Clinical Trial Protocol

	Document Number: **c43335244-03**
EU Trial No. **UTN:**	2023-509889-38-00 U1111-1301-0891
BI Trial No.	1305-0039
BI Investigational Medicinal Product	BI 1015550
Title	The effect of food on the pharmacokinetics of BI 1015550 (Formulation C2) following single oral dose administration in healthy subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover design)
Lay Title	A study in healthy people to test how BI 1015550 is taken up in the body when given with or without food
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: +[redacted] Fax: +[redacted]
[redacted] **Investigator**	[redacted] Phone: +[redacted]
Current Version, Date	Version 3.0, 16 May 2024
Original Protocol Date	13 Feb 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	13 February 2024
Revision date	16 May 2024
BI trial number	1305-0039
Title of trial	The effect of food on the pharmacokinetics of BI 1015550 (Formulation C2) following single oral dose administration in healthy subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover design)
[redacted] **Investigator**	[redacted]
Trial site	
Clinical phase	I
Trial rationale	This trial is intended to investigate the effect of food on the pharmacokinetics of the BI 1015550 Formulation C2 as the to-be marketed formulation which is different from the phase 3 formulation
Trial objectives	The main objective is to investigate the effect of food on the pharmacokinetics of the 18 mg tablet of BI 1015550.
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of R-BI 1015550 Secondary endpoints: $AUC_{0-\infty}$ of R-BI 1015550
Trial design	Open-label, randomised, single-dose, two-period, two-sequence crossover design
Number of subjects	
total entered	18
on each treatment	18
Diagnosis	Not applicable
Main inclusion criteria	Healthy male or female subjects (at least 6 subjects of each sex), age of 18 to 50 years (inclusive) with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Reference treatment	BI 1015550 Formulation C2 as film-coated 18 mg tablet – Reference, R
dose	18 mg (one tablet)
mode of admin.	One 18 mg tablet orally with 240 mL of water after an overnight fast of at least 10 h

Test treatment	BI 1015550 Formulation C2 as film-coated 18 mg tablet – Test, T
dose **mode of administration**	18 mg (one tablet) One 18 mg tablet orally with 240 mL of water after a high-fat, high-calorie breakfast
Duration of treatment	Each of the two treatments is administered once
Statistical methods	For the main objective, the relative bioavailability will be estimated by the ratio of the geometric means (T/R) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK $_{blood}$[9]	12-lead ECG[10]	Vital signs (BP, PR)[8]	Questioning for AEs and concomitant therapy[6]
SCR	1	-28 to -1			Screening (SCR)[1]	A		x	x	
1/2 (two identical periods separated by a wash-out of at least 10 days	2/3	-1	-24:00	08:00	Admission to trial site	B x[5]		x	x	x
		1	-1:00	07:00	Allocation to treatment[2] (visit 2 only)		x[2]	x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (Treatment T, only)					
			0:00	08:00	Drug administration					
			0:15	08:15			x			
			0:30	08:30			x			
			0:45	08:45			x			
			1:00	09:00			x			x
			1:15	09:15			x			
			1:30	09:30			x			
			1:45	09:45			x			
			2:00	10:00	240 mL fluid intake		x			x
			2:30	10:30			x			
			3:00	11:00			x			
			3:30	11:30			x			
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x			x
			6:00	14:00			x			
			8:00	16:00	Snack (voluntary)[3]		x			
			11:00	19:00	Dinner[3]					
			12:00	20:00			x			x
		2	24:00	08:00		B	x	x	x	x
			34:00	18:00			x			
		3	48:00	08:00	Breakfast (voluntary), discharge from trial site		x			x
			58:00	18:00	Ambulatory visit		x			
		4	72:00	08:00	Ambulatory visit		x			x
		5	96:00	08:00	Ambulatory visit		x			x
		6	120:00	08:00	Ambulatory visit		x			x
		7	144:00	08:00	Ambulatory visit		x			
FU	4	17 to 28[11]			End of study (EoS) examination[4]	B		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 and pregnancy test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/ exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (EoS), the EoS examination includes physical examination, vital signs, ECG, safety laboratory including pregnancy test, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test as well as urine pregnancy test in all women will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the times indicated in the Flow Chart above.
7. Letters A and B define different sets of safety laboratory examinations (for details, refer to Section 5.2.3).

8 For details of vital signs evaluation, refer to Section 5.2.2. **Body weight will be determined at screening and EoS, refer to 5.2.1.**
9. For details of PK blood sampling, refer to Section 5.3.2.1.
10. For details of 12-lead ECG, refer to Section 5.2.4.
11. From Day 7 to Day 14 after the last drug administration

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
C2	Formulation C2 is TiO_2-free formulation
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
COVID-19	SARS-CoV-2 induced disease
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
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
EDTA	Ethylenediaminetetraacetic acid
EFD	Embryo-Fetal Development
EoS	End of Study
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean

IB	Investigator's brochure
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NOAEL	No observed adverse effect level
NCA	Non-Compartmental Analysis
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
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)
R	Reference treatment
REP	Residual effect period
R_{max}	Maximum rate of urinary excretion
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Screening
SMQ	Standardized MedDRA Queries
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
[redacted]	
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

[redacted]

WOCBP	Woman of child bearing potential
WNOCBP	Woman not of child bearing potential

1. INTRODUCTION

BI 1015550 is an oral preferential PDE4B inhibitor being developed by BI for the treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF) and Progressive Pulmonary Fibrosis (PPF). It is currently investigated in a clinical phase 3 program.

1.1 MEDICAL BACKGROUND

For information about IPF and PPF, refer to the current Investigator's Brochure (IB) [c02094779].

1.2 DRUG PROFILE

For detailed information about the drug profile of BI 1015550, refer to the current Investigator's Brochure (IB) [c02094779].

1.2.1 Clincal pharmacokinetics

BI 1015550 has a chiral sulfur within the sulfoxide group. The administered BI 1015550 product in the clinical trials is in essentially chirally pure (R)-BI1015550 form (>99.5% chiral purity). [redacted] R-BI 1015550 was clearly identified as the predominant circulating enantiomer and (S)-enantiomer was determined to be a minor metabolite of (R)-enantiomer.

The previous pharmacokinetic (PK) characterization has utilized non-chiral assay that measured mixture of R-BI 1015550 and S-BI 1015550 as total BI 1015550. After oral administration, BI 1015550 is rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1-4 h post-dose. [redacted] After single and multiple oral doses, BI 1015550 exposure (C_{max} and $AUC_{0-\infty}$) appeared to increase dose proportionally. [redacted]. Accumulation ratio based on C_{max} and AUC were 1.66 and 1.87, respectively. Administration of BI 1015550 Formulation C1 (used in phase 3 trial) together with food did not change the exposure to BI 1015550 to a clinically relevant extent.

[redacted]

1.2.2 Clinical safety

BI 1015550 showed acceptable safety and tolerability following single dose administrations up to 48 mg and multiple administrations for up to 12 weeks with up to 18 mg BID.

In healthy volunteer studies, headache, abdominal pain, nausea and diarrhoea, all of mild to moderate intensity, were the most commonly reported events. A trend toward weight loss in subjects treated with BI 1015550 was observed in study 1305-0011 [c22991937] in healthy

volunteers. No severe, serious, fatal AEs, nor SUSARS have been reported in the healthy volunteer studies.

In patients with IPF, two clinical studies have been completed with BI 1015550: a Phase Ic MRD study in patients without background antifibrotic treatment (1305-0012, c25085412) and a proof-of-clinical principle phase 2 study in patients stratified by background antifibrotic treatment (1305-0013, c37065416).

Overall, in Phase Ic and II trials in patients with IPF, BI 1015550 at a dose of 18 mg bid for up to 12 weeks showed acceptable safety and tolerability, in phase 2, also with background antifibrotic treatment (nintedanib or pirfenidone). In phase 2, the most common AEs were GI events (more specifically diarrhoea), which were reported with a higher frequency under BI 1015550 treatment (vs. placebo) and in patients with background antifibrotic treatment.

In the phase 2 trial which investigated treatment with BI 1015550 18 mg bid for 12 weeks in patients with IPF, diarrhoea was the most common AE leading to discontinuation of treatment (3 out of 97 treated patients [3.1%]) and all AEs leading to discontinuation were reported in the BI 1015550 group. The frequency of SAEs in patients was numerically higher in placebo-treated patients, which was driven by placebo-treated patients without antifibrotic background treatment. Two patients with IPF treated with BI 1015550 had fatal AEs: one case of COVID-19 pneumonia and one case of suspected condition aggravated/suspected vasculitis; in both cases, risk factors were present. One AESI was reported (the fatal AE of suspected vasculitis), and evaluation by an external, independent DMC could neither confirm the diagnosis of vasculitis, nor a causal relationship with BI 1015550. There were no AESIs of hepatic injury. No relevant patterns, clusters or imbalances were observed for any of the other safety topics of interest, including depression, anxiety, malignancies, insomnia, major adverse cardiac events, or tachyarrhythmia. No clinically relevant changes in vital signs (including body weight) or ECG parameters (including QTc) were observed. No changes in the C-SSRS and no AEs of suicidal ideation or behaviour were reported during trial treatment.

1.2.3 Residual Effect Period

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

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 1015550 tablets used in the phase 3 safety and efficacy trials (Formulation C1) contain, amongst others, titanium dioxide as a standard pharmaceutical excipient in common amounts. BI decided to produce a titanium dioxide-free tablet BI 1015550 Formulation C2 as the formulation to-be marketed.

This study will be performed to test the effect of food on the pharmacokinetics of the BI 1015550 Formulation C2 which is different than the formulation used in the phase 3 (Formulation C1).

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 the BI 1015550 Formulation C2.

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.

Potential side effects of BI 1015550 will be under continuous evaluation during clinical development. Vasculitis and foetal loss are considered as important potential risk based only on non-clinical findings. 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, 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		
Vasculitis	Vasculopathy is an established preclinical toxicity finding of PDE4 inhibitors. Vasculitis has been shown in rats and minipigs following oral administration of BI 1015550 but not in monkeys treated for up to 39 weeks. Vasculitis is listed as an important potential risk for the marketed PDE4 inhibitor apremilast. In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans.	Close clinical monitoring for AEs of vasculitis. Treatment will be interrupted in case of any suspected vasculitis adverse event.
Weight decrease in underweight patients (BMI < 18.5 kg/m^2)	For the marketed PDE4i apremilast and roflumilast weight loss in underweight participants is an identified important risk.	Inclusion of subjects with BMI > 18.5 only is a routine inclusion criterion in Phase I. Subjects who reach a BMI < 18.5kg/m^2, and subsequently experience unexplained and

	[redacted]	clinically significant weight loss (>10%) will be discontinued from trial treatment. Weight will be monitored throughout the study. With 2 single dose administrations of BI 1015550, the risk is considered to be very low.

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		
Reproductive toxicity: foetal loss, decreased fertility	No teratogenicity was seen 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 preclinical findings (class-effect), clinical data showed no effect on male fertility and sperm in humans. Foetal loss was increased in female rats treated with BI 1015550.	Women of childbearing potential (WOCBP) need to use a highly effective method of contraception from 30 days before first intake of trial drug [redacted] WOCBP taking oral contraceptives (OCs) also have to ensure the use of one barrier method during sexual intercourse with their partner, e.g., condom to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhea. Thorough counselling about appropriate contraceptive measures. Repeated pregnancy testing. Discontinuation of trial treatment in case of pregnancy.
Major Adverse Cardiovascular Events (MACE) and tachyarrhythmia	Important potential risk for marketed PDE4 inhibitor apremilast. In preclinical studies with BI 1015550, no adverse cardiovascular findings were detected - focal myocardial degeneration or necrosis in monkeys were with no apparent vascular changes.	These risks will be addressed by careful safety monitoring and safety measures, e.g., close clinical monitoring for AEs; regular monitoring of vital signs and ECG assessments. Subjects will stay in the Phase I unit under close medical surveillance until at least 24 h after the drug

	In clinical trials with BI 1015550, no relevant findings were observed.	administration in each treatment period.

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		
Psychiatric disorders: Depression and anxiety Suicidality	For the marketed PDE4i depression is listed as side effect and they are associated with increased risk of depression with some patients reporting suicidal ideation and attempts and also reported cases of completed suicide. In IPF patients treated with 18 mg BI 1015550 bid up to 12 weeks, no on treatment events of suicidal ideation or behaviour and no events of depression or anxiety were reported. Prospective assessment of suicidal ideation and behaviour and depression are not required in single-dose trials in healthy volunteers.	The risk after 2 single dose administrations in Phase I (done on site) is considered to be low and will be addressed by careful close clinical monitoring for AEs and increased awareness by the investigator for signs and symptoms of depression 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.
Severe infections including, serious, opportunistic and mycobacterium tuberculosis infections	Inhibition of the immune response due to the anti-inflammatory mode of action of BI 1015550 potentially increases the risk of severe and serious infections. Serious infections were balanced between placebo and BI 1015550 in phase 2 trial. Nasopharyngitis was more frequently reported under treatment with BI 1015550 in Phase Ic/II but not in Phase I trials and the numbers were very small.	Screening procedures for infections are defined for this trial. Subjects with any relevant chronic or acute infections are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Treatment interruption in case of severe acute infection until the subject has recovered based on the investigator's medical judgement. Close monitoring to detect potential infections promptly will minimise the risk of serious infection.

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		
Malignancies	Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus, theoretically decrease immune defence against malignancies.	Subjects with a recent history of malignancy within 5 years will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue trial treatment. Diagnostics and treatment have to be initiated according to local standard of care. The risk after 2 single dose administrations in Phase I is considered low.
Gastrointestinal disorders (e.g., diarrhoea, nausea, vomiting, abdominal pain)	Vomiting and diarrhoea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. In phase 2 study of BI 1015550, diarrhoea was the most frequently reported AE.	Increased awareness of symptoms. Careful monitoring of hydration in subjects with diarrhoea recommended. Symptomatic treatment if required.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety. Increased awareness and expedited reporting (AESI).
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, acceptable in the framework of trial participation.	Medical expertise of the trial site.
Local skin irritation and discomfort.	General risk from ECG stickers, acceptable in the	Medical expertise of the trial site.

	framework of trial participation.	

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

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 C_{max} [redacted] following an 18 mg BID dose, the worst-case seminal fluid level is anticipated to be 460 nM. Assuming a seminal fluid volume of 5 mL, a worst-case 100% absorption from the vagina, and a plasma volume of 3.5L, the resulting plasma concentration in the woman would be 0.66 nM. This concentration is approximately 3,500-fold below the most conservative maximum plasma level of 2,300 nM 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 a lack of genotoxicity suggest that barrier methods of contraception should not be required for a male administered BI 1015550 [c39775503].

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 1015550 is well understood. BI 1015550 is an oral preferential inhibitor of the PDE4B with broad anti-inflammatory and antifibrotic activities.

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. In the current trial, adequate safety monitoring including vital signs, ECG, safety laboratory and AE monitoring has been implemented. Taking into account these safety measures, as well as available preclinical and clinical data, potential risks to healthy subjects are considered to be low and outweighed by the benefit of a successful clinical development of BI 1015550 in the context of the unmet medical need in IPF and other forms of progressive pulmonary fibrosis.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective is to investigate the effect of food on the pharmacokinetics of the 18 mg tablet BI 1015550 Formulation C2.

2.1.2 Primary endpoints

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

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

- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

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

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

[redacted]

[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)
- Body weight

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, randomised, single dose, two period, two-way crossover trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be as follows:

- One 18 mg BI 1015550 Formulation C2 film-coated tablet administered to subjects in the *fasting* state (R).
- One 18 mg BI 1015550 Formulation C2 film-coated tablet administered to subjects in the *fed* state (T).

Subjects will be randomly allocated to the 2 treatment sequences (T- -R or R-T). For details, refer to Section 4.1.

There will be a washout period of at least 10 days between the administrations of each treatment.

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

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

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

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 18 healthy male and female subjects (at least 6 of each sex) 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 or female 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 50 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
5. Female subject meets any of the following criteria for a highly effective contraception from at least 30 days before the first administration of trial medication until 7 days after last administration

   Highly effective methods of contraception include:

   - Use of oral hormonal contraception that prevents ovulation, *plus condom*
   - Use of combined (estrogen and progestogen containing) hormonal contraception that prevents ovulation (intravaginal or transdermal)
   - Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants)
   - Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
   - Sexually abstinent is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject
   - Bilateral tubal occlusion
6. Women of not of childbearing potential (WNOCBP) include:
   - Permanently surgically sterilised (including hysterectomy, bilateral oophorectomy and bilateral salpingectomy)
   - Postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)
7. WNOCBP are not required to use any methods of contraception. Female subjects should not participate in egg donation and male subjects should not participate in sperm donation from the first study drug administration, for the duration of the study and for at least 7 days after the last study drug administration

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 50 to 90 bpm at screening
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance, in particular, hepatic parameters (ALT, AST, total bilirubin) or renal parameters (creatinine) exceeding the ULN at screening
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 assessed as clinically relevant by the investigator
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 depression and suicidal behaviour
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections within the 30 days prior first drug administration
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 in situ carcinoma of uterine cervix
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)
13. Intake of an investigational drug in another clinical trial within 90 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
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 12 g per day for females and 24 g per day for males)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval e.g., QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (e.g., 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. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
25. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 7 days after trial completion
26. For female subjects: Positive pregnancy test
27. Concomitant intake of strong CYP3A inhibitors (e.g., amprenavir, indinavir, nelfinavir, ritonavir, itraconazole or ketoconazole) and unselective PDE inhibitors (e.g., theophylline, roflumilast, apremilast)
28. History or signs of vasculitis
29. Relevant immunodeficiency
30. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of screening
31. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) 1 and 2 antibody results at screening
32. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
33. Subjects who are, or are immediate family members of, a study site or sponsor employee

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-study 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 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 (e.g., pregnancy, surgery, adverse events (AEs), or diseases), in particular, if an AE of severe intensity or a serious adverse event (SAE) occurs.
5. The subject fulfils the criteria of a 'Potential Severe DILI' (see Section 5.2.6.1.4) and/or needs to be followed up according to the DILI checklist provided in the ISF.
6. The subject has relevant individual QT prolongations, i.e., a QTcF increase of greater than 60 ms from baseline and/or with absolute QT or QTcF greater than 500 ms, as confirmed by a repeat ECG recording.
7. Subjects that experience an unexplained and clinically significant (>10%) weight loss during trial treatment.
8. If any of the following AEs is reported, the treatment has to be discontinued:
   - Severe or serious infections, opportunistic or mycobacterium tuberculosis infections
   - Malignancies
   - Vasculitis

Of note, depending on the current status of the COVID-19 pandemic/ endemic, all subjects with confirmed SARS CoV-2 infection will be handled in accordance with local guidance and SOPs meaning that any confirmed SARS CoV-2 infection during the conduct of the trial will lead to discontinuation of the subject (refer to Section 1.4.2).

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

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.

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 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 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).

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

3.3.5 Replacement of subjects

In case more than 6 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced, that is, additional subjects may be randomized, 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 sequence as the subject he or she replaces.

In case of replacement of subjects, the trial site should ensure that the requirements for distribution of sex (at least 6 of each sex) are still met within the overall group of treated subjects.

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 (Formulation C2)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	18 mg
Posology:	1-0-0
Mode of administration:	Oral

4.1.2 Selection of doses in the trial

The doses selected for this trial are standard clinical doses.

4.1.3 Method of assigning subjects to treatment groups

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

Prior to the start of the trial, subjects willing to participate will be recruited to cohorts according to their temporal availability. In the morning of Day 1 (Visit 2), subjects will be allocated to treatment sequences prior to the first administration of trial medication according to the randomisation scheme.

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

All subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable.

The randomisation procedure is described in Section 7.4.

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage/ fasting state	Total dose
Reference (R)	BI 1015550	Film-coated tablet (Formulation C2 - TiO_2 free)	18 mg	1 tablet (18 mg) -fasting	18 mg
Test (T)	BI 1015550	Film-coated tablet (Formulation C2 - TiO_2 free)	18 mg	1 tablet (18 mg) - fed	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 standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, if correct dosage cannot be ensured otherwise.

In the fed treatment period (T), the subjects will start to consume a high-fat, high-calorie meal 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance ‘Assessing the effects of food on drugs in INDs and NDAs (June 2022)’’ [R23-0862]. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 2 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

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).

The treatments will be separated by a wash-out phase of at least 10 days.

4.1.5 Blinding and procedures for unblinding

The table below summarizes the masking/blinding level of individual functions, roles and responsibilities involved in the trial.

Table 4.1.5: 1 Blinding level of individual functions

Role/function	Timing of Unblinding/ receiving access to the treatment information (including rationale)
Subject/Participant	Subjects will be aware of the order of the 2 treatments as soon as the treatment sequence has been assigned.
Investigator/Site Staff	As requested to prepare trial site prior to first subject entered.
Sponsor trial team and data	Unblinded as requested.
Bioanalytical Staff	Persons directly involved in bioanalyses of PK samples will be blinded to trial treatments until data ready for final analysis.
Pharmacokineticist/ Pharmacometrician	Unblinded as requested.
Unblinded Pharmacist/ Pharmacy staff	Prior to first subject entered.

During the time a role/function is blinded according to the table above, the randomisation schemes and medication kit lists (i.e., the treatment information) are kept restricted by the global Randomization Team per Sponsor SOP.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

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

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

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

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

This trial is covered by the FDA requirements 21CFR320. Therefore, the packaging and labelling must be performed in such a way that the required reserve samples are available for storage by the investigational site and that the trial materials can be chosen in a random way by the Investigator.

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
- 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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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.

Vasculitis

In case of events suspicious for vasculitis, trial treatment will be discontinued. A thorough work-up has to be initiated including at least but not limited to

- appropriate imaging, including angiography
- biopsy, if possible
- appropriate laboratory screening, including measurements of vasculitis markers at the local lab, see Section 5.2.3. In addition, an analysis of the previously collected and stored samples will need to be requested and considered.
- thorough documentation of all reported symptoms

Referral to a vasculitis expert is recommended. If required, vasculitis treatment should be initiated according to standard of care.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. 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 milk served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices are not permitted from 7 days before the first administration of trial medication until after the last PK sample in the trial is collected.

Dietary supplements and products containing St. John's wort (Hypericum perforatum) are not permitted from 30 days before the first administration of trial medication until after the last PK sample in the trial is collected.

Subjects should refrain from eating food containing poppy seeds for 48 h prior to screening and for 48 h prior to admission until the end of in-house confinement in each treatment period.

Methylxanthine-containing drinks or foods (e.g., coffee, tea, cola, energy drinks, or chocolate) are not allowed during in house confinement.

Smoking is not allowed during in-house confinement.

Alcoholic beverages are not allowed from 48 h before administration of trial medication until the end of in-house confinement in each treatment period.

No blood or plasma (outside of this study) must be donated from screening until for at least 90 days following the last dose of study medication.

There is no evidence of phototoxicity. So, no restrictions related to sun exposure are required.

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

4.2.2.3 Contraception requirements

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

Female subjects should not participate in egg donation and male subjects should not participate in sperm donation from dosing, for the duration of the study and for at least 7 days after last IMP administration.

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, ethnicity, 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 examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including the 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 a blood pressure monitor (e.g., Philips IntelliVne MP70/X2, [redacted] at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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

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

Table 5.2.3: 1 Routine laboratory tests

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

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

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		
Vasculitis markers*	MPO-ANCA	X	X
	PR3-ANCA	X	X
	IL-6	X	X
	Antiglomerular basement membrane (GBM) antibodies	X	X
	Rheumatoid factor		
	Antinuclear antibodies		
	Complement C3, C4, CH 50, anti-C1q antibodies.	X	X

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 and 3 on Day -1 and Day 2, and EoS (for time points refer to Flow Chart)
* Samples are taken, stored appropriately at the site and only analysed if signs and symptoms of vasculitis appear.

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 pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of study examination. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA
	Barbiturates
	Benzodiazepine
	Cannabis
	Cocaine
	Methadone
	Methamphetamines/MDMA/Ecstasy
	Opiates
	Phencyclidine
	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative)
	Hepatitis B core antibody (qualitative)
	Hepatitis C antibodies (qualitative)
	HIV-1 and HIV-2 antibody (qualitative)
	Hepatitis B DNA PCR (quantitative)[1]
	QuantiFERON®-TB Gold Test (IGRA)
COVID-19 (nasopharyngeal swab)[2]	SARS CoV-2 PCR test or antigen test at screening and prior to admission in each treatment period
Pregnancy tests	In *serum*: Beta human chorionic gonadotropin (beta-HCG) at screening and EoS
	In *urine*: Beta human chorionic gonadotropin (beta-HCG)

[1] to be conducted if Hepatitis B core antibody is positive and Hepatitis B surface antigen is negative.
[2] if needed due to the current status of the pandemic/endemic, evaluation will be performed at screening and shortly (within 72 h) before admission to trial site as per Flow Chart.

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g., Dräger Alcotest®, [redacted] 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 at [redacted], with the exception of drug screening and pregnancy tests in urine. These tests will be performed at the trial site using [redacted]SURESTEP Urine Drug Test and [redacted]hCG URINE TestPack™ Plus with OBC, respectively, or comparable test systems.

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

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

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g., CardioSoft EKG System, [redacted] at the times provided in the Flow Chart.

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

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

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the trial.

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

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)
- If <3 stools please report as 'frequent bowel movements'

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:

  1. AST (aspartate aminotransferase) and/ or ALT (alanine aminotransferase) elevation ≥3x ULN and TB (total bilirubin) ≥2x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR

  2. AST and/ or ALT elevation ≥3x ULN and INR ≥1.5x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR

  3. AST and/ or ALT elevation ≥3x ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/ or eosinophilia (>5%), OR

  4. AST and/ or ALT elevation ≥5x 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.

- Vasculitis events

  In this CTP, 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.

  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) events of vasculitis, further work-up and management as outlined in Section 4.2.1 has to be followed, including biopsy, appropriate imaging/angiography, laboratory measures (e.g. ESR, additional lab sample for immunological and further inflammation markers).

- Serious infections, opportunistic or mycobacterium tuberculosis infections

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

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, e.g., 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, e.g., '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 study (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 study:
    - 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 study, 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

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

The outcome of the pregnancy 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

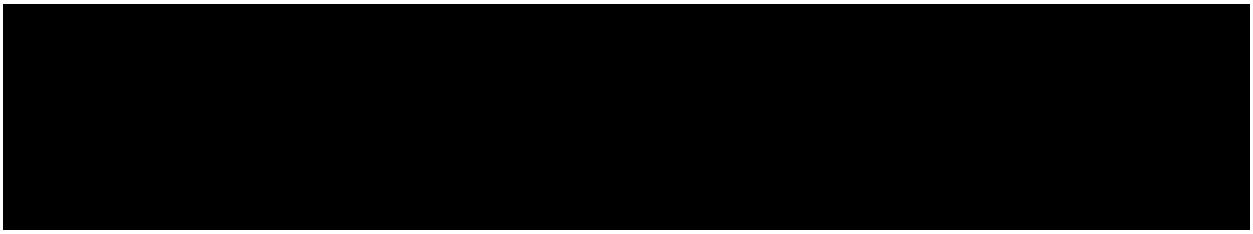
For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of R-BI 1015550 concentrations in plasma, at least 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. The first 0.5 mL withdrawn by an indwelling cannula will be discarded.
The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot (‘A1’) should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 90 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. Any remaining plasma will be the second aliquot (‘A2’) and will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time and aliquot (‘A1’ or ‘A2’).
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]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.4.1 Drug-Drug Interaction Biomarkers

Not applicable.

5.4.2 Pharmacodynamic biomarkers

Not applicable.

5.4.3 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

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.

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 study examination are provided in the Flow Chart.

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

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

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including 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.

The acceptable deviations from the nominal blood sampling times are as follows:

- The pre-dose samples will be taken ≤3h before dosing.
- 0 to 2 h post-dose samples will be taken within ± 2 min of the planned post-dose sampling time.
- 2.5 to 4 h post-dose samples will be taken within ± 5 min of the planned post-dose sampling time.
- 6 to 12 h post-dose samples will be taken within ± 10 min of the planned post-dose sampling time.
- 24 h or later post-dose samples will be taken within ± 60 min of the planned post-dose sampling 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.

Screening safety procedures, e.g., blood sampling for safety laboratory, ECGs, vital signs, alcohol breath tests and urinalysis can be repeated as clinically indicated upon the discretion of the investigator or sub-investigator, if there is a concern regarding a subject's safety or eligibility to participate in the trial.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days -1, 1 to 7 in each period). At least 10 days will separate drug administrations between each treatment.

On Day -1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion. For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

For the primary and secondary endpoints, the effect of food on pharmacokinetics of an 18 mg tablet BI 1015550 will be estimated by the ratios of the geometric means (Test/ Reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level.

Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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 R-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
- Use of restricted medications

Plasma and 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 tmax of the respective treatment (Median tmax is to be determined excluding the subjects experiencing emesis),
- A predose concentration is >5% Cmax value of that subject
- Missing samples/ concentration data at important phases of PK disposition curve

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

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

7.2.2 Primary endpoint analyses

Primary analyses

The primary endpoints (refer to Section 2.1.2) will be calculated with Non-Compartmental Analysis (NCA).

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: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2

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

π_j = the j^{th} period effect, j = 1, 2

τ_k = the k^{th} treatment effect, k = 1, 2

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

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

Point estimates for the ratios of the geometric means (Test/ Reference) for the primary 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.

Further exploratory analyses

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

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

7.2.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated with NCA and will be assessed statistically using the same methods as described for the primary endpoints.

[redacted]

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 randomised treatment will be discussed in the minutes of the Report Planning Meeting).

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

Measurements (e.g., ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the first treatment period. AEs recorded between second trial medication intake and end of REP (see Section 1.2.3) will be assigned to the second treatment period. Events occurring after the REP but prior to next intake or end of study 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.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, e.g., combined treatments, on-treatment totals, or periods without treatment effects (e.g., 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 without consideration of actual period.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

For laboratory data and vital signs, baseline is defined as measurement prior to first drug administration.

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

Subjects will be randomised to one of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation scheme will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 18 subjects in the trial with the aim of ≥ 12 evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (Test/ Reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The sample size for this trial was determined using assumptions on the intra-individual variability of the primary endpoints based on the previous trial 1305-0028 [c37740081] investigating formulation effect and food effect. The intra-individual geometric coefficient of variation (gCV) for R-BI 1015550 was estimated to be about 23% for C_{max} and 8% for AUC.

For various assumptions around the gCV of 25% , Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (T/ R). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.5: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/ R) for different gCVs in a 2x2 crossover trial (N=18)

N	gCV [%]	Precision upper CL** / relative BA estimate	90% CI [%] of respective ratio*		
			95	100	105
12	20	1.22	(77.91; 115.83)	(82.01; 121.93)	(86.12; 128.03)
12	25	1.28	(74.25; 121.56)	(78.15; 127.95)	(82.06; 134.35)
12	30	1.34	(70.81; 127.46)	(74.54; 134.16)	(78.26; 140.87)
18	20	1.16	(81.95; 110.13)	(86.26; 115.92)	(90.58; 121.72)
18	25	1.2	(79.06; 114.16)	(83.22; 120.17)	(87.38; 126.17)
18	30	1.25	(76.31; 118.26)	(80.33; 124.49)	(84.35; 130.71)

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

The calculation was performed as described by Julious [R11-5230] using R Version 4.2.2.

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

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

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

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to finalisation of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (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.

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.

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.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

In EU/ EEA countries, this trial is sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, 5216 Ingelheim am Rhein, Germany.

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 Mangers (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 ([redacted]).

Analyses of R-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 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

R23-0862 Food and Drug Administration. Guidance for industry: assessing the effects of food on drugs in INDs and NDAs – clinical pharmacology considerations (June 2022, clinical pharmacology). 2022

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R17-2617 Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015;74:2107-2116.

R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992.

9.2 UNPUBLISHED REFERENCES

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

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

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.

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.

c37740081 Relative bioavailability comparison of BI 1015550 as the intended commercial formulation (iCF) versus trial formulation 2 and iCF with and without food following oral administration in healthy subjects (an open-label, randomised, single-dose, three-way crossover trial). 1305-0028.

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

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

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		25 Apr 2024
EU Trial number		2023-509889-38-00
BI Trial number		1305-0039
BI Investigational Medicinal Product		BI 1015550
Title of protocol		The effect of food on the pharmacokinetics of BI 1015550 (Formulation C2) following single oral dose administration in healthy subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover design)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		Flowchart
Description of change		Visit number 5 changed to visit number 4. Deletion of pharmacogenomics sampling in the footnote number 1.
Rationale for change		Correction of a formatting oversight. No pharmacogenomics sampling is planned.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inserting Numbering
Rationale for change		Format CS numbering was missing (only administrative changes).
Section to be changed		5.2.3: 1 Routine laboratory test
Description of change		Table Haematology: deleted 4 excessive checkboxes.
Rationale for change		Correction of a formatting oversight.
Section to be changed		5.2.3: 1 Routine laboratory tests (cont.)
Description of change		Table Vasculitis markers: additional checkboxes added in the respective table.
Rationale for change		Correction of a formatting oversight.

11.2 GLOBAL AMENDMENT 2

Date of amendment		16 May 2024
EU Trial number		2023-509889-38-00
BI Trial number		1305-0039
BI Investigational Medicinal Product		BI 1015550
Title of protocol		The effect of food on the pharmacokinetics of BI 1015550 (Formulation C2) following single oral dose administration in healthy subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover design)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		5.2.3: 1 Routine laboratory tests
Description of change		Pregnancy test entered to table 5.2.3: 2 Exclusionary laboratory tests.
Rationale for change		Entered into correct table 5.2.3. due to inconsistency.
Section to be changed		5.2.3: 1 Routine laboratory tests (cont.)
Description of change		Table Vasculitis markers: ‘Anti-C1q antibodies (immune complex-associated small-vessel vasculitis)’ was deleted.
Rationale for change		Correction due to inconsistency.
Section to be changed		Flowchart
Description of change		Foodnote number 4. “Pregnancy test” added, foodnote number 7. word “below” deleted
Rationale for change		Correction due to inconsistency

APPROVAL / SIGNATURE PAGE

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Title: The effect of food on the pharmacokinetics of BI 1015550 (Formulation C2) following single oral dose administration in healthy subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	16 May 2024 16:03 CEST
Approval-Clinical Program [redacted]		16 May 2024 16:17 CEST
Author-Trial Statistician		17 May 2024 08:05 CEST
Verification-Paper Signature Completion		17 May 2024 09:20 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**