Clinical Trial Protocol

	Document Number: **c40254926-03**
EU CT No.	2022-502860-19-00
UTN	U1111-1291-3312
BI Trial No.	1479-0010 [redacted]
BI Investigational Medicinal Product	BI 1810631
Title	Relative bioavailability of BI 1810631 following oral administration [redacted] in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial)
Lay Title	A study in healthy men to test how BI 1810631 is taken up in the body when [redacted]
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 3.0, 13 Nov 2023
Original Protocol Date	23 May 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	23 May 2023
Revision date	13 Nov 2023
BI trial number	1479-0010
Title of trial	Relative bioavailability of BI 1810631 following oral administration [redacted] in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	To assess the effect of a [redacted] on the pharmacokinetics of a single dose of BI 1810631 given as [redacted]. The resulting data are required to inform recommendations for intake of BI 1810631 [redacted]
Trial objective	To investigate the relative bioavailability of [redacted] of BI 1810631 [redacted]
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1810631 Secondary endpoints: $AUC_{0-\infty}$ of BI 1810631
Trial design	Randomised, open-label, single-dose two-way crossover design
Number of subjects **total entered** **on each treatment**	 16 16
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product **dose** **mode of administration**	BI 1810631 [redacted] [redacted] Oral intake with 240 mL of water in [redacted]

Duration of treatment	One day (single dose) for each treatment
Statistical methods	To assess the [redacted] on the relative bioavailability, the ratios of the geometric means (test/reference) for the primary and secondary endpoints will be estimated. 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 nested 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[9]	Safety laboratory [8]	[redacted]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	A		x	x	x
1/2 (two identical periods separated by a wash-out interval of at least [redacted] BI 1810631 administrations)	2/3	-1	-24:00	08:00	Admission to trial site[11]	B[10]		x	x	x[5]
			-13:00	19:00	[redacted]					
		1	-2:00	06:00	Allocation to treatment[2] (visit 2 only)		x[2]			x
			-0:30	07:30	[redacted]					
			0:00	08:00	**Drug administration: BI 1810631**					x
			0:30	08:30			x			x
			1:00	09:00			x			x
			1:30	09:30			x			x
			2:00	10:00	240 mL fluid intake		x			x
			3:00	11:00			x			x
			4:00	12:00	240 mL fluid intake, [redacted]		x	x	x	x
			6:00	14:00			x			x
			8:00	16:00	[redacted]		x			
			10:00	18:00			x			x
			11:00	19:00	[redacted]					
			12:00	20:00			x			x
		2	24:00	08:00		B	x	x	x	x
			36:00	20:00			x			x
		3	48:00	08:00	Discharge from trial site		x			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	B	x			x
		7	144:00	08:00	Ambulatory visit		x			x
		8	168:00	08:00	Ambulatory visit		x			x
FU	4	15 to 22			End of study (EoS) examination[4]	C		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and check of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, [redacted] will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Review of relevant inclusion/exclusion criteria for confirmation of eligibility (in period 1 only).
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. [redacted]
8. Letters A, B and C describe different sets of safety laboratory examinations. For details see Section 5.2.3
9. [redacted]
10. Including urine drug screening and alcohol breath test
11. SARS-CoV-2 PCR test will be performed if it is needed due to the current status of the pandemic.

TABLE OF CONTENTS

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
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EGFR	the epidermal growth factor receptor
EoS	End of Study (synonym for End of Trial)
ErbB	Epidermal growth factor
FU	Follow-up
GCP	Good Clinical Practice

gCV	Geometric coefficient of variation
gMean	Geometric mean
HER2	Human epidermal growth factor receptor 2
HGB	Hemoglobin
IB	Investigator's brochure
ICF	Informed consent form
iCF	intended commercial formulation
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NF	New formulation
NSCLC	non-small-cell lung cancer
NTproBNP	N terminal prohormone of brain natriuretic peptide
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
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
RTK	transmembrane receptor tyrosine kinases
SAE	Serious adverse event
SCR	Screening
[redacted]	
SOP	Standard operating procedure
T	Test product or treatment
TF1	Trial Formulation 1
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set

t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VS	Vital signs
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of child-bearing potential
YVMA	HER2 mutation with 12 base pair in-frame insertion YVMA (p.A775-G776insYVMA)

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family of homologous transmembrane receptor tyrosine kinases. The family of ErbB transmembrane receptor tyrosine kinases (RTKs) consists of the four members EGFR (ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3) and HER4 (ErbB4), which fulfil essential functions during development [R20-1872, R09-6185, R20-1990]. ErbB signalling is initiated upon binding of the extracellular domains of EGFR, HER3 or HER4 to their respective ligands and subsequent homo- or heterodimerization of ErbB family members. HER2, for which no ligand has been identified, is the preferred dimerization partner for the other ErbB members. Once an active ligand-receptor complex has been formed, the intracellular tyrosine kinase domains of EGFR, HER2 or HER4 are activated by auto- or transphosphorylation and subsequently elicit a signal transduction cascade most notably engaging the mitogen-activated protein kinase and/or the phosphoinositide 3-kinase pathways [R20-1872, R09-6185, R20-1990].

Aberrant ErbB signalling is implicated in several pathophysiological conditions including cancer or neurological diseases. In cancer, ErbB signalling is hyper-activated through mutations that render the RTK constitutively active by promoting dimerization or shifting the equilibrium towards the active conformer of the kinase and/or through amplification and consequent over-expression of the RTK. Both oncogenic mechanisms increase the net output of ErbB signalling and thereby promote cell survival, cell growth and proliferation [P15-01211].

More recently, increasing attention has been given to the emerging impact of oncogenic HER2 activation through somatic gene mutation. The majority of these HER2 mutant cancers have not been associated with concurrent HER2 gene amplification. Mutations are found across all exons of the HER2 gene including exon 20, with significant heterogeneity both between and within human cancer types. The highest prevalence of HER2 mutations is observed in prostate neuroendocrine cancer, metastatic cutaneous squamous cell carcinoma, and bladder cancer (all >10% of cases). A significant HER2 mutation prevalence is also found in more common cancers, including lung, colorectal and breast cancers, indicating a large additional patient base that could potentially be targeted with HER2-directed therapies [P19-10412].

Mutations in HER2 have been identified as oncogenic drivers and occur in 2 to 3% of non-small-cell lung cancer (NSCLC). HER2 mutations most commonly consist of a 12 base pair in-frame insertion YVMA (p.A775_G776insYVMA) in exon 20 [P19-00456, P20-09250]. There is no standard targeted treatment for NSCLC with HER2 aberrations including HER2 exon 20 insertion mutations. Clinically approved tyrosine kinase inhibitors have not been shown to be efficacious in these patients, as they are limited by EGFR wild type mediated dose limiting toxicity. Therefore there is a clear unmet medical need for new treatment options for NSCLC patients with HER2 insertion mutations.

1.2 DRUG PROFILE

For a comprehensive description of BI 1810631 refer to the IB [c32836122].

1.2.1 Mode of action

BI 1810631 is an EGFR wild type sparing, selective HER2 inhibitor with potent inhibitory activity on [redacted] HER2 mutations including the HER2 YVMA insertion allele. It is intended to treat patients with advanced solid tumors with HER2 aberrations.

1.2.2 Data from studies in humans

Prior to the current trial, BI 1810631 was administered in the ongoing first-in-man trial in patients with cancer 1479-0001 and in one PK study in healthy volunteers (trial 1479-0003).

A short summary of the trials and drug-related adverse events in these trials is provided here. For details on PK, safety, and efficacy refer to the IB [c32836122].

Short description of patient first-in-man trial 1479-0001

1479-0001 is an open-label, Phase I dose escalation trial, with dose confirmation and expansion, of BI 1810631 [redacted] in patients with advanced or metastatic solid tumors with HER2 aberrations. Patients are continuously treated in different dose groups with [redacted] dosing schemes. PK, safety, and efficacy data are collected. So far, [redacted] were treated in the dose escalation part with BI 1810631 either in one of the [redacted] or the [redacted]. described here is 09 Mar 2023.

Short description of healthy volunteer trial 1479-0003

At the time of CTP finalization, trial 1479-0003 is in the reporting phase. Trial 1479-0003 was an open-label, randomized, 4-way crossover Phase I trial. The trial investigated relative bioavailability of BI 1810631 after administration as [redacted] on the pharmacokinetics of a single dose of BI 1810631 in plasma and investigated the effect of multiple-dose treatment with [redacted] on the pharmacokinetics of a single dose of BI 1810631. Thirteen healthy male volunteers were dosed with single doses of [redacted] BI 1810631 in 4 treatment periods in randomized order, separated by wash-out intervals of [redacted]. The 4 treatments were:

- R: [redacted] BI 1810631 trial formulation 1 (TF1) [redacted]
- T1: [redacted] BI 1810631 new formulation (NF) [redacted]
- T2: [redacted] BI 1810631 NF after [redacted]
- T3: [redacted] BI 1810631 NF after [redacted].

Safety and tolerability data of patient first-in-man trial 1479-0001 (preliminary data)

For an overview of available safety and tolerability data of trial 1479-0001 refer to the IB [c32836122]. The following text and tables in this protocol focus on drug-related AEs.

Overall, [redacted] had an AE assessed as drug-related by the investigator. The most common drug-related AEs were [redacted]

[redacted]

According to the IB there are two further cases of drug related [redacted] after the data lock point for the IB and this protocol (9 Mar 2023) with the follow up for the clinical course ongoing [c32836122].

Table 1.2.2: 1 Number (%) of patients with drug-related AEs by dose group and preferred term- on treatment period, [redacted] cohorts (preliminary data)

Preferred term	[redacted]				
	[N (%)]	[N (%)]	[N (%)]	[N (%)]	[N (%)]
Number of patients	[redacted]				
Total with drug-related AEs					
[redacted]					

Table 1.2.2.: 2 Number (%) of patients with drug-related AEs by dose group and preferred term- on-treatment period, [redacted] cohorts (preliminary data)

Preferred term	[redacted]				
	[N (%)]	[N (%)]	[N (%)]	[N (%)]	[N (%)]
Number of patients	[redacted]				
Total with drug-related AEs					
[redacted]					

Safety and tolerability data of healthy volunteer trial 1479-0003

In trial 1479-0003, in which oral single doses of [redacted] BI 1810631 were administered to healthy volunteers, [redacted] For more details refer to the IB [c32836122].

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of [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

In previous trial 1479-0003, a [redacted] observed for BI 1810631 [redacted] (see Section 1.2.2). The [redacted] It is required for the final label and to obtain market approval for BI 1810631 in e.g. [redacted] to investigate [redacted] in 1479-0003 trial. Thus, the rationale for performing the trial is to assess [redacted] BI 1810631 given [redacted]

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1810631 for treatment of patients with advanced solid tumours with HER2 aberrations.

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.

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 1810631		
[redacted]	• [redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only two single doses with appropriate wash-out • [redacted]
[redacted]	• [redacted]	• [redacted] defined in the Flow Chart
Interstitial lung disease (ILD) and Pneumonitis	• Not observed for BI 1810631 so far, however reported from other tyrosine kinase inhibitors	• Subjects are protected from this finding by administration of only two single doses with appropriate wash-out • AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Subjects with pre-existing ILD/pneumonitis or other respiratory disorder are excluded from trial participation (see exclusion criteria 4 and 5)

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]	• [redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Physical examination of subjects at end-of-study visit • Protection of subjects by administration of only two single doses
[redacted]	• [redacted]	• Safety laboratory (see Section 5.2.3) includes [redacted] • Protection of subjects by administration of only two single doses with appropriate wash-out
[redacted]	• [redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only two single doses with appropriate wash-out • Following administration of BI 1810631, subjects will be in-house under close observation for at least 48 hours

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]	• [redacted]	• [redacted]
Drug-related AEs observed in patients in trial 1479-0001	After multiple dosing with BI 1810631, AEs assessed as drug-related were reported (see Section 1.2.2.)	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Following administration of BI 1810631, subjects will be in-house under close observation for at least 48 hours • Protection of subjects by administration of only two single doses with appropriate wash-out
Uncertainties due to the early stage of development	[redacted]. However, BI 1810631 is currently in early development and there may be unknown risks of treatment with BI 1810631	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Following administration of BI 1810631, subjects will be in-house under close observation for at least 48 hours • Safety Lab, VS and ECGs after dosing (see Flow Chart) • Protection of subjects by administration of only two single doses with appropriate wash-out

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]	Rare but severe event, thus under constant surveillance by sponsors and regulators. [redacted]	[redacted]
[redacted]	[redacted]	• Only healthy volunteers will be included in the trial and exposed to a maximum two doses of BI 1810631. • [redacted] •
Trial procedures		
Blood sampling: 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
ECG recording: Skin irritation, redness, itching	General risk by ECG electrodes, acceptable in the framework of trial participation.	Exclusion of subjects from trial participation with known clinically relevant hypersensitivity reactions to adhesive tapes.

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

1.4.3 Discussion

There is significant medical need in cancer patients harbouring HER2 mutations for effective, safe and well-tolerated therapies. BI 1810631 is an EGFR wild-type sparing selective HER2 inhibitor with potent inhibitory activity on [redacted] HER2 mutations.

It provides a unique opportunity for the treatment of NSCLC patients harbouring HER2 mutations, and data further suggest that BI 1810631 could be [redacted]

BI 1810631 has been adequately characterized in preclinical studies. Preclinically identified toxicities are addressed by appropriate mitigation (see Section 1.4.2). Moreover, preliminary data from two clinical trials are available (see Section 1.2.2) that support the [redacted] planned for the current trial. In particular, BI 1810631 has been given at multiple doses of up to [redacted] and of up to [redacted] over at least 21 days to patients in first-in-man trial 1479-0001, and in that study, BI 1810631 [redacted]

This trial is required to inform the label of BI 1810631 and to acquire market approval in e.g. [redacted] The resulting data are used to assess the [redacted]

Considering the medical need for an effective and safe treatment of solid tumours with HER2 mutations, the benefit of this trial is assessed to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of a [redacted] of BI 1810631 [redacted]

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1810631:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time 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 BI 1810631:

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

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 1810631 will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, randomised, single-dose, two-way crossover trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be [redacted] of BI 1810631 [redacted] administered to subjects [redacted] (Test, T) and [redacted] of BI 1810631 [redacted] administered to subjects in the [redacted] (Reference, R). The subjects will be randomly allocated to the 2 treatment sequences (R-T or T-R). For details, refer to Section 4.1.

There will be a washout period of [redacted] between the administrations of BI 1810631 in subsequent treatment periods. A graphic of the trial design is displayed in Figure 3.1: 1 below.

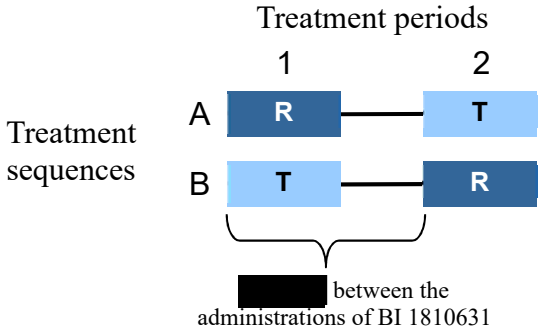

Figure 3.1: 1 Trial design

Each treatment sequence (A, B) includes 8 healthy volunteers, i.e., 16 volunteers in total. In each treatment period (1, 2), the healthy volunteers receive [redacted] of BI 1810631 [redacted].

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

The washout phase of [redacted] between the drug administrations of subsequent treatment periods is chosen to diminish the impact of possible carryover effects.

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of BI 1810631, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation and any kind of vaccination)
13. Intake of an investigational drug in another clinical trial within 60 days or within five half-lives, whichever is longer of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. [redacted]
15. [redacted]
16. Alcohol abuse (consumption of more than 24 g per day)
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 [redacted] of the trial site
21. A marked prolongation of QT/QTcF interval (such as QTcF intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. Male subjects with WOCBP partner who are unwilling to use highly effective contraception from time point of administration of BI 1810631 until 30 days after the last administration of BI 1810631. Highly effective methods of contraception are:

    - Subject is sexually abstinent, if this is in line with his usual lifestyle.

- Subject is vasectomized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and uses condom
- Use of intrauterine device or intrauterine hormone-releasing system by female partner plus use of condom
- Use of progestogen-only hormonal contraception by female partner that inhibits ovulation (injectables or implants) plus use of condom
- Use of combined (estrogen and progestogen containing) hormonal contraception by female partner that prevents ovulation (oral, intravaginal, or transdermal) plus use of condom
- Bilateral tubal occlusion in the female partner plus use of condom

Sperm donation is not allowed from the time point of first administration of BI 1810631 until 30 days after the last administration of BI 1810631.

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2) 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 is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment

4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases).
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
6. The subject has a QTcF increase of greater than 60 ms from baseline in connection with absolute QTc greater than 500 ms, as confirmed by a repeat ECG recording.
7. The subject experiences a drug-related adverse event of severe intensity or a serious adverse event.

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of CTCAE grade 2 or grade 3 severity (except for grade 2 headache), or if at least one drug-related serious adverse event is reported

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

3.3.5 Replacement of subjects

In case more than 4 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacologist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 4. A replacement subject will be assigned a unique randomization number, and will be assigned to the same treatment sequence as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

BI 1810631 will be provided by BI Pharma GmbH & Co. KG, Germany.

Substance:	BI 1810631
Pharmaceutical formulation:	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	
Mode of administration:	Oral
Duration of use:	Single dose in treatment R and T

4.1.2 Selection of doses in the trial

The dose selected for this trial is expected [redacted]

4.1.3 Method of assigning subjects to treatment groups

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

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation scheme will be allocated to the subjects according to respective internal regulation. Subjects are then assigned to a treatment sequence according to the randomisation scheme.

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

For safety considerations, the subjects will be divided into at least 2 cohorts, with at maximum 6 subjects in the first cohort. Cohort 1 and Cohort 2 will be separated by at least 1 week (between dosings in treatment period 1).

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	Total dose
T (Test)	BI 1810631	[redacted]			
R (Reference)	BI 1810631				

Administration of trial medication in the Reference period [redacted]. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing or sitting 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, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

In one treatment period (Treatment T), the subjects [redacted]

Table 4.1.4: 2 [redacted]

[redacted]

Subjects will be kept under close medical surveillance until 48 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). For

measurement of vital signs and ECGs a resting time of at least 5 minutes in the supine position is permitted.

The treatments will be separated by a wash-out phase of [redacted] between BI 1810631 administrations.

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	This open label trial will provide the subject treatment information as soon as treatment has been assigned.
Investigator/Site Staff	As requested to prepare trial site prior to first subject entered. The randomization scheme will be provided to the trial site prior to randomization for preparation of medication.
Sponsor trial team and data	Unblinded as requested.
Bioanalytical Staff	Persons directly involved in bioanalyses of PK samples will be blinded to trial treatments.
Pharmacologist/ Pharmacometrician	As requested for analysis.
Unblinded Pharmacist/ Pharmacy staff	Prior to first subject entered if necessary

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 product BI 1810631 will be provided by BI. It will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).
The label will be prepared according to regulation (EU) No 536/2014, Annex 6, omitting certain particulars with the following justification:
The "keep out of reach of children" statement was omitted from 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 (TIC), which will be issued to each trial participant.

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

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- 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

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

In case of [redacted]

Table 4.2.1: 1 Grade-specific treatment recommendations of [redacted]

Severity (CTCAE grading)	Description	Treatment recommendations
[redacted]		

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

In case of AEs requiring analgesic / antiphlogistic treatment such as headache, short-term use of ibuprofen is acceptable.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to [redacted] those provided by the staff. [redacted]

From 1 h before drug intake until [redacted], fluid intake is restricted [redacted], the water administered with the drug, and an additional 240 mL of water [redacted] (mandatory for all subjects). From [redacted] until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages are forbidden from 4 days before the first administration of trial medication until after the last PK sample taken of the trial.

[redacted] are not permitted from 7 days before the first administration of trial medication until after the last PK sample of the trial is collected.

[redacted]

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

4.2.2.3 Contraception requirements

Subjects whose sexual partner is a WOCBP must be sexually abstinent or use highly effective contraception starting from the first dose of BI 1810631 and for at least 30 days after the last dose of BI 1810631. See Section 3.3.3 for required contraceptive measures.

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

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 (Philips IntelliVne MP70/X2)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 [redacted]

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	X
	Prothrombin time (Quick)	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]			
	Lactic Dehydrogenase	X	--	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	[redacted]	X	X	X
Substrates	Glucose (Plasma)	X	--	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	--	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Cholesterol, total	X	--	X
	Triglyceride	X	--	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine HGB (qual)	X	X	X
	Urine leucocyte esterase (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment[1]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

[1] microscopic examination if erythrocytes, leukocytes, nitrite, or protein are abnormal in urine

A: Safety laboratory at screening, B: Safety laboratory during the study and C: safety laboratory at end-of-trial visit

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

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine THC Cocaine Methadone Methamphetamines/MDMA/Ecstasy Morphine 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)

To encourage compliance with alcoholic restrictions, a breath alcohol test (Dräger Alcotest®) 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 tests. These tests will be performed at the trial site using [redacted] SURESTEP Urine drug Test Cassette or comparable test systems. The SARS-CoV-2 PCR test will be performed at [redacted] prior to admission, if it is needed due to the current status of the pandemic.
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 (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.

All locally printed ECGs will be signed and dated by the investigator or a designee and evaluated in the SDB. 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.

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

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

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [R18-1357].

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

The following must be collected and documented on the appropriate CRF(s) by the investigator and/or delegated study team members on behalf of the investigator:

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

For reporting of safety information to the Agency by the sponsor please refer to section 8.4.

5.2.6.2.3 Pregnancy

Once the subject has been enrolled in the clinical trial and has taken BI 1810631, and if a partner of the male trial participant becomes pregnant, the investigator must report any BI 1810631 exposure during pregnancy in a partner of the male trial participant by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner. Reporting and consenting must be in line with local regulations.

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 the female partner's pregnancy itself is not to be reported as an AE, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1810631 concentrations in plasma, [redacted] of blood will be drawn from an antecubital or forearm vein into an [redacted] 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 [redacted] blood samples will be centrifuged for [redacted]. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least [redacted] of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within [redacted], with interim storage of blood samples and aliquots [redacted] 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 [redacted] at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately [redacted] or below until analysis

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

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

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

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 trial examination are provided in the Flow Chart.

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

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

If scheduled in the Flow Chart at the same time [redacted], 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.

For procedures scheduled for days 4, 5, 6, 7 and 8, a time window of ± 120 min around planned time applies.

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.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days -1 to Day 8 in each period). [redacted] will separate drug administrations in the first and second treatment periods.

In the morning of Day -1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 48 h following BI 1810631 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 trial examination.

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

6.2.3 Follow-up period and trial completion

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 1810631 [redacted] 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 drug BI 1810631 will be calculated according to the relevant BI internal procedures.

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

Important protocol deviations may be:

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration of BI 1810631 is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: 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, ..., 8

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.

[redacted]

7.2.3 Secondary endpoint analyses

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

[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 (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before data base lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range 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 the last measurement prior to trial medication intake of respective treatment period.

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

Subjects will be randomised to one of the 2 treatment sequences (R-T, T-R) 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 16 subjects in the trial, including up to 4 dropouts or non-PK evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for BI 1810631 in previous trial 1479-0003 [c40238670] was [redacted].

For various assumptions the gCV is considered [redacted] and up to [redacted]. Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference) based on the ratios of geometric means observed in the previous trial 1479-0003, i.e. gMean ratio around [redacted] and [redacted] For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means based on a sample size of N=12, 14 and 16 evaluable subjects.

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=12, 14, 16)*

N	gCV [%]	Precision upper CL** / relative BA estimate	90% CI [%] of respective ratio*		
			50	75	100
[redacted]					

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

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 4.1.2.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the 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. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

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

8.1 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.

8.2 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements including Clinical Trial Regulation Art. 42.

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.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant'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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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 first act of recruitment represents the start of the trial and is defined as the date when the first trial participant (subject) in the whole trial signs informed consent.

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] 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 Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted].

Safety laboratory tests will be performed by the local [redacted]).

Analyses of BI 1810631 concentrations in plasma will be [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 by a contract research organization appointed by BI.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		08 Aug 2023
EUCT No.		2022-502860-19-00
BI Trial number		1479-0010 [redacted]
BI Investigational Medicinal Product(s)		BI 1810631
Title of protocol		Relative bioavailability of BI 1810631 following oral administration [redacted] in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		3.3.3
Description of change		Further specification of exclusion criteria #13
Rationale for change		To exclude intake of investigational drug in another trial within 60 days or within five half-lives, whichever is longer. Request from competent authorities.
Section to be changed		5.2.6.2.2 and 8.4
Description of change		Addition of obligation of the sponsor to report safety information to the agency.
Rationale for change		Request from competent authorities

11.2 GLOBAL AMENDMENT 2

Date of amendment		13 Nov 2023
EUCT No.		2022-502860-19-00
BI Trial number		1479-0010 [redacted]
BI Investigational Medicinal Product(s)		BI 1810631
Title of protocol		Relative bioavailability of BI 1810631 following oral administration [redacted] in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		Title Page
Description of change		Clinical Trial Leader changed
Rationale for change		Change in Clinical Trial Leader

APPROVAL / SIGNATURE PAGE

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Title: Relative bioavailability of BI 1810631 following oral administration [redacted] in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial)

Signatures (obtained electronically)

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