

Clinical Trial Protocol

Document Number:		c43691238-02
EU Trial No.	2023-510495-31-00	
Universal Trial No. (UTN)	U1111-1303-4345	
BI Trial No.	1479-0019	
BI Investigational Medicinal Product	Zongertinib (BI 1810631)	
Title	Bioequivalence of zongertinib tablets from two different manufacturers following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover trial)	
Lay Title	A study in healthy people to see how zongertinib is taken up into the blood when given as tablets made by two different manufacturers	
Clinical Phase	I	
Clinical Trial Leader	<div></div>	
<div>Investigator</div>	<div></div>	
Current Version, Date	Version 2.0, 14 Mar 2024	
Original Protocol Date	01 Feb 2024	
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	01 Feb 2024
Revision date	Not applicable
BI trial number	1479-0019
Title of trial	Bioequivalence of zongertinib tablets from two different manufacturers following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover trial)
Investigator	
Trial site	
Clinical phase	I
Trial rationale	To establish bioequivalence between zongertinib tablets manufactured by two different manufacturers.
Trial objective(s)	To establish bioequivalence between zongertinib tablets manufactured by two different manufacturers.
Trial endpoints	Primary endpoints: AUC _{0-72h} and C _{max} of zongertinib Secondary endpoints: t _{max} of zongertinib
Trial design	Randomised, open-label, two-period, two-sequence crossover trial
Number of subjects	56
total entered	
on each treatment	56
Diagnosis	Not applicable
Main inclusion criteria	Healthy male/female subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m ² (inclusive)
Test product(s)	Zongertinib (BI 1810631) – manufactured by
dose	
mode of administration	Oral

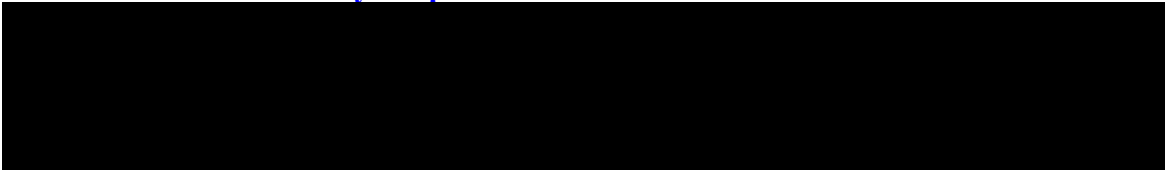
Reference product(s)	Zongertinib (BI 1810631) – manufactured by [REDACTED]
dose	[REDACTED]
mode of admin.	Oral [REDACTED]
Duration of treatment	Single dose for each treatment [REDACTED]
Statistical methods	<p>The assessment of bioequivalence will be based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (gMean) (test/reference) for the primary endpoints using an acceptance range of 80.00 to 125.00%. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. 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 and quantiles from the t-distribution.</p> <p>Descriptive statistics will be calculated for all endpoints.</p>

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK _{blood} zongertinib	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy ⁶
SCR	1	-21 to -1			Screening (SCR) ¹	A		x	x	
1/2 (two identical periods between zongertinib administrations)	2/3	-1	-13:00	19:00	Admission to trial site					x
		1 ⁷	-2:00	06:00	Allocation to treatment ² (visit 2 only)	B ⁵	x ²	x ²	x ²	x ²
			0:00	08:00	Drug administration: zongertinib					
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00			x			
			2:30	10:30			x			
			3:00	11:00			x			
			3:30	11:30			x			
			4:00	12:00			x			x
			5:00	13:00						
			6:00	14:00			x			
			8:00	16:00			x			
			10:00	18:00			x			
			11:00	19:00						
			12:00	20:00			x			x
		2 ⁷	24:00	08:00		B	x	x	x	x
			36:00	20:00			x			x
		3	48:00	08:00	Discharge from trial site		x			x
		4	72:00	08:00	Ambulatory visit		x			x
FU	4	15 to 18			End of study (EoS) examination ⁴	C		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, Electrocardiogramm (ECG), safety laboratory (including drug screening, [REDACTED] test and pregnancy test in women), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the [REDACTED] will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs (Adverse Events) and concomitant therapies.
5. Including drug screening, [REDACTED] test and alcohol breath test as well as pregnancy test in women will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Standardized [REDACTED] throughout the day during stationary phase of the trial.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
AUC0-∞	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
%AUCtz-∞	Percentage of AUC0-∞ obtained by extrapolation
AUCt1-t2	Area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2
AUC0-tz	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC0-72h	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72h
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CI	Confidence interval
Cmax	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
EudraCT	European Clinical Trials Database
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRTpo	Mean residence time of the analyte in the body after oral administration
PDX	Patient derived xenografts
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set

PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate (HR), e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
T	Test
TMF	Trial master file
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
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V _{ss}	Apparent volume of distribution at steady state after intravascular administration
V _z	Apparent volume of distribution during the terminal phase after intravascular administration
V _z /F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

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

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

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

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

1.2 DRUG PROFILE

1.2.1 Zongertinib

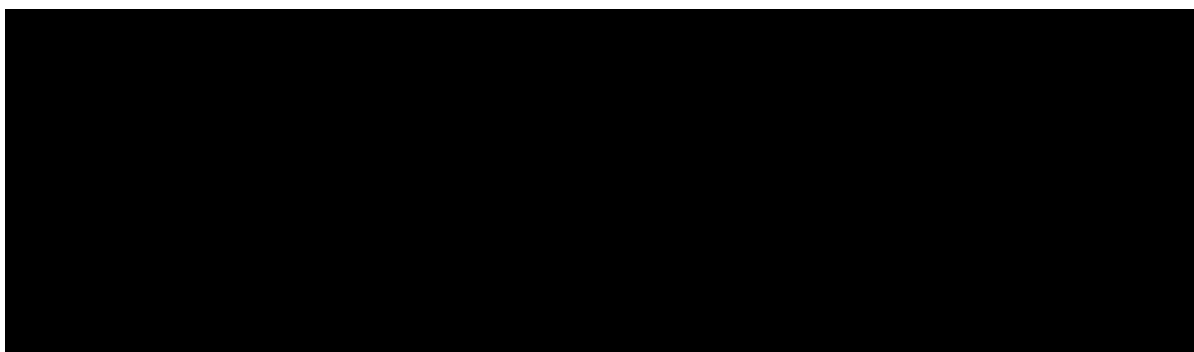
A summary of the drug profile is provided below. For detailed information, refer to the current Investigator's Brochure [[c32836122](#)].

