastrointestinal disorders are very common or common side effect of the approved antifibrotics.	• Increased awareness of symptoms. • Careful monitoring of hydration in patients with diarrhoea recommended. • Symptomatic treatment, e.g. loperamide, if required
Reproductive toxicity: • Fetal loss • Decreased fertility	• No teratogenicity was seen in 2 species in preclinical studies and exposure with BI 1015550 via the semen is expected to be very low. • In rats, male and female fertility was potentially reduced. Long term toxicity studies with BI 1015550 in rat and monkey showed no microscopic evidence of changes in female reproductive organs or male spermatogenesis. For another PDE4 inhibitor with comparable nonclinical findings, clinical data showed no effect on male fertility and sperm in humans. • In monkeys, a sporadic prolongation in menstrual cycles was observed at approximately ≥4-fold human exposure at 18 mg BI 1015550 bid. • Fetal loss was increased in female rats treated with BI 1015550.	Only male subjects will be screened for this study
General safety topics		
Drug-induced liver injury (DILI)	• Rare but severe event, standard topic of interest for products in development thus under constant surveillance by sponsors and regulators.	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Trial procedures		
Blood Sampling	• As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain.	• These risks will be addressed by careful safety monitoring and risk mitigation measures such as o close clinical monitoring for AEs; o selection of experienced sites and site staff

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In addition, the following general safety measures will be applied in order to minimize the risk to the healthy volunteers:

- Careful dose selection
- Subjects will be hospitalised throughout the study from Day -1 to Day 8
- Adequate safety monitoring will be performed (e.g., vital signs including ECGs, safety laboratory tests, and adverse events).

The total volume of blood withdrawn per subjects during the entire trial will not exceed 400 mL. This is less than the volume of a normal blood donation (500 mL). No health-related risk to subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 1015550 is well understood.

In the context of the unmet medical need and anticipated benefit of BI 1015550, the benefit risk evaluation of the compound, based upon the available preclinical and clinical information, is favourable.

Considering the medical need for the development of a better tolerated and more effective treatment for patients with BI 1015550, the expected benefit outweighs the potential risks.

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate pharmacokinetics (PK) of R-BI 1015550 in Japanese healthy male subjects following oral administration of single BI 1015550 dose of 9 mg or 18 mg.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for R-BI 1015550:

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

2.1.3 Secondary endpoints

Not applicable

[redacted]

2.2.2.1 Safety and tolerability

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

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure (BP), pulse rate (PR), respiratory rate (RR))

[redacted]

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This single dose trial is designed as open-label to subject, investigator, and sponsor functions (refer to Section 4.1.5) and non-randomised within parallel dose groups.

It is planned to include a total of 12 healthy male subjects in the trial. The subjects will be assigned to 2 groups consisting of 6 subjects per group (see Table 3.1: 1). In case of subjects not completed the trial, up to 8 replacement will be recruited for whole study, see section 3.3.5.

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups

Dose group	**1**	**2**
Dose	9 mg	18 mg
No. of subjects entered	6	6
No. of subjects receiving active	6	6

The groups will be dosed in parallel. At any time during the ongoing study, further dosing will be stopped in case of safety and tolerability concerns based on the pre-specified trial-specific stopping criteria (refer to Section 3.3.4.3).

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

The study will be conducted according to a single-dose, open-label, non-randomised, and parallel-group design.

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

The placebo group is not needed since primary objective is to evaluate PK parameters but not to evaluate safety.

The single doses to be tested in this trial are those used in the pivotal Phase III trials.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 12 healthy male subjects will enter the trial. Subjects will be recruited by the contracted third vendor.

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.

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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, RR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 45 years (inclusive)
3. BMI of 18.5 to 25 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, RR 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 40 to 90 mmHg, or PR outside the range of 40 to 99 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
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 or in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix

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11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days 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 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 30 g per day)
17. Drug abuse or positive drug screening
18. Blood donation of more than 400 mL within 12 weeks or 200 mL within 30 days or plasma donation within 2 weeks prior to administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in male) or any other relevant ECG finding at screening.
22. A history of additional risk factors for Torsade de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. History of disease that affects the present situation
25. Laboratory test indicative of an ongoing SARS-CoV-2/COVID-19 infection on Day -1 or prior to admission, and/ or any clinical symptom suggestive for this disease.

In addition, the following trial-specific exclusion criteria apply:

26. Any lifetime history of suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
27. History of vasculitis

For restrictions of the trial, refer to Section 4.2.2.

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

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

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

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

If new 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.

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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 and dose stopping criteria

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reason 4 is 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 product
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious AEs, or any safety information invalidating the earlier positive benefit-risk assessment (see Section 3.3.4.1)

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 some subjects do not complete the trial (including subjects non-evaluable for PK), they may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment as the subject he replaces.

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	9 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	Single dose

The characteristics of the reference product are given below:

Substance:	BI 1015550
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	18 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	Single dose

4.1.2 Selection of doses in the trial

The doses selected for this trial are the standard clinical dose investigated in the phase 3 clinical trials (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability.

As soon as enough subjects are allocated to 1 of 2 dose groups, the following subjects will be allocated to remaining dose group. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the trial

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includes healthy subjects of only Japanese ethnicity, relevant imbalances between the dose groups are not expected.

It is an open-label trial without randomisation.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 BI 1015550 treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
1	BI 1015550	Tablet	9 mg	1 film-coated tablet, single dose	9 mg
2	BI 1015550	Tablet	18 mg	1 film-coated tablet single dose	18 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting/standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, 1 authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination) or to sleep.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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. This is considered acceptable because the potential for bias is low and does not outweigh practical considerations. Emergency envelopes will not be provided, since the treatments of all subjects are known in this open-label trial.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

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The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Approval/notification of the regulatory authority, e.g. competent authority (CA)
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator’s possession.

All unused trial 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.

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4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

The use of known PDE-inhibitors such as: theophyllin, theobromin, sildenafil, tadalafil, vardenafil, apremilast and roflumilast must be avoided during the whole course of the study. Further, the use of known inhibitors and inducers of CYP3A and P-gp activity is not allowed.

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose on Day 1 (mandatory for all subjects).

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 4 h before until 4 h after each administration of trial medication.

Smoking is not allowed during in-house confinement.

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

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial.

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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).

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5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

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

5.2.2 Vital signs

Systolic and diastolic BP as well as PR or heart rate (HR) (HR is considered to be equal to PR), and RR will be measured at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. Blood pressures and pulse rate 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 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.

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Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells [WBC] /Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal) and as per judgement by the investigator)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	--
	Prothrombin time	X	--	--
	Prothrombin time – INR (International Normalization Ratio)	X	--	--
	Fibrinogen	X	--	--
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day 2 and Day6 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 2 on Day1 and Visit 3 (end of trial examination)

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Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X		X
	Urine Protein (qual)	X		X
	Urine Glucose (qual)	X		X
	Urine Ketone (qual)	X		X
	Urobilinogen (qual)	X		X
	Urine Bilirubin (qual)	X		X
	Urine RBC/Erythrocytes (qual)	X		X
	Urine WBC/Leucocytes (qual)	X		X
	Urine pH	X		X
Urine sediment (microscopic examination	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day 6 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 2 on Day1 and Visit 3 (end of trial examination)

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

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Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methamphetamines/MDMA/Ecstacy Opiates Phencyclidine Tricyclic antidepressants Oxycodone Propoxyphene
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antigen and/or antibody (qualitative) Syphilis test (RPR, TP antibody method)
Infectious test	SARS CoV2 / COVID-19

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

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed by the local laboratory of 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

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart.

To achieve a stable HR 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 recording will always precede all other trial procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

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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 recorded for safety reasons.

All ECGs will be stored stored electronically on the local ECG machine. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether 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.

Adverse event report for diarrhea events
In case of events of diarrhoea the following definitions should be followed:
Diarrhoea is defined ≥3 loose/liquid stools per day (WHO definition)

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

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- 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

An event that possibly leads to disability will be handled as 'deemed serious for any other reason' and, therefore, reported as an SAE.

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 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:

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- An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

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

- Severe or serious infections, opportunistic or mycobacterium tuberculosis infections
  The opportunistic infections include pneumocystis jirovecii, Human Polyoma-1 virus disease including polyomavirus-associated nephropathy, Cytomegalie Virus, post-transplant 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
- Vasculitis events
  In this trial protocol vasculitis is defined as any 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.

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.

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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.

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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.

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5.2.6.2.3 Pregnancy

Once the male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner.

The ISF will contain the trial specific information and consent for the pregnant partner.

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 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 [redacted], R-[redacted]-BI 1015550 concentrations in plasma, 3 mL of 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. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

Sample handling will be described in detail in a separate lab manual.

Until transfer on dry ice to the analytical laboratory, the plasma samples will be stored at approximately -20°C or below at the trial site.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, barcode and planned sampling time. Further information such as matrix and analyte may also be provided.

The trial samples will be discarded6 months after the end of the trial.

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[redacted]

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.4.1 Pharmacodynamic biomarkers

Not applicable.

5.4.2 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.6.1 Pharmacogenomic evaluation

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, ECG, and blood laboratory tests will be ± 30 min for the first 24 h after trial drug administration and ± 120 min thereafter. Urine laboratory test can be performed between wake-up to the scheduled time.

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening 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 5.2.2 to 5.2.5.

6.2.2 Treatment period

Each subject will receive one dose of trial medication (BI 1015550) at Visit 2.

Trial medication will be taken orally following an overnight fasting of at least 10 hours by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Trial participants will be admitted to the trial site in the morning of Day -1 and kept under close medical surveillance for at least 24 h following the drug administration. The subjects

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will then be allowed to leave the trial site after formal EoS assessment by the investigator or [redacted] designee on Day 8.

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

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from the time of the subject's written informed consent until the end of trial examination.

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

6.2.3 Follow-up period and trial completion

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

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

If a subject discontinues from the trial, the subject will be followed until the investigator or sub-investigator is convinced of the subject's safety. If follow-up is not possible or comes to an end, follow-up should be formally completed after discussion with the sponsor. If a subject stop attending trial assessments, the investigator should assess the subject's status as comprehensively as possible and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate in further assessments; he or she cannot be compelled.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

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

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the trial; i.e., confidence intervals are considered as interval estimates for effects.

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 treatment assignment will be determined based on the first treatment the subjects received. 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 the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for BI 1015550 will be calculated according to the relevant BI internal procedure.

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 dose of trial medication taken

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- 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),
- Missing samples/concentration data at important phases of PK disposition curve.

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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 as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

The primary endpoints as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the PKS and will be descriptive in nature.

7.2.3 Secondary endpoint analyses

No secondary endpoint analysis will be performed.

[redacted]

7.2.5 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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 for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, 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,

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measurements performed or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between the trial medication intake and end of REP (see Section 1.2.6) will be assigned to the treatment period. Events occurring after the REP but prior to 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 will be reported to Pharmacovigilance only and will not be captured in the trial database.

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 dose group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as 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 formal 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 procedure.

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

7.4 RANDOMISATION

Not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 12 subjects in this trial and a total of up to 20 subjects including up to 8 replaced subjects in this trial. The planned sample size is not based on a

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power calculation. The size of 6 subjects per dose group (6 on active treatment) is commonly used in single dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics.

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. 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.

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 responsible Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and 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 investigator or delegate must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen and technical terms and expressions avoided, if possible.

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.

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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.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

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.

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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 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.

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8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

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

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

8.6 TRIAL MILESTONES

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

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

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

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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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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 Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted]

Safety laboratory tests will be performed by the local laboratory of the trial site.

Analyses of BI 1015550 concentrations in plasma will be performed at [redacted]

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

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

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

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9.2 UNPUBLISHED REFERENCES

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10. APPENDIX

Not applicable.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c42256721 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Pharmacokinetics of R-BI 1015550 after single oral doses of BI 1015550 in Japanese healthy male subjects (open-label, non-randomised, and parallel group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	07 Aug 2023 09:18 CEST
Author-Trial Statistician		07 Aug 2023 14:28 CEST
Approval-Clinical Program [redacted]		07 Aug 2023 15:37 CEST
Verification-Paper Signature Completion		08 Aug 2023 08:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed