Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c35764659-03**
EudraCT No.	2022-000268-23	
BI Trial No.	1479-0003	
BI Investigational Medicinal Product	BI 1810631	
Title	Relative bioavailability of BI 1810631 as two different oral formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial)	
Lay Title	A study in healthy men to compare two different oral formulations of BI 1810631 and to test how food or rabeprazole influence the amount of BI 1810631 in the blood	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax [redacted]	
Principal Investigator	[redacted] Phone: + [redacted] Fax: + [redacted]	
Status	Final Protocol **(Revised Protocol (based on global amendment 02))**	
Version and Date	Version: 3.0	Date: 25 May 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	14 March 2022
Revision date	25 May 2022
BI trial number	1479-0003
Title of trial	Relative bioavailability of BI 1810631 as two different oral formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial)
Principal Investigator:	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	[redacted] For this, relative bioavailability of TF1 and new formulation (NF) is assessed. Moreover the trial intends to inform on the effect of food and of the proton pump inhibitor rabeprazole on the PK of BI 1810631 after administration as NF in order to inform management of food and concomitant medications.
Trial objectives	To investigate • the relative bioavailability of two different BI 1810631 [redacted] formulations (trial formulation 1, TF1, Reference, R; and new formulation, NF, Test 1, T1) under fasting conditions • the relative bioavailability of BI 1810631 NF under fasting (T1) and fed (T2) conditions • the relative bioavailability of BI 1810631 NF given alone (T1) and together with the proton pump inhibitor rabeprazole (T3) under fasting conditions
Trial design	Randomised, open-label, four-way crossover
Trial endpoints:	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1810631 Secondary endpoint: $AUC_{0-\infty}$ of BI 1810631
Number of subjects **total entered**	[redacted]

each treatment	[redacted]
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1	BI 1810631 [redacted] (trial formulation 1, TF1), strengths [redacted]
dose	[redacted]
mode of admin.	Oral with 240 mL of water [redacted]
Test product 2	BI 1810631 [redacted] (new formulation, NF), strength [redacted]
dose	[redacted]
mode of admin.	Oral with 240 mL of water [redacted]
Test product 3	PARIET® (rabeprazole) gastroresistant tablet, strength 20 mg
dose	40 mg (2 tablets à 20 mg)
mode of admin.	Oral with 240 mL of water
Duration of treatment	TF1 fasted (Reference, R): BI 1810631 [redacted] single dose [redacted] on Day 1, fasted NF fasted (Test 1, T1): BI 1810631 [redacted] single dose [redacted] on Day 1, fasted NF fed (Test 2, T2): BI 1810631 [redacted] single dose [redacted] on Day 1, fed NF fasted + rabeprazole (Test 3, T3): - BI 1810631 [redacted] single dose on Day 1 [redacted], fasted - rabeprazole 40 mg once daily (2 tablets à 20 mg) on Days -4 to 1

Statistical methods	Comparisons of interest: NF fasted (Test 1, T1) vs. TF1 fasted (Reference, R) NF fed (Test 2, T2) vs. NF fasted (Test 1, T1) NF fasted + rabeprazole (Test 3, T3) vs. NF fasted (Test 1, T1) Relative bioavailability will be estimated by the ratios of the geometric means (T1/R, T2/T1 and T3/T1) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects 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 FOR "TF1 FASTED", "NF FASTED", AND "NF FED"

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK (BI 1810631, blood)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [5]
SCR	1	-28 to -5			Screening (SCR)[1]	A		x	x	
[redacted] between BI 1810631 administrations in subsequent periods)	2/ 3/ 4/ 5	-5	-122:00	07:00	Ambulatory visit[6]	B[6]				x[6]
		-4	-98:00	07:00	Ambulatory visit, treatment allocation[6]	B[7,8]				x
		-1	-13:00	20:00	Admission to trial site					x
		1	-2:00	07:00			x[2]	x[2]	x[2]	x[2]
			-0:30	08:30	[redacted]					
			0:00	09:00	**Admin.:** [redacted] **BI 1810631**[10]					
			0:30	09:30			x			
			1:00	10:00			x			
			1:30	10:30			x			
			2:00	11:00	240 mL fluid intake		x	x	x	x
			3:00	12:00			x			
			4:00	13:00	240 mL fluid intake, [redacted]		x	x	x	x
			6:00	15:00			x			
			7:00	16:00	[redacted]					
			8:00	17:00			x			
			10:00	19:00	[redacted]		x			
			12:00	21:00			x			x
		2	24:00	09:00	Breakfast (voluntary)[3], discharge from trial site	B	x	x	x	x
			34:00	19:00	Ambulatory visit		x			x
		3	46:00	07:00	Ambulatory visit		x			x
		4	70:00	07:00	Ambulatory visit		x			x
		5	94:00	07:00	Ambulatory visit		x			x
		6	118:00	07:00	Ambulatory visit		x			x
FU	6	15 to 22			End of study (EoS) examination[4]	B		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The procedure is to be performed and completed within the 3 h prior to BI 1810631 administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. Including physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. 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.
6. Only in period 1. Safety laboratory on Day -5 (including AE&CT questioning on Day -5) can be omitted if the screening examination is performed on Day -5. Procedures on Day -5 can be performed anytime on Day -5.
7. Safety laboratory B only in periods 2, 3, and 4.
8. Including urine drug screening and alcohol breath test in all four periods
9. Only in treatment "NF fed"
10. Formulation TF1 in treatment "TF1 fasted" and formulation NF in treatments "NF fasted" and "NF fed"