Mode of action

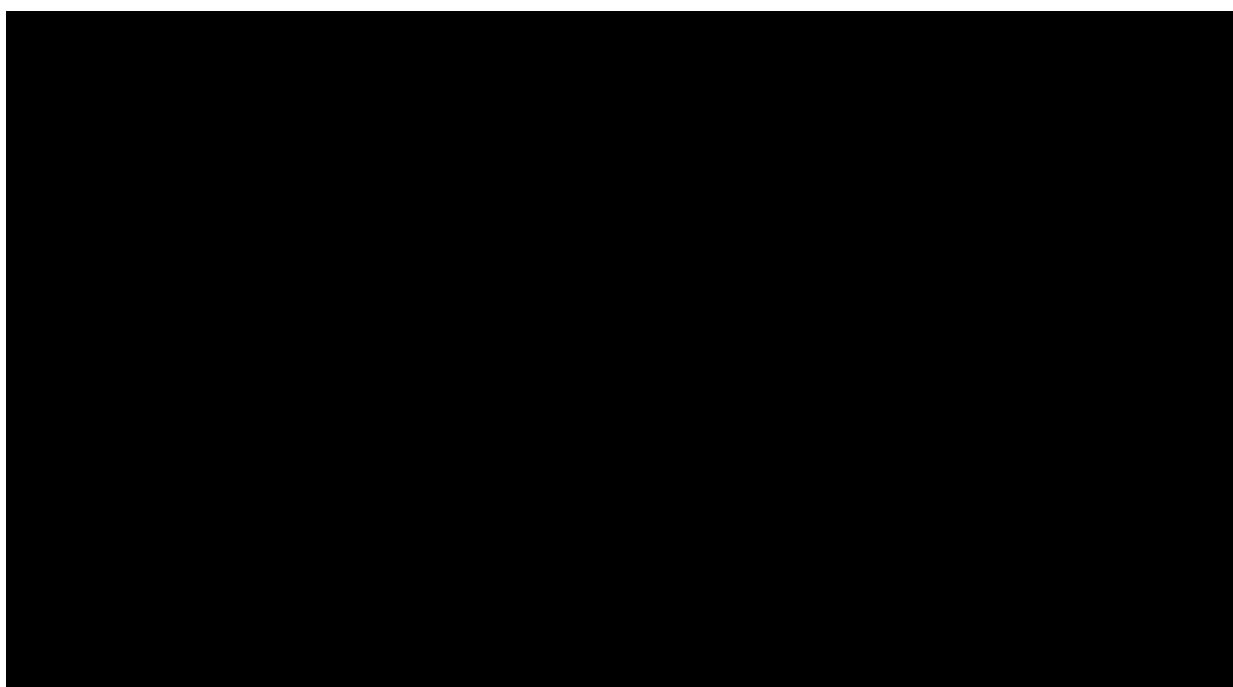
Zongertinib is an EGFR wild type sparing, selective HER2 inhibitor with potent inhibitory activity on all oncogenic HER2 mutations including the HER2 YVMA insertion allele.

Data from non-clinical studies

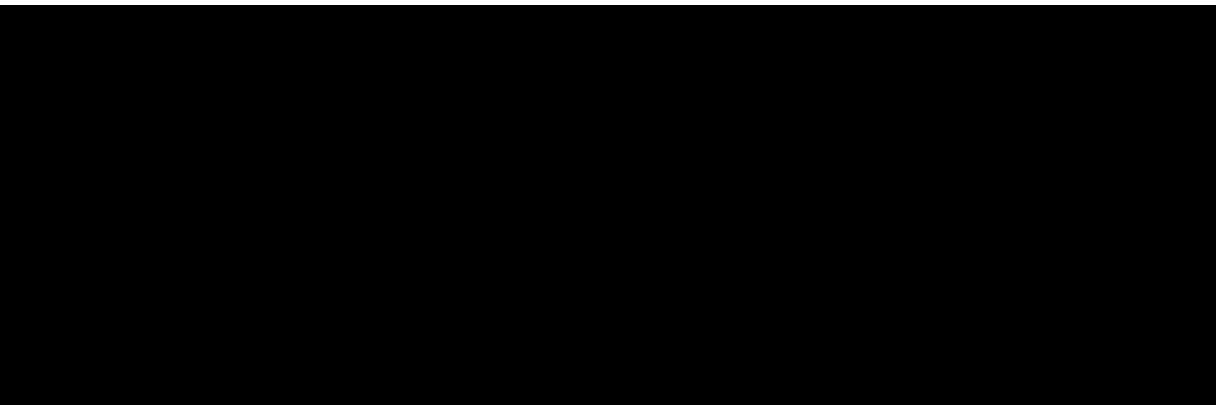
Non-clinical pharmacology



Non-clinical pharmacokinetics



Safety pharmacology / Toxicology



Data from clinical studies

Prior to the current trial, BI 1810631 was administered in the ongoing first-in-man trial in patients with cancer 1479-0001 and in five PK studies in healthy volunteers (trial 1479-0003, 1479-0004, 1479-0006, 1479-0010, 1479-00011).

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

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

1479-0001 is an open-label, Phase I dose escalation trial, with dose confirmation and expansion, of BI 1810631 as monotherapy in patients with advanced or metastatic solid tumors with HER2 aberrations. Patients are continuously treated in different dose groups with [REDACTED] PK, safety, and efficacy data are collected.

Patients were treated in the dose escalation phase with escalating doses of zongertinib (BI 1810631) monotherapy administered [REDACTED] as well as in the dose expansion phase with [REDACTED] (38 patients) and [REDACTED] (41 patients).

Overall, the median treatment duration was 147 days and the exposure ranged from 1 to 568 days during the dose escalation at data cut-off; during the dose expansion, the median treatment duration was 64 days and the exposure ranged from 1 to 147 days. Data cut time point for the data described here is 15 Sep 2023.

Short description of healthy volunteer trial 1479-0003

At the time of CTP finalization, trial 1479-0003 is in the reporting phase. Trial 1479-0003 was an open-label, randomized, 4-way crossover Phase I trial. The trial investigated relative

bioavailability of BI 1810631 after administration as two different formulations (trial formulation 1 [TF1] and new formulation [NF]), investigated the [REDACTED]

[REDACTED]. Thirteen healthy male volunteers were dosed with single doses of [REDACTED] BI 1810631 in 4 treatment periods in randomized order, [REDACTED]

[REDACTED] The 4 treatments were:

- R: [REDACTED] BI 1810631 trial formulation 1 (TF1) [REDACTED]

- T1 [REDACTED] BI 1810631 new formulation (NF) [REDACTED]

- T2 [REDACTED] BI 1810631 NF [REDACTED]

- T3 [REDACTED] BI 1810631 NF [REDACTED]

rabeprazole.

Short description of healthy volunteer trial 1479-0004

In trial 1479-0004, the [REDACTED] of BI 1810631 in 16 healthy male subjects (an open-label, two-period, fixed-sequence trial) was tested.

Short description of healthy volunteer trial 1479-0006

In trial 1479-0006, a phase I, open-label trial in two parallel parts investigated mass balance, metabolism, and basic pharmacokinetics of BI 1810631 [REDACTED] and investigated absolute bioavailability of BI 1810631 [REDACTED]

[REDACTED] in 15 healthy male volunteers.

Short description of healthy volunteer trial 1479-0010

In trial 1479-0010, the relative bioavailability of [REDACTED] BI 1810631 following oral administration [REDACTED] in 16 healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial) was tested.

Short description of healthy volunteer trial 1479-0011

In trial 1479-0011, [REDACTED] of BI 1810631 was tested in 16 healthy male subjects (an open-label, two-period, fixed-sequence trial).

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

Overall, zongertinib (BI 1810631) was well tolerated in patients in trial 1479-0001 and the majority of drug-related Adverse Events (AEs) was manageable. The MTD has not been reached in both treatment schedules. AEs leading to dose reductions, treatment interruptions, and treatment

discontinuations were infrequent.

During dose escalation, the most frequent AEs were diarrhoea (24 patients, 39.3%), followed by anaemia (13 patients, 21.3%), ALT increased (11 patients, 18.0%), AST increased (11 patients, 18.0%), blood alkaline phosphatase increased (10 patients, 16.4%), blood creatinine increased (10 patients, 16.4%) and COVID-19 (7 patients, 11.5%).

Dose limiting toxicities during the MTD evaluation period were diarrhoea Grade 3 () and platelet count decreased Grade 3 (). In total, 25 (41%) patients had an SAE, with 1 patient (1.6%) having SAEs that were considered drug-related by the investigator (Grade 3 ALT increased and Grade 3 AST increased). Reported fatal AEs were not drug-related.

During dose expansion, most frequent AEs were diarrhoea (28 patients, 35.4%), anaemia (15 patients, 19%), ALT increased (10 patients, 12.7%), AST increased (10 patients, 12.7%), decreased appetite (9 patients, 11.4%), lymphocyte count decreased (9 patients, 11.4%) and dysgeusia (8 patients, 10, 1%). Dose limiting toxicities during the MTD evaluation period were diarrhoea Grade 3, febrile neutropenia Grade 3 and immune thrombocytopenia Grade 4 (all at 240 mg QD). SAEs were reported in 9 (11.4%) of patients. SAEs assessed as drug-related by the investigator occurred in 5 patients (6.3%). These were ALT increased and AST increased (in 2 patients each, 2.5%), as well as hepatic failure, immune thrombocytopenia, intestinal obstruction and neutrophil count decreased (in 1 patient each, 1.3%). Reported fatal AEs were not drug-related.

Hepatotoxicity

Elevations of liver enzymes and bilirubin have been reported during treatment with zongertinib (BI 1810631) in trial 1479-0001. AEs in the SMQ liver related investigations, signs and symptoms occurred in 20 patients (32.8%) during dose escalation and in 19 patients (24.1%) during dose expansion. During dose escalation, liver related investigations were Grade 3 in 6 patients (9.8%) and during dose expansion, Grade 3 or 4 in 2 patients (2.5%) each. First onset of the liver related investigations was within 30 days in 13 patients (21.3%) during dose escalation and in 16 patients (20.3%) during dose expansion. During dose escalation, liver related investigations led to interruption of trial medication in 5 patients (8.2%) and to permanent treatment discontinuation or dose reduction in 1 patient each (1.6%). During dose expansion, liver related investigations led to dose reduction or treatment interruption in 2 patients (2.8%) each.

Two cases of severe hepatic AEs have been reported.

A patient had occasional right hypochondrium pain, choluria, progressive jaundice, and diarrhoea starting on Day 36 of treatment with () zongertinib (BI 1810631) (). One week later the patient was admitted to the hospital with hepatic failure and prolonged prothrombin time. During hospitalisation, study medication was interrupted, and the patient was treated with N-acetylcysteine and methylprednisolone over 7 days. After discharge from

the hospital treatment continued with 50 mg prednisolone. The patient was recovering and restarted study drug on Day 63 [REDACTED]. Liver enzymes and bilirubin were further normalising. The patient had COVID-19 infection and was treated with Remdisivir starting on Day 25 of study treatment as possible confounding factors.

A second patient who was treated with [REDACTED] zongertinib (BI 1810631) [REDACTED] over 42 days developed, despite interruption of study drug due to ALT, AST Grade 2 and total bilirubin Grade 1, further increases of ALT and AST up to Grade 4 (>20.0x ULN), increased total bilirubin up to Grade 3 (>3x ULN), and coagulopathy Grade 3 on Day 55. On Day 57, the patient had developed subacute hepatic failure Grade 4, cholestasis Grade 4 and hypoalbuminaemia Grade 2. Treatment of the AEs included hepatoprotective and anticholestatic agents as well as dexamethasone. Liver enzymes and total bilirubin were improving between Days 66 and 76. During the further course the patient developed infection (on Day 81) and subsequent sepsis (on Day 86) with fatal outcome 7 days later. Further evaluations are ongoing.

Diarrhoea

Diarrhoea was reported during treatment with zongertinib (BI 1810631) and was of mainly of Grade 1 and 2. Diarrhoea occurred in 24 patients (39.3%) during dose escalation and in 28 patients (35.4%) during dose expansion. Diarrhoea was Grade 3, in 3 patients (4.9%) during dose escalation, and in 2 patients (2.5%) during dose expansion. Due to observed long-lasting periods in some patients, a proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal agents should start at first signs of diarrhoea.

Preclinical Embryotoxicity

Based on findings from animal studies and its possible mechanism of action, zongertinib (BI 1810631) could cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of zongertinib (BI 1810631) to pregnant rats during organogenesis caused embryo-fetal death. Pregnant women are not to be treated with zongertinib (BI 1810631).

Females of reproductive potential and male patients with female partners of reproductive potential are to be advised to use dual highly effective contraception (meaning e.g. the use of one highly effective non-barrier method and one barrier method resulting in a low failure rate of less than 1% per year) during treatment and for at least 30 days after the last dose.

Safety and tolerability data of healthy volunteer trial 1479-0003

In trial 1479-0003, in which oral [REDACTED] BI 1810631 were administered to healthy volunteers, there were no SAEs, no Adverse events of special interest (AESI), and no other significant AEs. All AEs were of CTCAE Grade 1 or 2 severity, and none of the AEs were assessed as drug-related.

Available safety data including AEs, Electrocardiogram (ECGs), VS, and safety laboratory indicate that [REDACTED]

[REDACTED] BI 1810631 were safe and well tolerated in trial 1479-0003. For more details refer to the IB [[c32836122](#)].

Safety and tolerability data of healthy volunteer trial 1479-0004

There were no deaths, no serious AEs, no CTCAE grade 3, 4, or 5 AEs, and no protocol-specified AEs of special interest reported. A grade 1 AE of diplopia led to the premature discontinuation [REDACTED] in 1 subject (6.3%) and was the only significant AE in the trial, according to ICH E3. The event was considered related to trial drug and resolved without therapy. All AEs were reported as resolved by the end of the trial, except an AE of hand fracture which was not considered related to trial drug. No relevant changes in laboratory values, vital signs, or ECGs were reported as AEs.

Preliminary Safety and tolerability data of healthy volunteer trial 1479-0006

There were no SAEs, no AESIs, and no other significant AEs. All AEs were of CTCAE Grade 1 severity. In part A and B, only Diarrhoea (in 2 HVs) and abdominal pain (all Grade 1) were assessed as drug-related.

Available safety data including AEs, ECGs, VS, and safety laboratory indicate that [REDACTED]
[REDACTED] BI 1810631 were safe and well tolerated in trial 1479-0006.

Preliminary Safety and tolerability data of healthy volunteer trial 1479-0010

There were no SAEs, no AESIs, and no CTCAE grade 3, 4 and 5 AEs.

Available safety data including AEs, ECGs, VS, and safety laboratory indicate that [REDACTED]
[REDACTED] BI 1810631 were safe and well tolerated in trial 1479-0010.

Preliminary Safety and tolerability data of healthy volunteer trial 1479-0011

There were no SAEs, no AESIs, and no other significant AEs. All AEs were of CTCAE Grade 1 severity. One HV had fatigue Grade 1 assessed as drug-related, Available safety data including AEs, ECGs, VS, and safety laboratory indicate that [REDACTED]

[REDACTED] BI 1810631 were safe and well tolerated in trial 1479-0011.

Clinical Pharmacology

Preliminary, exploratory PK analysis in trial 1479-0001 indicated [REDACTED]

[REDACTED]
[REDACTED] The observed PK profile of zongertinib appears to be compatible with [REDACTED]
dosing to achieve efficacious plasma exposure, which is also suggested by the observed clinical responses in the respective [REDACTED] dose groups.

PK results of trial 1479-0003 in healthy volunteers indicate similar bioavailability between the original formulation and a new formulation, that is functionally similar to the [REDACTED] formulation used in further clinical development. The new formulation showed a negative [REDACTED] and its bioavailability was [REDACTED]

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of single doses of BI 1810631 is conservatively estimated as 14 days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Zongertinib tablets were manufactured by two different manufacturers [REDACTED]). It is required to demonstrate bioequivalence between tablets [REDACTED]

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

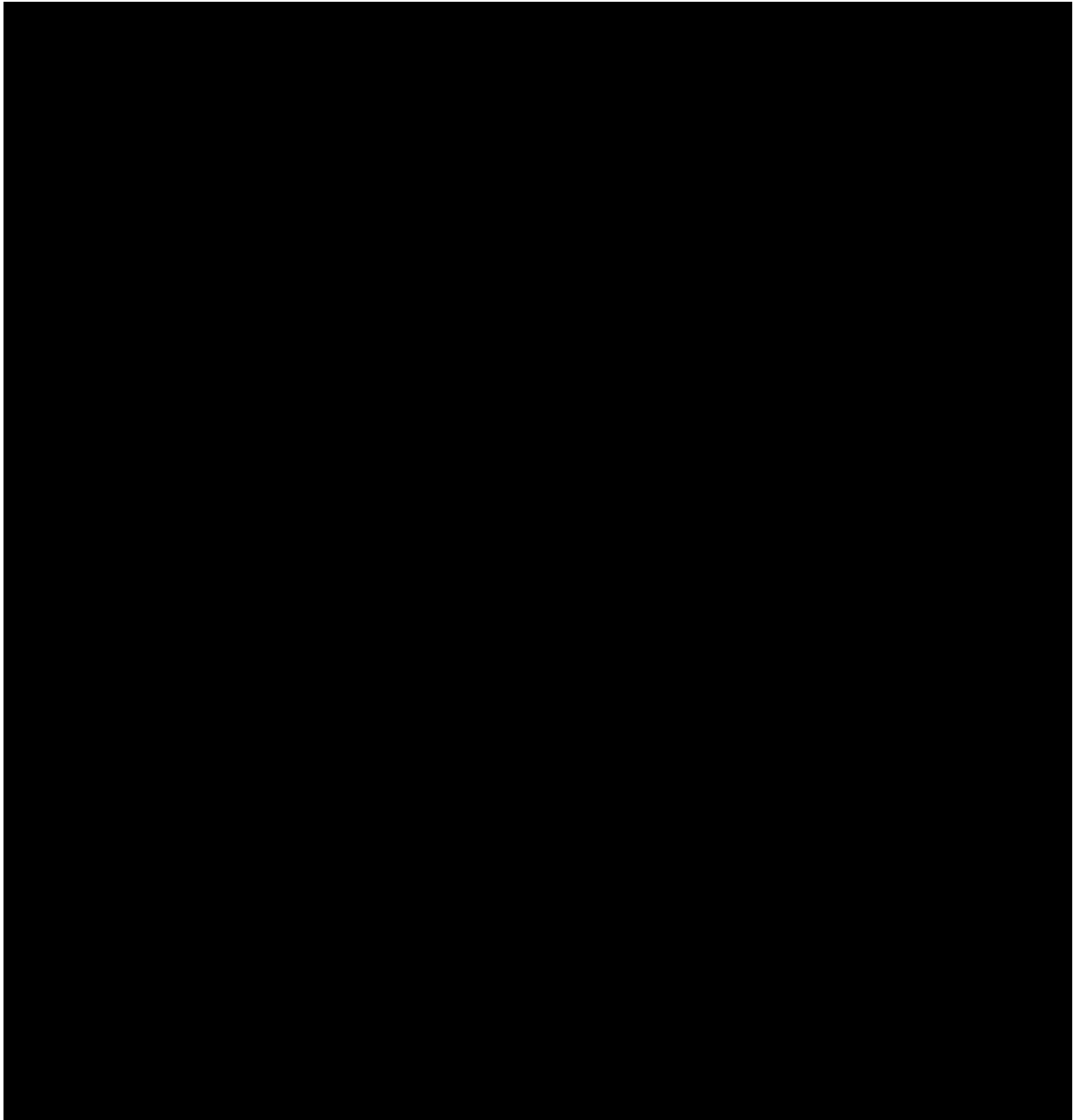
Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of zongertinib for treatment of patients with advanced solid tumours with HER2 aberrations.

1.4.2 Risks

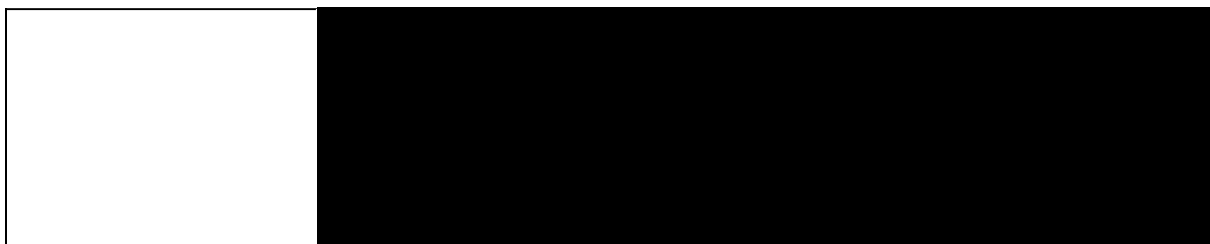
Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table [1.4.2: 1](#).

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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
<i>Investigational Medicinal Product: Zongertinib (BI 1810631)</i>		
Unexpected AEs and laboratory abnormalities	Risk is due to limited clinical experience with zongertinib (BI 1810631)	Close monitoring of safety data.

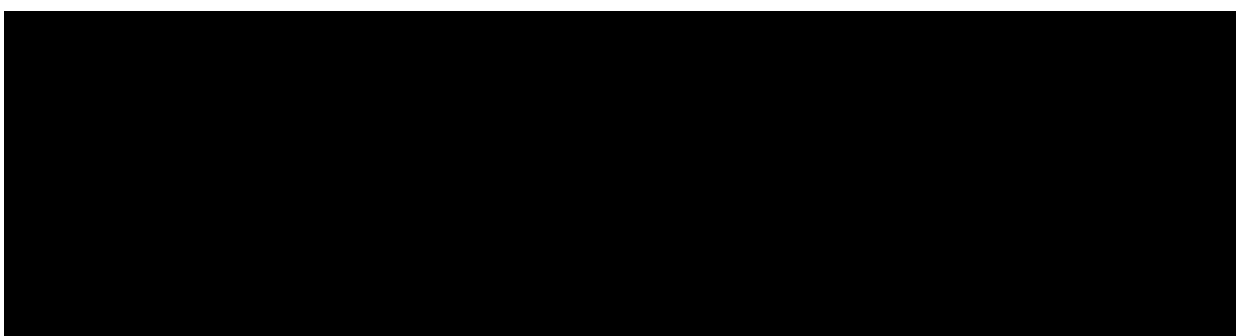


Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
<i>Investigational Medicinal Product: Zongertinib (BI 1810631)</i>		



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

1.4.3 Discussion



In summary, safety measures are implemented in the trial to mitigate possible risks. Considering the medical need for the development of a better tolerated and more effective treatment for patients diagnosed with solid tumors the expected benefit outweighs the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to establish the bioequivalence of [REDACTED] of zongertinib tablet manufactured by [REDACTED] (Test, T) compared with [REDACTED] of zongertinib tablet manufactured by [REDACTED] (Reference, R) following oral administration.

2.1.2 Primary endpoint(s)

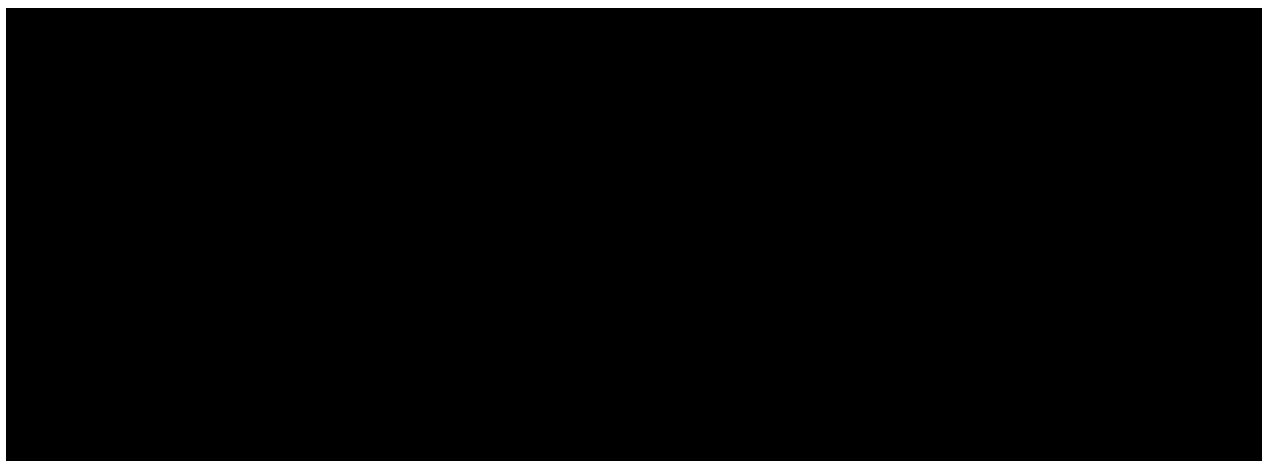
The following pharmacokinetic parameters will be determined for zongertinib:

- AUC_{0-72h} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72h)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for zongertinib:

- t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)



2.2.2.2 Safety and tolerability

Safety and tolerability of zongertinib will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, randomized, single-dose, two period, two-sequence crossover trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be [REDACTED] zongertininib tablet manufactured by [REDACTED] (T) administered to subjects [REDACTED] zongertininib tablet manufactured by [REDACTED] (R) administered to subjects [REDACTED]. The subjects will be randomly allocated to the 2 treatment sequences (T-R or R-T). For details, refer to Section [4.1](#).

There will be a washout period [REDACTED] between the 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 GROUP(S)

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

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 56 healthy male and female subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (blood pressure (BP), PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (inclusive)
3. BMI (Body mass index of 18.5 to 29.9 kg/m² (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Either male subject, or female subject who meet any of the following criteria for a highly effective contraception from at least 30 days before the first administration of trial medication until 30 days after trial completion:
 - Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants), *plus condom*
 - Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
 - Sexually abstinent
 - A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) and provided that partner is the sole sexual partner of the trial participant
 - Surgically sterilised (including hysterectomy or bilateral tubular occlusion)
 - Postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)

7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days or within five half-lives, whichever is longer of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. [REDACTED] is defined as currently [REDACTED]
15. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
16. Drug abuse, positive [REDACTED] test or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Ovum or sperm donation is not permitted until 30 days after last drug administration.
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (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. Women of childbearing potential (WOCBP) and men able to father a child who are unwilling to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly in combination with a barrier method.

25. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 30 days after trial completion

26. For female subjects: Positive pregnancy test.

For restrictions of the trial, refer to Section [4.2.2](#).

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section [1.2.2](#)) the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, 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 it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section [5.2.6.2.3](#).

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

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

3.3.5 Replacement of subjects


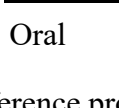
In case more than 4 subjects do not complete the trial (including subjects non- evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Clinical Pharmacologist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 17 subjects. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment sequence as the subject he or she replaces.

4. TREATMENTS


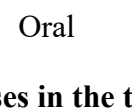
4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Name: Zongertinib
Substance: BI 1810631
Pharmaceutical formulation: Film-coated tablet (Test)
Source: BI Pharma GmbH & Co. KG, Germany
Unit strength: 
Posology: 
Mode of administration: Oral

The characteristics of the reference product are given below:

Name: Zongertinib
Substance: BI 1810631
Pharmaceutical formulation: Film-coated tablet (Reference)
Source: BI Pharma GmbH & Co. KG, Germany
Unit strength: 
Posology: 
Mode of administration: Oral

4.1.2 Selection of doses in the trial and dose modifications

The dose selected for this trial is  used for further development of zongertinib (see Section [1.2](#)).

4.1.3 Method of assigning subjects to treatment groups

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

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

Due to logistical the group will be split into several cohorts as required.

The randomisation procedure is described in Section [7.4](#).

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1810631	Film-coated tablet			
R (Reference)	BI 1810631	Film-coated tablet			

Administration of trial medication will be performed after subjects have [REDACTED]. The investigator (or authorised designee) will administer the trial medication as an oral dose [REDACTED] to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 48 h after drug administration. During the first 5 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The treatments will be separated by a wash-out phase [REDACTED]

4.1.5 Blinding and procedures for unblinding

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations. Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

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

4.1.6 Packaging, labelling, and re-supply

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

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

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

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

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

As per FDA requirement reserve samples are available for storage by the investigational site and that the trial materials can be chosen in a random way by the Investigator.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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 except for hormonal contraceptives. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised [REDACTED] at the times indicated in the [Flow Chart](#). [REDACTED]

From 1 h before drug intake [REDACTED] is restricted to the water administered [REDACTED] (mandatory for all subjects). [REDACTED] until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages, [REDACTED], and dietary supplements [REDACTED] are not permitted from 7 days before the first administration of trial medication until EoS.

[REDACTED] are not allowed from 24 h before until 24 h after each administration of trial medication.

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

4.2.2.3 Contraception requirements

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

WOCBP (for the definition please refer to Section [3.3.2](#) and men able to father a child must abstain from intercourse or use two medically approved methods of birth control throughout the trial, and for a period of at least 30 days after last trial drug intake, one barrier method, and one highly effective non-barrier method.

Additionally ovum or sperm donation is not permitted until 30 days after last drug administration.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, 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 at the times indicated in the

[Flow Chart](#), after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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

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

Table 5.2.3: 1 Routine laboratory tests

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

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

A: parameters to be determined at screening examination

B: parameters to be determined during the study (for time points refer to [Flow Chart](#))

C: parameters to be determined at end of trial examination

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests, [REDACTED] test and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. Drug screening and [REDACTED] test 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/ Methylenedioxyamphetamine (MDA) Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
[REDACTED] test (urine)	[REDACTED]
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with [REDACTED] and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial site, with the exception of drug screening and [REDACTED] tests.

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

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

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

5.2.4 Electrocardiogram

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

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

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

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

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the electronic case report form (eCRF) only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered ‘Always Serious’

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which, by their nature, can always be considered to be ‘serious’ even though they may not have met the criteria of an SAE as defined above.

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Potential severe DILI
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

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

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

No AEsIs have been defined for this trial.

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 and will not be reported in the CTR.

- After the individual subject's end of trial:
 - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section [5.2.6.2.2](#)), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1810631 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K₂-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the [Flow Chart](#). Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis

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

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

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.4.1 Drug-Drug Interaction Biomarkers

Not applicable.

5.4.2 Pharmacodynamic biomarkers

Not applicable.

5.4.3 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

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

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

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

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 and run-in period(s)

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections [5.2.1](#) to [5.2.5](#).

6.2.2 Treatment period(s)

Each subject is expected to participate in 2 treatment periods. [REDACTED] will separate drug administrations in the first and second treatment periods.

On Day-1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 48 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness as indicated in the Flow Chart. On all other trial days, subjects will be treated in an ambulatory fashion.

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

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

For details on times of all other trial procedures, refer to the [Flow Chart](#).

6.2.3 Follow-up period and trial completion

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

Although there are multiple primary endpoints, an alpha adjustment is not needed because it is required that all primary endpoints meet the equivalence criterion as described below simultaneously. Therefore, a one-sided alpha of 5% will be used for testing.

The assessment of bioequivalence will be based upon two-sided 90% confidence intervals (CIs) for the ratio of the geometric means (test/reference) for the primary and secondary endpoints using an acceptance range of 80.00 - to 125.00%. This method is equivalent to the two-sided t-test procedure, each at the 5% significance level.

The following hypotheses are tested:

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta$ or $\mu_T - \mu_R \geq \delta$

where μ_T and μ_R are the means of the log-transformed endpoint for the test and reference treatments, respectively, and δ is the bioequivalence limit that defines the acceptance range on the logarithmic scale. Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

In this trial, the bioequivalence limit δ is $\ln(1.25)$. By back-transforming (exponentiating), this translates to an acceptance range of 80.00 to 125.00% for the ratio of the geometric means (test/reference) for endpoints on the original scale.

The rejection of the null hypothesis at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range $(-\delta, \delta)$.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section [2.1](#) and [2.2.2](#) for drug zongertinib will be calculated according to the relevant BI internal procedures.

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

Important protocol deviations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- 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 are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Descriptive and inferential statistics of PK parameters will be based on the PKs.

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

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as

random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

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

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

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

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

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

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

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for $\log(T)$ - $\log(R)$ will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t -distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Bioequivalence is considered established if the 90% confidence intervals of the geometric means for the primary endpoints are contained in the pre-defined acceptance range, see Section 7.1.

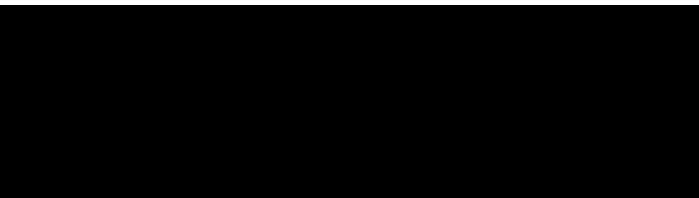
Further exploratory analyses

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

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

7.2.3 Secondary endpoint analyses

The secondary endpoints (refer to Section [2.1.3](#)) will be calculated according to the relevant BI internal procedures and will be assessed descriptively.



7.2.5 Safety analyses

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

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section [4.1](#)) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section [1.2.2](#)) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact 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 sequence 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.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

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

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

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

7.5 DETERMINATION OF SAMPLE SIZE

The sample size for this trial was determined using assumptions on the intra-individual variability of the primary endpoints based on the results reported in previous BI trials 1479-0003([c40238724](#)) and 1479-0004 ([c42362953](#)).

We assumed an intra-individual coefficients of variation (gCV) of 20% and 30% for AUC₀₋₇₂ and C_{max} for zongertinib, respectively. The gCV for AUC₀₋₇₂ was decided based on the values of 14.2% and 13.8% for AUC_{0-∞} and AUC_{0-tz} in trial 1479-0003 and 18.0% and 20.4% for AUC_{0-∞} and AUC_{0-tz} in trial 1479-0004, respectively. The gCV of 30% for C_{max} was also decided based on the value of 30.5% and 28.7% for C_{max} in trial 1479-0003 and trial 1479-0004.

A sample size of 52 subjects is needed to achieve 90% power to reject both one-sided null hypotheses for C_{max} each at the 5% level of significance in favour of bioequivalence. While a sample size of 26 subjects would suffice to achieve the analogous result for AUC₀₋₇₂.

Due to the high correlation between the primary endpoints, only C_{max} will be considered for power calculations. Using a sample size of 52 subjects (26 per sequence group), the power to reject both one-sided null hypotheses for one parameter each at the 5% level of significance in favour of bioequivalence is displayed in Table 7.5: 1, under various assumptions for the T/R ratio. To account for the uncertainty of the assumed gCV, a range of gCVs around 30% is also presented.

Table 7.5:1 Power for concluding bioequivalence (acceptance range 80-125%) based on a geometric coefficient of variation (gCV) around 30% and for different expected ratios of geometric means (test/reference) in a 2×2 crossover trial (N=52)

gCV[%]	Ratio[%]*		
	95	100	105
20	99.7	100.0	99.7
25	96.9	99.6	97.2
30	90.2	97.1	90.9
35	80.7	90.2	81.6

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

From the above table, a sample size of 52 will yield approximately 90% power to conclude bioequivalence for an assumed gCV of 30% if the ratio is not more than 5% different from the ratio of 100% which reflects no difference in exposure. In addition, this sample size still provides approximately 80% power in case the gCV is 35%.

Accounting for up to 4 dropouts or non PK evaluable subjects, a total of N = 56 subjects are planned to be entered into the trial.

The calculations were performed as described by Diletti et al. [R94-1445] using the function power.TOST() of the R package PowerTOST Version 1.5-4 in R Version 4.2.1.

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 regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

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

8.1 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 or the subject's legally accepted representative.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section [4.1.5](#) for rules about emergency code breaks. For drug accountability, refer to Section [4.1.8](#).

8.3.1 Source documents

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

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

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

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

- Sample and data usage have to be in accordance with the informed consent
- 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 [REDACTED]
[REDACTED]

The trial will be conducted at [REDACTED]
[REDACTED] under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [REDACTED]
[REDACTED]

The contracted laboratory for safety laboratory tests is [REDACTED]

Analyses of BI 1810631 concentrations in plasma will be performed at [REDACTED]
[REDACTED]

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

Data management and statistical evaluation will be done by BI and/or a Contract Research Organisation according to BI SOPs.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P11-09424

P15-01211

P19-00456

P19-10412

P20-09250

R09-6185

R18-1357

R20-1872

R20-1990

R94-1445

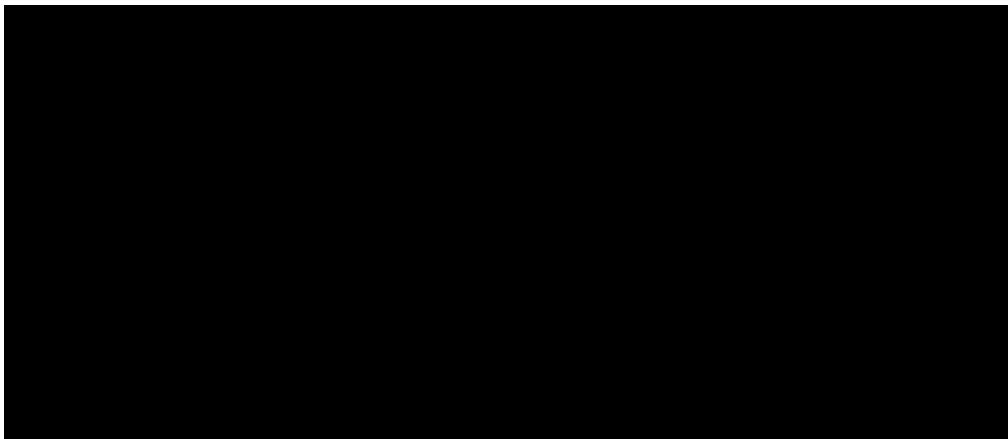
R94-1529

9.2 UNPUBLISHED REFERENCES

c32836122

c40238724

c42362953



10. APPENDICES

Not applicable.

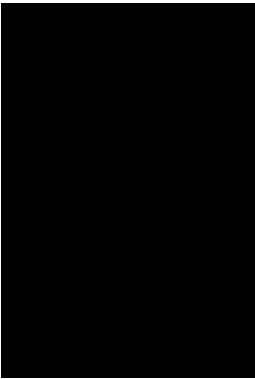

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE**Document Number:** c43691238**Technical Version Number:**2.0**Document Name:** clinical-trial-protocol-version-02

Title: Bioequivalence of zongertinib tablets from two different manufacturers following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval		15 Mar 2024 09:27 CET
Approval-Clinical Program 		15 Mar 2024 10:11 CET
Author-Trial Statistician		18 Mar 2024 11:18 CET
Verification-Paper Signature Completion		18 Mar 2024 11:47 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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