FLOW CHART FOR "NF FASTED + RABEPRAZOLE"

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK (BI 1810631, blood)	PK (rabeprazole, blood)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [5]
SCR	1	-28 to -5			Screening (SCR)[1]	A			x	x	
[redacted] between BI 1810631 administrations in subsequent periods) 1/2/3/4 (wash-out of at least	2 / 3 / 4 / 5	-5	-122:00	07:00	Ambulatory visit[6]	B[6]					x[6]
		-4	-98:00	07:00	Ambulatory visit, treatment allocation[6] **Admin.: rabeprazole 40 mg**	B[7,8,9]					x[9]
		-3	-74:00	07:00	Ambulatory visit, **Admin.: rabeprazole 40 mg**						x[9]
		-2	-50:00	07:00	Ambulatory visit, **Admin.: rabeprazole 40 mg**						x[9]
		-1	-26:00	07:00	Ambulatory visit, **Admin.: rabeprazole 40 mg**						x[9]
			-13:00	20:00	Admission to trial site						x
		1	-2:00	07:00	**Admin.: rabeprazole 40 mg**		x[2]	x[9]	x[2]	x[2]	x[2]
			0:00	09:00	**Admin.: [redacted] BI 1810631 NF**			x[10]			
			0:30	09:30			x				
			1:00	10:00			x				
			1:30	10:30			x	x			
			2:00	11:00	240 mL fluid intake		x	x	x	x	x
			3:00	12:00			x				
			4:00	13:00	240 mL fluid intake, [redacted]		x		x	x	x
			6:00	15:00			x				
			7:00	16:00	[redacted]						
			8:00	17:00			x				
			10:00	19:00	[redacted]		x				
			12:00	21:00			x				x
		2	24:00	09:00	Breakfast (voluntary)[3], discharge from trial site	B	x		x	x	x
			34:00	19:00	Ambulatory visit		x				x
		3	46:00	07:00	Ambulatory visit		x				x
		4	70:00	07:00	Ambulatory visit		x				x
		5	94:00	07:00	Ambulatory visit		x				x
		6	118:00	07:00	Ambulatory visit		x				x
FU	6	15 to 22			End of study (EoS) examination[4]	B			x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The procedure is to be performed and completed within the 3 h prior to BI 1810631 administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. Including physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. 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.
6. Only in period 1. Safety laboratory on Day -5 (including AE&CT questioning on Day -5) can be omitted if the screening examination is performed on Day -5. Procedures on Day -5 can be performed anytime on Day -5.
7. Safety laboratory B only in periods 2, 3, and 4.
8. Including urine drug screening and alcohol breath test in all four periods
9. Taken within 2 hours before rabeprazole dosing.
10. Within 10 minutes before the planned intake of BI 1810631. BI 1810631 intake should be on time.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
AR	Accumulation ratio
AUC_{0-12}	Area under the concentration time curve of the analyte in plasma over the time interval from 0 to 12 hours
$AUC_{0-\infty}$	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
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
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
BI	Boehringer Ingelheim
b.i.d.	Twice daily
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
[redacted]	[redacted]
DBL	Data base lock
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram

eCRF	Electronic case report form
eDC	Electronic data capture
[redacted]	[redacted]
EGFR	Epidermal growth factor receptor
EoS	End of study
EudraCT	European Clinical Trials Database
FDA	U.S. Food & Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HER2	Human epidermal growth factor receptor 2
IB	Investigator's brochure
IEC	Independent Ethics Committee
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
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NF	New formulation
NSCLC	Non-small-cell lung cancer
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PPI	Proton pump inhibitor
PR	Pulse rate
q.d.	Once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
[redacted]	[redacted]
SmPC	Summary of Product Characteristics

SOP	Standard operating procedure
ss	(at) steady state
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
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. In 2018 there were approximately 18 million new cancer cases and 9.6 million cancer-related deaths worldwide [R18-3308]. In the majority of cases the disease is diagnosed in late, advanced stages and the vast majority of patients progress on available treatments and succumb to their disease. These statistics highlight a substantial need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

[redacted]

The highest prevalence of [redacted] is observed in [redacted], [redacted] (all >10% of cases). However, a significant [redacted] prevalence is also found in more common [redacted], [redacted], indicating a large patient base that could potentially be targeted with [redacted]

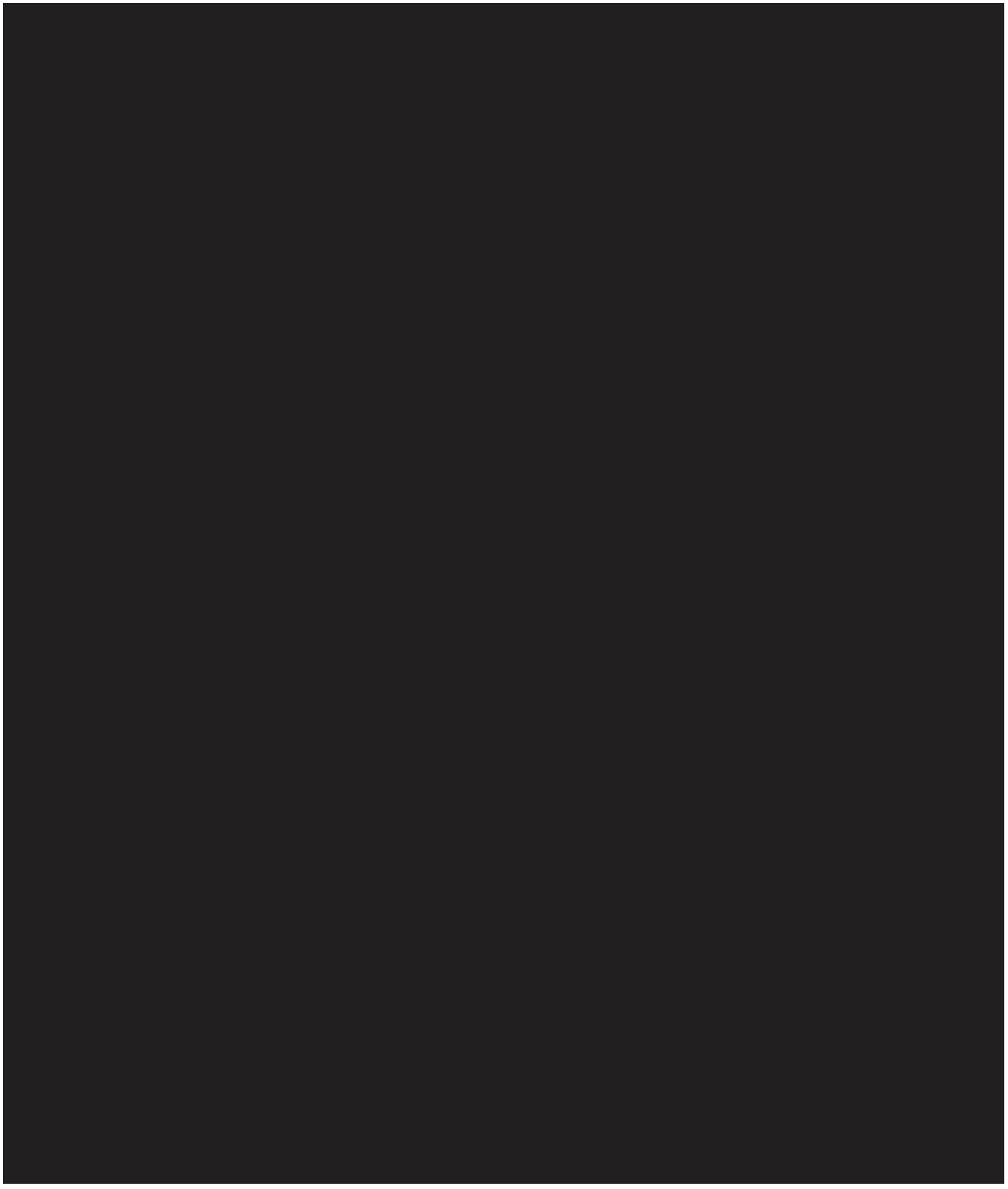
Mutations in [redacted] have been identified as [redacted] and occur in 2 to 3% of [redacted] There is no standard targeted treatment for [redacted]. Clinically approved [redacted] have not been shown to be efficacious in these patients, as they are limited by [redacted] mediated dose limiting toxicity. Therefore there is a clear unmet medical need for new treatment options for [redacted].

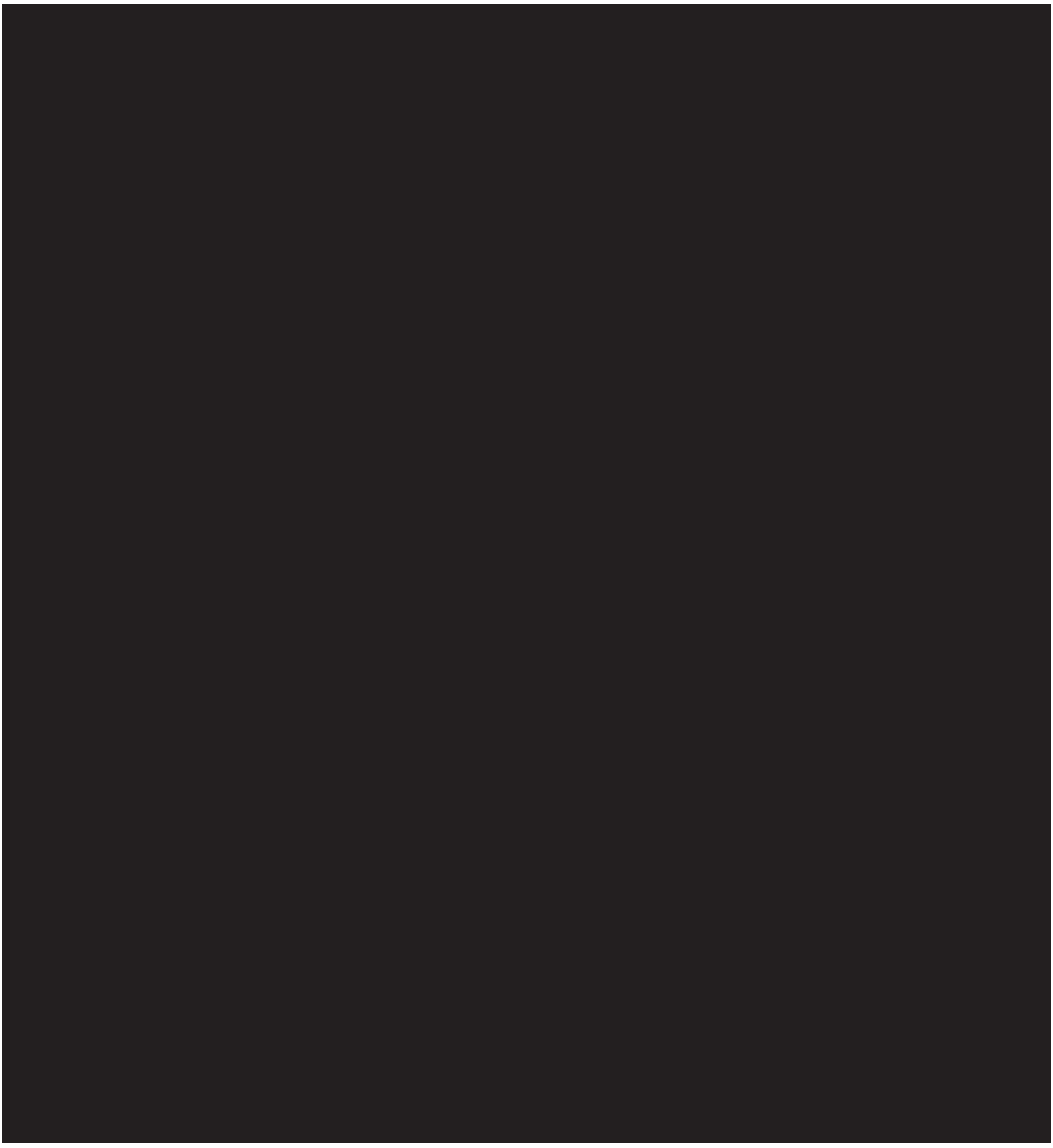
The development of a [redacted] may constitute a valid therapeutic option for patients with NSCLC and multiple other cancers with HER2 aberrations.

1.2 DRUG PROFILE

1.2.1 BI 1810631

For a more detailed description of the BI 1810631 profile, please refer to the current Investigator's Brochure (IB) [c32836122].





1.2.2 Rabeprazole

Rabeprazole is a proton pump inhibitor (PPI) indicated for treatment of diseases that profit of an increased gastric pH such as ulcus ventriculi, ulcus duodeni, reflux esophagitis or

Zollinger-Ellison syndrome as well as in combination with suitable antibiotics for eradication of Helicobacter pylori.

Rabeprazole suppresses gastric acid secretion via inhibition of the H^+/K^+ ATPase. As a weak base, rabeprazole is quickly resorbed after oral administration and accumulates in the acidic milieu of the gastric parietal cells. After oral administration of a dose of 20 mg, the onset of the antisecretory activity is within 1 h, and the maximal effect is achieved within 2-4 h. The duration of the suppression is up to 48 h. Upon repeated daily administration, the suppression of acid secretion increases and reaches a steady state after 3 days. After stopping of the medication, the secretory activity normalizes within 2 to 3 days.

In the IMP Pariet®, a gastro-resistant coating is applied to protect the acid-labile rabeprazole. After passage through the stomach, resorption is fast, with C_{max} reached after approx. 3.5 h. In healthy volunteers the elimination half-life ($t_{1/2}$) is approx. 1 h (range: 0.7-1.5 h), and there is no relevant impact of food or the time of day on rabeprazole absorption.

For a clinical DDI study with a proton pump inhibitor, the FDA draft guidance on evaluation of gastric pH-dependent drug interactions with acid-reducing agents [R22-0176] recommends the use of a PPI that is expected to provide a near maximum effect on pH elevation such as esomeprazole or rabeprazole. A pre-treatment with PPI for e.g., 4 to 5 days is recommended to reach the pharmacodynamic steady state before administering the investigational drug [R22-0176]. For the current study, rabeprazole is selected, [redacted]

In the range of 5 mg qd to 40 mg qd rabeprazole, decrease in intragastric acidity is dose-related and is most pronounced after 40 mg qd [R22-0649, R22-0650, R22-0651]. Thus, 40 mg qd rabeprazole is selected for the current study as it may represent a worst-case scenario.

The dose of 40 mg rabeprazole is lower than the maximal dose of rabeprazole as per the SmPC, i.e. for treatment of Zollinger-Ellison syndrome the maximal dose is a starting dose of 60 mg once daily that may be increased to up to 120 mg per day (with 100 mg as a maximal individual dose). Moreover, 40 mg rabeprazole q.d. has been given in several healthy volunteer studies, e.g. in three DDI studies [R22-0653, R22-0655, R22-0654] or in two studies for intragastric pH investigation [R22-0650, R22-0651]. In these studies, the overall tolerability of rabeprazole appeared good.

For a more detailed description of the rabeprazole profile, please refer to the current SmPC of the IMP Pariet® [R21-4490].

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

[redacted]

- The current trial investigates the relative bioavailability of BI 1810631 as new formulation (NF) compared to [redacted] in order to [redacted] and support the use of [redacted] formulation in further clinical trials. For standardization, this will be done under fasting condition.

Moreover, the effect of food on the PK of BI 1810631 is not known.

- The current trial investigates the relative bioavailability of BI 1810631 as NF when given [redacted] compared to the fasting condition. Resulting data are planned to inform the management of food relative to BI 1810631 intake.

[redacted]

- The current trial investigates the relative bioavailability of BI 1810631 as NF when given together with a PPI compared to when given alone. For standardization, this will be done under fasting condition. Resulting data are planned to inform management of concomitant medication with gastric acid-reducing agents.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Expected benefit for the target population

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. There is significant medical need in cancer patients harbouring [redacted] for effective, safe and well-tolerated therapies. [redacted]. It provides a unique

opportunity for the treatment of [redacted], and data further suggest that BI 1810631 could be [redacted].

1.4.2 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

ECG electrodes may cause local and typically transient skin reactions.

The total volume of blood withdrawn per subject during the entire study 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 Drug-related risks and safety measures - BI 1810631

Based on the mode of action, the pharmacological target, and the non-clinical toxicology data, BI 1810631 is not considered a high risk compound for clinical studies.

[redacted]

Risk mitigation:

- Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously
- [redacted]

[redacted]

Risk mitigation:

- Subjects [redacted] and will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously

[redacted]

- Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously

[redacted]

[redacted]

Safety data in humans from trial 1479-0001

[redacted]

- Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously

[redacted]

1.4.4 Drug-related risks and safety measures – rabeprazole

The most frequent reported adverse drug reactions in clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, exanthema and dry mouth. A comprehensive list of so far observed adverse events associated with rabeprazole may be found in the SmPC of Pariet® [R21-4490]. Overall, the risks associated with 5-day treatment with 40 mg/day rabeprazole are considered low.

Risk mitigation:

- Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously

1.4.5 Risks related to the drug-drug interaction between BI 1810631 and rabeprazole

Potential effects of rabeprazole on BI 1810631

Potential effects of BI 1810631 on rabeprazole

[redacted]

Risk mitigation:

- Subjects will be in-house at the trial site under close medical observation for [redacted] administration of BI 1810631 [redacted] rabeprazole. They will only be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.
- Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously

1.4.6 Risk assessment in the context of SARS-CoV-2 pandemic

This Phase I study is planned to be conducted in healthy volunteers, aged [redacted]. This population [redacted] of severe COVID-19 infection, and study participation [redacted] infected with SARS-CoV-2 beyond the potential risk associated with any need for the study participant to leave his home for study related activities. To date [redacted] suggesting an association between COVID-19 and [redacted] by BI 1810631. [redacted]

1.4.7 Overall benefit-risk assessment

There is significant medical need in cancer patients harbouring [redacted] for effective, safe and well-tolerated therapies. [redacted] It provides a unique opportunity for the treatment of [redacted], and data further suggest that BI 1810631 [redacted].

BI 1810631 has been adequately characterized in preclinical studies. Preclinically identified toxicities are addressed by appropriate mitigation (see Section 1.4.3). Prior to the current trial, BI 1810631 has been given at multiple doses of [redacted] to patients. [redacted]

The current study is needed to support the development of BI 1810631, as it supports [redacted]. Moreover it generates data on food effect, which is expected to inform whether there is need to take BI 1810631 dependent on food intake. The trial also generates data on [redacted].

Considering the medical need for an effective and safe treatment of [redacted], 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 objectives of this trial are to investigate

- the relative bioavailability of two different BI 1810631 [redacted] formulations (trial formulation 1, TF1, Reference, R; and new formulation, NF, Test 1, T1) under fasting conditions

- the relative bioavailability of BI 1810631 NF under fasting (T1) and fed (T2) conditions

- the relative bioavailability of BI 1810631 NF given alone (T1) and together with the proton pump inhibitor rabeprazole (T3) under fasting conditions

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 interval from 0 to the last quantifiable data point)

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for 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 AND PLAN

The study will be performed as a randomised, open-label, four-way crossover trial in healthy male subjects in order to compare test treatment T1 to reference treatment R and to compare test treatments T2 and T3 to test treatment T1. The treatments are:

- [redacted] BI 1810631 as treatment TF1 ("TF1, fasted") given as [redacted] BI 1810631 TF1 (Reference R)
- [redacted] BI 1810631 as treatment NF ("NF fasted") given as [redacted] BI 1810631 NF (Test 1, T1)
- [redacted] BI 1810631 as treatment NF after [redacted] given as [redacted] BI 1810631 NF (Test 2, T2)
- [redacted] BI 1810631 as treatment NF [redacted] BI 1810631 NF) after multiple doses of rabeprazole 40 mg (2 tablets à 20 mg Pariet® on Days -4 to 1; "NF fasted + rabeprazole"; Test 3, T3)

The subjects will be randomly allocated to the 4 treatment sequences:

1) "TF1 fasted"-"NF fasted"-"NF fed"-"NF fasted + rabeprazole" (R – T1 – T2 – T3)
2) "NF fasted"-"NF fasted + rabeprazole"-"TF1 fasted"-"NF fed" (T1 – T3 – R – T2)
3) "NF fed"-"TF1 fasted"-"NF fasted + rabeprazole"-"NF fasted" (T2 – R – T3 – T1)
4) "NF fasted + rabeprazole"-"NF fed"-"NF fasted"-"TF1 fasted" (T3 – T2 – T1 – R)

For details, refer to Section 4.1.

There will be a [redacted] BI 1810631 in subsequent treatments.

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 GROUPS

For relative bioavailability trials, the randomized 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]. Therefore, all four treatments are randomized in their order.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte, which are not expected to be influenced by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

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

Only male subjects are included in the study [redacted].

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 study 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 45 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
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 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 dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. During COVID-19 pandemic: Laboratory test indicative of an ongoing SARS-CoV-2 infection
25. Male subjects with WOCBP partner who are unwilling to use highly effective contraception from time point of first administration of BI 1810631 until 30 days after the last administration of BI 1810631. Highly effective methods of contraception are:
    - Subject is sexually abstinent
    - 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 study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.3), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will discontinue 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

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

Headaches occur frequently in Phase I studies in healthy volunteers, even after placebo treatment [R22-0652]. Relationship of headache to study treatment may be difficult to assess and, if in doubt, may be attributed to study drug. The current study includes four treatment periods [redacted], thus the cumulative number of incidental headaches may be high. Moreover, headaches are frequently observed during rabeprazole treatment [R21-4490], and the dose of rabeprazole is high (see Section 4.1.2). Therefore, grade 2 headaches are excepted from the count for trial discontinuation criterion 5 to avoid unnecessary discontinuation.

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 objectives of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 1/3 of the total number of evaluable subjects anticipated to complete the trial. A replacement subject will be assigned a

unique trial subject number, and will be assigned to the same sequence as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 1810631 trial formulation 1 (TF1) and new formulation (NF [redacted]) will be provided by BI Pharma GmbH & Co. KG to the trial site. "NF" and [redacted] are used interchangeably in this clinical trial protocol. The trial site will obtain Rabeprazole (Pariet®) from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of test product 1 are given below:

Substance:	BI 1810631
Pharmaceutical formulation:	[redacted] "TF1" (trial formulation 1)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]-0-0
Mode of administration:	oral
Duration of use:	1 single dose on Day 1 of the period with treatment "TF1 fasted"

The characteristics of test product 2 are given below:

Substance:	BI 1810631
Pharmaceutical formulation:	[redacted] formulation [NF])
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]
Mode of administration:	oral
Duration of use:	1 single dose on Day 1 of the periods with treatments "NF fasted", "NF fed", and "NF fasted + rabeprazole"

The characteristics of test product 3 are given below:

Name:	Pariet®
Substance:	Rabeprazole sodium
Pharmaceutical formulation:	Gastroresistant tablet
Source:	Public pharmacy (Market authorization holder: [redacted])
Unit strength:	20 mg (corresponding to 18.85 mg rabeprazole)
Posology:	2-0-0
Mode of administration:	oral
Duration of use:	q.d. on Days -4 to 1 of the period with treatment "NF fasted +

rabeprazole"

4.1.2 Selection of doses in the trial

BI 1810631

In the current trial single doses of BI 1810631 will be given as "TF1 fasted", "NF fasted", "NF fed" and "NF fasted + rabeprazole".

[redacted]

Rabeprazole

A dose of 40 mg rabeprazole sodium q.d. is expected to result in a maximal intragastric pH effect (see Section 1.2.2) and is lower than the maximal dose recommended for therapy by the SmPC of the IMP Pariet® (R21-4490). The duration of 5 days total dosing enables reaching a pharmacodynamic steady state before dosing with BI 1810631 and is recommended by FDA guidance [R22-0176].

4.1.3 Method of assigning subjects to treatment groups

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

According to the planned sample size, and for safety considerations, at least 2 cohorts are planned. Prior to the start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability. In the morning of Day -4 (Visit 2), subjects will be allocated to treatment sequences prior to the first administration of trial medication. For this purpose, numbers of the randomisation list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation scheme.

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a randomized four-period crossover study. All subjects are planned to undergo treatment in all four periods. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
TF1 fasted (R)	BI 1810631	[redacted] "TF1"	[redacted]	[redacted] on Day 1	[redacted]
NF fasted (T1)	BI 1810631	[redacted] (=NF)	[redacted]	[redacted] on Day 1	[redacted]
NF fed (T2)	BI 1810631	[redacted] (=NF)	[redacted]	[redacted] on Day 1	[redacted]
NF fasted + rabeprazole (T3)	BI 1810631 Rabeprazole sodium	[redacted] (=NF) Gastroresistant tablet	[redacted] 20 mg	[redacted] on Day 1 2 tablets à 20 mg q.d. on Days -4 to 1	[redacted]

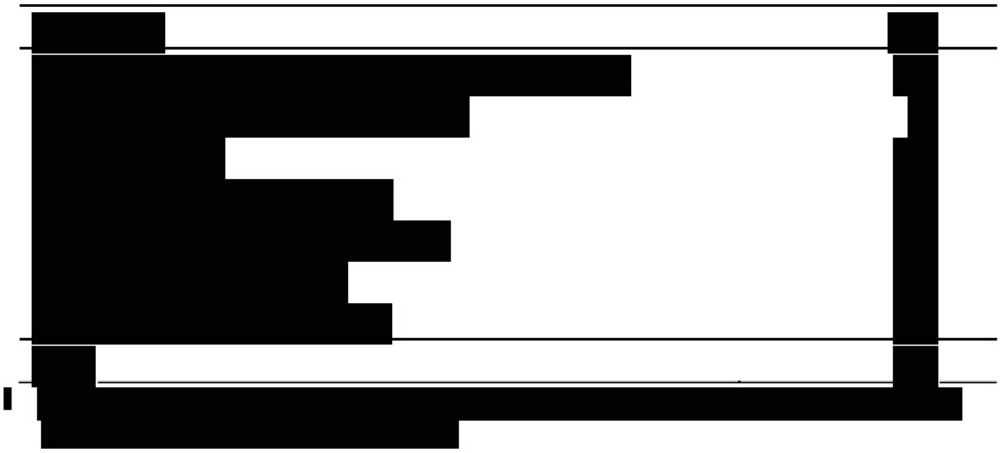
Administration of BI 1810631 will be performed [redacted]

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects [redacted]. 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 the period with treatment "NF fed" (T2), the subjects [redacted]

[redacted]

Table 4.1.4: 2 [redacted]



Subjects will be kept under close medical surveillance until 24 h after administration of BI 1810631. [redacted]

The treatments will be separated by a wash-out interval 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
Subject/Participant	This open label trial will provide the subject treatment information as soon as treatment has been assigned.
Investigator/Site Staff	This open label trial will provide the investigator with the subject/participant's treatment information as soon as treatment has been assigned.
Sponsor trial team and data	Unblinded as requested.
Bioanalytical Staff	Persons directly involved in bioanalyses of PK samples are unblinded.
Pharmacokineticist/ Pharmacometrician	As requested for analysis.

The randomization list will be provided to all involved functions on request.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

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

Packaging and labelling of BI 1810631 will be performed in such a way that the required reserve samples as per FDA requirements 21CFR320 are available for storage by the investigational site and that the trial drugs can be chosen in a random way by the Investigator.

Rabeprazole will be obtained by the trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

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 that are delivered from the sponsor (BI 1810631) when the following requirements are fulfilled:

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

Pariet® (rabeprazole) may be purchased at any time by the investigational site.

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

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The

investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

In case of AEs requiring analgesic / antiphlogistic treatment such as headache, ibuprofen may be given.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff.

From 1 h before BI 1810631 intake until lunch, fluid intake is restricted to , the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). In addition, in period "NF fasted + rabeprazole", fluid intake on Day 1 is restricted from 1 h before rabeprazole intake until 1 h thereafter to the water administered with the

drug. During in-house stay, from lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

[redacted]

Alcoholic beverages are not permitted from [redacted] before each administration of BI 1810631 until after the last PK sample of the respective study period is collected.

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

[redacted]

Excessive physical activity (such as competitive sport) should be avoided from [redacted] 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 [redacted] dose of BI 1810631.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of 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 (Dinamap Pro 100, [redacted] at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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

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

Deviations of laboratory results from normal range will be assessed for clinical relevance by a physician, and clinically relevant deviations will be reported as baseline conditions / as parts of baseline conditions or as adverse events / as parts of adverse events, as applicable.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	White Blood Cells/Leukocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]		
	Lactic Dehydrogenase	X	X
	Lipase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	--
	C-Reactive Protein (Quant)	X	X
	Cholesterol, total	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Calcium	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X
Urinalysis[1] (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leukocytes (qual)	X	X
	Urine pH	X	X
Urine sediment[1]	Only positive findings will be reported[2]		

[1] microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine
[2] e.g., the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes
A: Safety laboratory at screening. B: Safety laboratory during the study and 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 prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test [redacted]) will be performed prior to each treatment period, and may be repeated at any time during the study 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] urine drug test, or comparable test systems. In case of drug screening confirmation test, testing may be done at [redacted] (address see above).

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

5.2.4 Electrocardiogram

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

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

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

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

All locally printed ECGs will be evaluated by the investigator or a designee. 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 further AEs, which, by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

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

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

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.
The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the

ISF or via eDC as applicable. 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.

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:

- 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 or trial database 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 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 immediately after becoming aware of the event (without undue delay) to the sponsor's unique entry point (the country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

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

5.2.6.2.3 Information required

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 assessed as 'chronic' or 'stable', or no further information can be obtained.

[redacted]

[redacted]

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 and rabeprazole concentrations in [redacted] of blood will be drawn from an antecubital or forearm vein into a [redacted] blood drawing tube at the times indicated in the Flow Chart. For each analyte a separate blood sample will be taken. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

[redacted]

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

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites. 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 study samples will be discarded after

completion of the additional investigations but not later than 5 years after the CTR is archived.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

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

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

5.7 APPROPRIATENESS OF MEASUREMENTS

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

clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

In period “NF fasted + rabeprazole”, a time window of +/- 120 min around planned time applies to rabeprazole dosings in the mornings of Days -4 to -2. In that period, in the morning of Day -1, a time window of +/- 60 min around planned time applies to rabeprazole dosing.

In periods “TF1 fasted”, “NF fasted”, and “NF fed”, a time window of +/- 180 min around planned time applies to procedures in the morning of Day -4.

On the evening of Day -1, a time window of +/- 180 min applies to the planned procedures; in any case admission is to be completed no later than 10 hours prior to BI 1810631 administration on Day 1.

For time windows before drug administration in the mornings of Days -4 to 1 refer to the Flow Chart.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1 and ± 60 min on Day 2 if not specified otherwise in the Flow Chart.

For PK samples and other procedures starting from planned time of 46 hours (inclusive) after administration, a time window of +/- 120 minutes applies.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

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

6.2.2 Treatment periods

Each subject is expected to participate in 4 treatment periods (period 1: Day -5 until Day 6; periods 2-4: Day -4 until Day 6). [redacted] will separate administrations of BI 1810631 in subsequent treatment periods.

Order of treatments is randomized; allocation to treatment sequence is in the morning of Day -4 of the first period.

In the evening of Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 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 study 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. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

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 STATISTICAL DESIGN – MODEL

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

NF fasted (T1) compared with TF1 fasted (R)

NF fed (T2) compared with NF fasted (T1)

NF fasted + rabeprazole (T3) compared with NF fasted (T1)

following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of NF fasted (T1) compared with TF1 fasted (R), NF fed (T2) compared with NF fasted (T1) and NF fasted + rabeprazole (T3) compared with NF fasted alone (T1) will be estimated by the ratios of the geometric means (T1/R, T2/T1 and T3/T1), 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.

7.3 PLANNED ANALYSES

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 violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he

contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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.

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.

Relevant protocol deviations may be

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

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

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

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

7.3.1 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, …,4,

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

π_j = the j^{th} period effect, j = 1, …,4,

τ_k = the k^{th} treatment effect, k = 1, …,4,

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 (T1/R, T2/T1 and T3/T1) 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(T1)-log(R), log(T2)-log(T1) and log(T3)-log(T1) 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]

7.3.2 Secondary endpoint analyses

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

7.3.4 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 (BI 1810631 or rabeprazole) in each period and end of REP (see Section 1.2.3) or start of a new trial medication intake will be assigned to the respective 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 final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

A preliminary, exploratory PK analysis of BI 1810631 and rabeprazole may be performed based on evaluable data at any time prior to data base lock. This may be necessary, e.g. in case the information is needed to inform other activities during the development of BI 1810631. In contrast to the final PK calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. No formal preliminary PK report will be written.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

It is not planned to impute missing values for safety parameters. For partial or missing AE onset and/or end dates, BI internal rules will be followed.

7.5.2 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.

7.6 RANDOMISATION

Subjects will be randomised to one of the 4 treatment sequences in a 1:1:1:1 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 list 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 list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of [redacted] subjects in the trial with the aim of ≥ [redacted] 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 the previous trial 1479-0001 (results given in 1.2.1) was roughly [redacted] for C_{max} and [redacted] for AUC.

For various assumptions of the gCV between [redacted] Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 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 4x4 crossover trial (N=12)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 4.0.1.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

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

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

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

For subjects enrolled during the COVID-19 pandemic: In addition to the study-specific informed consent, separate written consent will be obtained for testing for SARS-CoV-2 infection.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

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

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

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.

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

8.3.2 Direct access to source data and documents

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

described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] 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 (BI 1810631) will be provided by the [redacted]. Rabeprazole (Pariet®) will be purchased by the clinical site at a public pharmacy.

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

Analyses of BI 1810631 and rabeprazole concentrations in plasma will be performed at [redacted].

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

Data management and statistical evaluation will be done by BI or 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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R22-0176 Food and Drug Administration. Guidance for industry: evaluation of gastric pH-dependent drug interactions with acid-reducing agents: study design, data analysis, and clinical implications (draft guidance: this guidance document is being distributed for comment purposes only) (November 2020, clinical pharmacology). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2020.

[redacted]

[redacted]

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9.2 UNPUBLISHED REFERENCES

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[redacted]

10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		25 Apr 2022
EudraCT number		2022-000268-23
BI Trial number		1479-0003
BI Investigational Medicinal Product		BI 1810631
Title of protocol		Relative bioavailability of BI 1810631 as two different [redacted] formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1) Synopsis, Section 3.3.2: Inclusion criterion 2 2) Section 3.3.3: Exclusion criterion 10 3) Section 8.1
Description of change		1) Upper age limit reduced from 50 to 45 2) Any current malignancy or history of malignancy is now an exclusion criterion 3) Deletion of "the subject's legally acceptable representative"
Rationale for change		1) To address deficiency issued by competent authority (BfArM) 2) To address deficiency issued by competent authority (BfArM) 3) To address deficiency issued by competent authority (BfArM)

11.2 GLOBAL AMENDMENT 2

Date of amendment		25 May 2022
EudraCT number		2022-000268-23
BI Trial number		1479-0003
BI Investigational Medicinal Product		BI 1810631
Title of protocol		Relative bioavailability of BI 1810631 as two different oral formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1) Title page, Synopsis 2) Synopsis, Flow Chart, 1.2.1, 1.3, 1.4.7, 2.1.1, 3.1, 4.1, 4.1.1, 4.1.2, 4.1.4, 4.2.2.2, 6.1, 7.1, 7.2 3) Abbreviations 4) Section 7.4
Description of change		1) Replacement of "[redacted] formulations" with "oral formulations" in title and lay title 2) Replacement of intended commercial formulation (iCF) by new formulation (NF) and / or [redacted] formulation 3) Addition of abbreviations NF = new formulation and [redacted], deletion of abbreviation iCF = intended commercial formulation 4) Addition that a preliminary PK analysis of BI 1810631 and rabeprazole may be performed prior data base lock.
Rationale for change		1) [redacted]

		[redacted] 2) Abbreviation "iCF" is BI-internally already [redacted]. For differentiation against this iCF, the [redacted] formulation used in the current trial is now called "new formulation (NF)" or [redacted]. The use of the term [redacted] ensures alignment with the IMPD. The use of the term "NF" ensures that [redacted] 3) Abbreviations have to be added / deleted to support change N. 2. 4) A preliminary PK analysis may be necessary, e.g. in case the information is needed to inform other activities during the development of BI 1810631.

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-03

Title: Relative bioavailability of BI 1810631 as two different [redacted] formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program [redacted]	[redacted]	25 May 2022 15:11 CEST
Verification-Paper Signature Completion		25 May 2022 15:18 CEST
Author-Clinical Trial Leader		25 May 2022 16:12 CEST
Author-Trial Statistician		25 May 2022 22:46 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed