Clinical Trial Protocol

	Global ID_Version: **228892_986299_4.0**
Universal Trial No. (UTN)	U1111-1307-9446
BI Trial No.	1479-0020
BI Investigational Medicinal Product	Zongertinib (BI 1810631)
Title	Pharmacokinetics, safety and tolerability of zongertinib following oral administration in male and female participants of non-childbearing potential with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants of non-childbearing potential with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Lay Title	A study to test how zongertinib is taken up in the blood of people with and without liver problems
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 4.0, 17 Feb 2025
Original Protocol Date	26 Sep 2024

Proprietary confidential information
© 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	26 Sep 2024
Revision date	17 Feb 2025
BI trial number	1479-0020
Title of trial	Pharmacokinetics, safety and tolerability of zongertinib following oral administration in male and female participants of non-childbearing potential with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants of non-childbearing potential with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	In this trial, pharmacokinetics, safety and tolerability of zongertinib as single oral dose in participants with different degrees of hepatic impairment compared to individually matched participants with normal hepatic function will be assessed.
Trial objective	To investigate the effect of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on the pharmacokinetics, safety and tolerability of zongertinib.
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of zongertinib Secondary endpoints: AUC_{0-tz} of zongertinib
Trial design	Open-label, non-randomised, single-dose, parallel, individual-matched design trial
Number of subjects **total entered** **on each treatment**	32* Up to 16 hepatically impaired patients: • Group 1: 8 subjects with mild hepatic impairment (Child Pugh A, score 5-6 points) • Group 2: 8 subjects with moderate hepatic impairment (Child Pugh B, score 7-9 points) 8-16 participants with normal hepatic function: • Group 3: Up to 8-16 participants with normal hepatic function either matched to Group 1, Group 2 or both. * One participant with normal hepatic function may match one participant in one or both groups of participants with hepatic impairment. Thus, the total sample size may be 24 to 32 participants.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Diagnosis	Participants with hepatic impairment (Child-Pugh A or B) and participants with normal hepatic function (matched controls to the participants with hepatic impairment)
Main inclusion criteria	Male or female participant of non-childbearing potential with normal hepatic function, age of ≥ 18 and ≤ 80 years, body mass index (BMI) of 18.0 to 42 kg/m^2 (inclusive) For Group 1 and 2 only: hepatic impaired participants classified according to the Child-Pugh Score. Criteria for matching: age (± 10 years), sex and weight (± 15%) (see section 3.1)
Test product **dose** **mode of administration**	Zongertinib 120 mg (2x 60mg) Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	One day (single dose)
Statistical methods	The effect of hepatic impairment on the pharmacokinetic endpoints of single dose of zongertinib will be estimated by the ratios of geometric means of the respective pairwise comparison of interest, i.e. for each hepatic impairment group (Child-Turcotte-Pugh class A and B) vs the respective matched control subjects. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified for any comparison of interest. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect 'degree of hepatic impairment' and 'matched pair'. Descriptive statistics will be calculated for all endpoints.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -2			Screening (SCR)[1]	A		x	x	
1	2	-1	-24:00	08:00	Admission to trial site	x[5]				x
		1	-3:00	05:00		B[2]	x[2,7]	x[2]	x[2]	▲
			0:00	08:00	Drug administration together with 240 mL fluid intake after at least 10 hours fasting					
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x			
			2:30	10.30			x			
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake,		x	x	x	
			5.00	13.00	Lunch[3]					
			6:00	14:00			x			
			8:00	16:00	Snack (voluntary)[3]		x			
			10:00	18:00			x	x	x	
			11:00	19:00	Dinner[3]					
			12:00	20:00			x			
		2	24:00	08:00	Breakfast (voluntary) [3]	B	x	x	x	
			35:00	19:00	Dinner[3]					
			36:00	20:00			x			
		3	48:00	08:00			x			
		4	72:00	08:00		B	x			▼
		6	120:00	08:00	Discharge from trial site		x			
		8	168:00	08:00	Ambulatory visit	B	x			
FU	3	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, ECG, safety laboratory (including drug screening, pregnancy test and serology), 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 intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening, urine pregnancy test in women and alcohol breath test will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial.
7. Including blood sampling for protein binding.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

TABLE OF CONTENTS

TITLE PAGE 1
CLINICAL TRIAL PROTOCOL SYNOPSIS 2
FLOW CHART 4
TABLE OF CONTENTS 5
ABBREVIATIONS AND DEFINITIONS 9
1. INTRODUCTION 12
1.1 MEDICAL BACKGROUND 12
1.2 DRUG PROFILE 13
1.2.1 Zongertinib 13
1.2.2 Residual Effect Period 17
1.3 RATIONALE FOR PERFORMING THE TRIAL 17
1.4 BENEFIT - RISK ASSESSMENT 17
1.4.1 Benefits 17
1.4.2 Risks 17
1.4.3 Discussion 21
2. TRIAL OBJECTIVES AND ENDPOINTS 22
2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS 22
2.1.1 Main objectives 22
2.1.2 Primary endpoint(s) 22
2.1.3 Secondary endpoint 22
[redacted]
2.2.2.2 Safety and tolerability 23
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION 24
3.1 OVERALL TRIAL DESIGN 24
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) 26
3.3 SELECTION OF TRIAL POPULATION 26
3.3.1 Main diagnosis for trial entry 27
3.3.2 Inclusion criteria 28
3.3.2.1 Inclusion criteria applicable to all participants 28
3.3.3 Exclusion criteria 29
3.3.3.1 Exclusion criteria for all participants: 29
3.3.4 Withdrawal of subjects from treatment or assessments 31
3.3.4.1 Withdrawal from trial treatment 32
3.3.4.2 Withdrawal of consent to trial participation 32

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3.3.4.3 Discontinuation of the trial by the sponsor 32
3.3.5 Replacement of subjects 33
4. TREATMENTS 34
4.1 INVESTIGATIONAL TREATMENTS 34
4.1.1 Identity of the Investigational Medicinal Products 34
4.1.2 Selection of doses in the trial and dose modifications 34
4.1.3 Method of assigning subjects to treatment groups 34
4.1.4 Drug assignment and administration of doses for each subject 35
4.1.5 Blinding and procedures for unblinding 35
4.1.6 Packaging, labelling, and re-supply 35
4.1.7 Storage conditions 36
4.1.8 Drug accountability 36
4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS 36
4.2.1 Other treatments and emergency procedures 36
4.2.2 Restrictions 37
4.2.2.1 Restrictions regarding concomitant treatment 37
4.2.2.2 Restrictions on diet and life style 37
4.2.2.3 Contraception requirements 37
4.3 TREATMENT COMPLIANCE 38
5. ASSESSMENTS 39
5.1 ASSESSMENT OF EFFICACY 39
5.2 ASSESSMENT OF SAFETY 39
5.2.1 Physical examination 39
5.2.2 Vital signs 39
5.2.3 Safety laboratory parameters 39
5.2.4 Electrocardiogram 42
5.2.5 Other safety parameters 43
5.2.6 Assessment of adverse events 43
5.2.6.1 Definitions of adverse events 43
5.2.6.1.1 Adverse event 43
5.2.6.1.2 Serious adverse event 43
5.2.6.1.3 AEs considered ‘Always Serious’ 44
5.2.6.1.4 Adverse events of special interest 44
5.2.6.1.5 Intensity (severity) of AEs 46
5.2.6.1.6 Causal relationship of AEs 46
5.2.6.2 Adverse event collection and reporting 47
5.2.6.2.1 AE collection 47
5.2.6.2.2 AE reporting to the sponsor and timelines 48
5.2.6.2.3 Pregnancy 48
5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS 48
5.3.1 Assessment of pharmacokinetics 48

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5.3.2 Methods of sample collection 48
5.3.2.1 Blood sampling for pharmacokinetic analysis 48
5.3.2.2 Blood sampling for protein binding of zongertinib 49
[redacted]
[redacted]
5.7 APPROPRIATENESS OF MEASUREMENTS 50
6. INVESTIGATIONAL PLAN 51
6.1 VISIT SCHEDULE 51
6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS 51
6.2.1 Screening period 51
6.2.2 Treatment period 51
6.2.3 Follow-up period and trial completion 52
7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 53
7.1 NULL AND ALTERNATIVE HYPOTHESES 53
7.2 PLANNED ANALYSES 53
7.2.1 General considerations 53
7.2.1.1 Analysis sets 53
7.2.1.2 Pharmacokinetics 53
7.2.2 Primary endpoint analyses 54
7.2.3 Secondary endpoint analyses 55
[redacted]
7.2.5 Safety analyses 55
7.2.6 Interim analyses 56
7.3 HANDLING OF MISSING DATA 56
7.3.1 Safety 56
7.3.2 Pharmacokinetics 57
7.4 RANDOMISATION 57
7.5 DETERMINATION OF SAMPLE SIZE 57
8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE 58
8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT 58

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

8.2 DATA QUALITY ASSURANCE 59
8.3 RECORDS 59
8.3.1 Source documents 59
8.3.2 Direct access to source data and documents 60
8.3.3 Storage period of records 60
8.4 EXPEDITED REPORTING OF ADVERSE EVENTS 61
8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY 61
8.5.1 Collection, storage and future use of biological samples and corresponding data 61
8.6 TRIAL MILESTONES 61
8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL 62
9. REFERENCES 64
9.1 PUBLISHED REFERENCES 64
9.2 UNPUBLISHED REFERENCES 64
10. APPENDICES 66
11. DESCRIPTION OF GLOBAL AMENDMENT(S) 67
11.1 GLOBAL AMENDMENT 1 67
11.2 GLOBAL AMENDMENT 2 68
11.3 GLOBAL AMENDMEND 3 69

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	attributable, legible, contemporaneous, original, accurate (dimensions of data integrity)
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BID	Bis in die
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DDI	Drug-Drug-Interaction
DILI	Drug induced liver injury
DLT	Dose limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiogram

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EoS	End of Study (synonym for End of Trial)
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FE	Food effect
FU	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
gMean	Geometric mean
HER	Human epidermal growth factor receptor
IB	Investigator's brochure
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λz	Terminal rate constant of the analyte in plasma
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
NSCLC	Non-small-cell lung cancer
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PSPV	Patient Safety and Pharmacovigilance
PT	Preferred Term
QD	Quaque die
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
REF	Reference group

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

REP	Residual effect period
RTKs	Receptor tyrosine kinases
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TCP	Trial Clinical Pharmacologist
TCPK	Trial Clinical Pharmacokinetics
TIC	Trial Identification Card
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
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_{ss}	Apparent volume of distribution at steady state after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WHO	World Health Organization
WOCBP	Woman of childbearing potential

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

[redacted]

Non-clinical pharmacokinetics

[redacted]

Safety pharmacology / Toxicology

[redacted]

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

[redacted]

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).

[redacted]

Data from clinical studies

Zongertinib is in Phase I of clinical development and has been investigated in 83 patients in a first-in-human, dose escalation part (Phase Ia) and in 200 patients in 5 cohorts in the expansion part (Phase Ib) of trial 1479-0001 and in 76 healthy male participants in trials 1479-0003, 1479-0004, 1478-0006, 1479-0010, and 1479-0011 (data cut 29 Jan 2024) [c32836122].

Trial 1479-0001 (Beamion LUNG-1)

In Phase Ia and in Cohort 1 of Phase Ib, zongertinib was well tolerated across all doses, and the reported AEs were manageable. Most AEs were of low grade. Low rates of DLTs, SAEs, and AEs leading to dose interruption, reduction and treatment discontinuation were observed. Some patients experienced Grade 3 and 4 liver investigations after multiple dosing which were all improving, including 3 patients meeting the laboratory criteria of "Hy's law. The decision to move forward with [redacted] was confirmed. Potentially persistent or irreversible toxicities that might limit the options for patients to tolerate future therapies have not been observed thus far. In Cohorts 2 to 5 of Phase Ib, zongertinib was well tolerated in both [redacted] groups and the reported AEs were manageable. The safety profiles were comparable to the safety profile of Cohort 1 while considering specific characteristics of respective trial populations.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Trial 1479-0003

In this relative bioavailability (BA) and food effect trial (FE) trial, 8 out of 13 participants (61.5%) were reported with at least 1 treatment-emergent AE on zongertinib. At the PT level, the most frequently reported AE was COVID-19 (3 participants, 23.1%). Other PTs were reported for 1 participant each [c40238670]. Two AEs of CTCAE Grade 2 were reported (non-drug-related abdominal pain upper, contusion). All other AEs were Grade 1. All AEs were reported resolved by the end of the trial, except 1 AE of hordeolum that was not resolved. No investigator-defined drug related AEs were reported. No deaths, SAEs, AEs leading to discontinuation of trial drug, AESI, or other significant AEs were reported.

Trial 1479-0004

In this Drug-Drug-Interaction (DDI) trial with itraconazole, 4 out of 16 participants (25.0%) were reported with at least 1 AE on zongertinib. At the PT level, the most frequently reported AE was headache(3 participants, 18.8%). Other PTs were reported for not more than 1 participant in each treatment group [c42362953]. Investigator-defined drug-related AEs were reported for 2 out of 16 participants (12.5%; headache of CTCAE Grade 2) while on treatment with zongertinib. All AEs were of CTCAE Grade 1, except 2 AEs of Grade 2 headache, reported during trial period 1 (zongertinib alone) which were considered drug-related. All AEs were reported resolved by the end of the trial, except 1 AE of hand fracture which was not considered drug-related. No deaths, no SAEs, no CTCAE Grade 3, 4, or 5 AEs, and no protocol-specified AESIs were reported. A grade 1 AE of diplopia led to the premature discontinuation of itraconazole 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. No AE on zongertinib led to premature discontinuation of trial medication.

Trial 1479-0006

In this human ADME/BA trial, 7 out of 8 participants (88.0%) were reported with at least 1 AE on zongertinib (C-14) oral solution in Part A (ADME part) and 2 out of 7 participants (29.0%) were reported with at least 1 AE on zongertinib tablet and zongertinib (C-14) solution for infusion in Part B (absolute bioavailability part) of the trial. In Part A, at the PT level, the most frequently reported AEs were impetigo (4 participants, 50.0%), diarrhoea (3 participants, 38.0%), and headache (3 participants, 38.0%). Other PTs were reported for 1 participant each. In Part B, at the PT level, diarrhoea and catheter site bruise were reported for 1 participant and muscle spasms was reported for 1 participant [c43542365]. In Part A, investigator-defined drug-related AEs (abdominal pain and diarrhoea) were reported for 1 out of 8 participants (13.0%). In Part B, one drug-related AE of diarrhoea was reported for 1 out of 7 participants (14.0%). In both parts, all AEs were of CTCAE Grade 1, except 1 AE of Grade 2 tonsillitis reported in Part A, considered not related to trial drug. All AEs were reported resolved by the end of Part A, except 1 AE of impetigo which was not resolved and 1 AE of nasopharyngitis for which the outcome was unknown. All AEs were resolved by the end of Part B. In both parts, no deaths, no SAEs, no CTCAE Grade 3, 4, or 5 AEs, and no protocol-specified AESIs were reported. No AE on zongertinib led to discontinuation of trial drug.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Trial 1479-0010

In this BA/FE trial with 240mg zongertinib single dose, 11 out of 16 healthy male participants (68.8%) were reported with at least 1 AE on zongertinib. At the PT level, the most frequently reported AE was headache (4 participants, 25.0%). Other PTs were reported for 1 each participant [c43722140]. Participants reported AEs of CTCAE Grade 1 (7 participants, 43.8%) or Grade 2 (4 participants, 25.0%). Grade 2 headache as reported for 2 participants (12.5%); other Grade 2 AEs were reported for 1 participant each (pain, back pain, myalgia, presyncope, skin lesion). No Grade ≥3 AEs occurred. All AEs were reported resolved by the end of the trial, except 1 AE of paraesthesia, reported as recovering with sufficient follow-up and back pain, reported as likely related to the participants history. Investigator-defined drug-related AEs were reported for 5 participants (31.3%). On the PT level, the only drug-related AE reported for more than 1 participant was headache (3 participants, 18.8%). Other drug-related AEs were cough, fatigue and nausea (1 participant each, 6.3%). No deaths, SAEs, AEs leading to discontinuation of trial drug, AESI, or other significant AEs were reported.

Trial 1479-0011

In this DDI trial with carbamazepine, 13 out of 16 participants (81.0%) who received zongertinib as a single dose or together with multiple doses of carbamazepine were reported with at least 1 AE. AEs on zongertinib alone were reported for 11 out of 16 participants (69.0%). At the PT level, the most frequently reported AEs were fatigue (6 participants, 38.0%), constipation, back pain, and nasopharyngitis (3 participants each, 19.0%), abdominal discomfort, neck pain, and pruritus (2 participants each, 13.0%). Other PTs were reported for 1 participant only [c43437359]. Investigator-defined drug-related AEs were reported for 12 out of 16 participants (75.0%) who received zongertinib as a single dose or together with multiple doses of carbamazepine, in 10 out of 16 participants (63.0%) while on treatment with zongertinib alone, and in 11 out of 15 participants (73.0%) while on treatment with carbamazepine. Fatigue (1 participant, 6%) was the only drug-related AE reported on treatment with zongertinib alone. All AEs were of mild (Grade 1) or moderate (Grade 2) intensity and were reported as resolved by the end of the trial, except 1 drug-related AE of mild alopecia in 1 participant in the zongertinib and carbamazepine phase. No deaths, SAEs, no AEs of CTCAE Grade 3, 4 or 5, and no protocol-specified AESIs were reported. No AE led to premature discontinuation of trial drug.

Clinical Pharmacology

Preliminary, exploratory PK analysis in trial 1479-0001 indicated [redacted] The observed PK profile of zongertinib appears [redacted] to achieve efficacious plasma exposure, which is also suggested by the [redacted]

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of single doses of zongertinib 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

The liver plays a central role in the metabolism and elimination of many drugs, and hepatic disease may substantially alter drug absorption and disposition as a result of reduction in absolute cell mass and in cellular enzyme content or activity. Reduced hepatic blood flow in chronic hepatic disease may also decrease hepatic clearance.

Based on the data from human ADME trial 1479-0006 (see 1.2.1) zongertinib is mainly excreted via faeces (gMean 92.5%) and only 1.30% (gMean) via urine.

This exploratory trial is designed to investigate the effect of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on the pharmacokinetics, safety and tolerability of zongertinib. The data obtained in this trial will provide a basis for the treatment of patients with advanced solid tumours with HER2 aberrations with hepatic impairment including potential dose adaptation for these patients.

The design of this trial follows the FDA guideline for Industry “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” [R05-0337] and the EMA “Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function” [R05-0340].

For ethical and safety reasons, also in perspective of ongoing evaluation of potential hepatotoxicity of zongertinib patients with severely impaired hepatic function (Child-Pugh C) will not be enrolled in this trial.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for subjects with normal hepatic function or subjects with hepatic impairment. 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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: Zongertinib (BI 1810631)		
Unexpected AEs and laboratory abnormalities	Risk is due to limited clinical experience with zongertinib (BI 1810631)	Close monitoring of safety data.
Drug-induced liver injury (DILI)	Rare but can be a potentially severe event, thus under constant surveillance by sponsors and regulators for all drugs in development. Elevations of liver enzymes and bilirubin and other hepatic AEs 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 61 patients (30.5%). This included AEs ⩾ Grade 3, treatment interruptions, dose reductions and permanent discontinuations of trial medication.	Short treatment duration makes the occurrence of liver injury unlikely. In addition, timely detection, evaluation, and follow-up of liver function tests (laboratory parameters) are in place to ensure subjects´ safety.
Intestinal toxicity	Reversible intestinal effects in dogs after multiple dosing (fecal alterations, Goblet cell hyperplasia) [c32836122]. Reported diarrhoea during treatment with zongertinib (BI 1810631) in trial 1479-0001, was mainly of Grade 1 and 2. Grade 3 diarrhoea occurred in a few patients. (see Section 1.2).	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only two single doses with appropriate wash-out • Following administration of zongertinib (BI 1810631), subjects will be in-house under close observation

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: Zongertinib (BI 1810631)		
Mucositis	Lesions of oral mucosa observed in dog toxicology and general pharmacology studies [c32836122]. Stomatitis/mouth ulceration cases of Grade 1 and 2 were observed in patients in trial 1479-0001 .	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only one single dose
Reproductive and developmental toxicity	[redacted] [c32836122]. Through the ejaculate, zongertinib (BI 1810631) could potentially be transferred to a female partner of the male patient, be vaginally absorbed and could thus potentially harm the fetus.	• Volunteers will, together with their WOCBP (woman of childbearing potential) partner, use highly effective contraception from first dosing of BI 1810631 until 30 days after the last dosing with zongertinib (BI 1810631) (see also exclusion criteria in Section 3.3.3).
QT prolongation	Preclinical data indicate a low proarrhythmic potential of zongertinib (BI 1810631). In trial 1479.0001, ECG QT prolongation was reported as AE in 7 (3.5%) patients (The reported AEs were of Grade 1 and 2 [c40238724].	• Subjects with a marked QTc prolongation at baseline are excluded from participation in this trial (see exclusion criterion 21) • Subjects with a history of risk factors for Torsade de Pointes are excluded from participation in this trial (see exclusion criterion 22) • ECGs will be performed as defined in the Flow Chart
Toxicity to adrenal glands	Reversible changes to adrenal glands in rats after multiple dosing (increased organ weights, vacuolation, minimal single cell necrosis, hypertrophy of zona fasciculata/ reticularis) [c32836122]. Reversible changes to adrenal glands in dogs after multiple dosing (hyperplasia of zona glomerulosa) [c32836122]. Thus far, no adrenal glands disorder cases were reported in trial 1479-0001.	• Safety laboratory (see Section 5.2.3) includes serum electrolytes • Protection of subjects by administration of only one single dose

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: Zongertinib (BI 1810631)		
Hair discoloration	Yellow hair discoloration with indication for reversibility in rats and dogs [c32836122]. Thus far, no cases of hair discoloration reported in trial 1479-0001.	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Physical examination of subjects at end-of-study visit • Protection of subjects by administration of only two single doses
LVEF decrease	Risk is due to limited clinical experience with this drug and considering the potential effect of the other HER2 targeted agents on heart function. In trial 1479-0001, ejection fraction decreased was reported in 7 (3.5%) patients, The reported AEs were Grade 1 and Grade 2.	• Participants will only be exposed to one dose of zongertinib (BI 1810631) • ECGs will be performed as defined in the Flow Chart • Exclusion of participants with respective risk
Interstitial Lung Disease (ILD) and Pneumonitis	Thus far no ILD cases were observed in trial 1479-0001; however, ILD has been reported with other TKIs inhibiting HER2 or EGFR	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only one single dose • Following administration of zongertinib (BI 1810631), subjects will be in-house under close observation
Drug-related AEs observed in patients in trial 1479-0001	After multiple dosing with zongertinib (BI 1810631), AEs assessed as drug-related were reported (see Section 1.2.2.)	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Following administration of zongertinib (BI 1810631), subjects will be inhouse under close observation • Protection of subjects by administration of only one single dose

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: Zongertinib (BI 1810631)		
Uncertainties due to the early stage of development	Comparatively very high plasma exposures were explored in humans (see IB [c32836122]) and showed well tolerable and manageable safety profile so far (see Section 1.2.2 and IB [c32836122]). However, Zongertinib (BI 1810631) is currently in early development and there may be unknown risks of treatment with zongertinib (BI 1810631).	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Following administration of zongertinib (BI 1810631), subjects will be inhouse under close observation • Safety Lab, VS and ECGs after dosing (see Flow Chart) • Protection of subjects by administration of only one single dose

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

The nature of the target and the mechanism of action of zongertinib are well understood. Zongertinib inhibits tumor growth and induces tumor regression in pre-clinical models. In trial 1479-0001, strong preliminary efficacy signals were observed across most dose levels. Overall, zongertinib was well tolerated and the reported AEs were manageable (see also Section 1.2.1) also in the reported healthy volunteer trials. Subjects in this trial will receive a single dose of 120 mg zongertinib resulting in a total dose of 120 mg zongertinib for each participant. Even higher single doses of 240 mg zongertinib were well tolerated by healthy volunteers of 1479-0010 trial and repetitive higher doses up to 360 mg QD were tolerated by cancer patients of 1479-0001 (see Section 1.2.1).

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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this study is to investigate the effect of mild (Child-Pugh A, score 5-6) and moderate (Child-Pugh B, score 7-9) hepatic impairment on the PK of zongertinib.

2.1.2 Primary endpoint(s)

The following pharmacokinetic parameters will be determined for zongertinib:

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for zongertinib:

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



Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



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)

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomised, open-label, parallel, individual-matched trial in order to investigate PK of zongertinib, as well as well safety and tolerability in male and female participants of non-childbearing potential with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment compared to individually matched control participants. The treatment will be a single dose of 120 mg zongertinib administered in the fasting state.

- Group 1: 8 participants with mild hepatic impairment (Child-Pugh A)
- Group 2: 8 participants with moderate hepatic impairment (Child-Pugh B)
- Group 3: Up to 8-16 participants with normal hepatic function either matched to Group 1, Group 2 or both.

Matching criteria:

One participant with normal hepatic function may match one participant in one or both groups with hepatic impairment based on the following and needs to fulfil **all three criteria**:

- age (± 10 years)
- sex
- weight (± 15%)

Enrolment of participants will follow a staggered approach to ensure safety of participants (Figure 3.1: 1). Based on available PK data, only a minor exposure increase is expected for participants with mild hepatic impairment. Impact of moderate hepatic impairment on the PK is less understood, hence Group 1 (n=8) will start before Group 2 (n=8) and dosing of participants with normal hepatic function from Group 3 (n=8-16) will occur in parallel (as applicable for matching purposes). The final sample size of Group 3 depends on the enrolment of subjects to Groups 1 and 2 (see below).

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

[redacted]

After the first 2 participants of Group 1 have been dosed, 3 additional participants will be enrolled if no abnormalities are detected in the safety laboratory within first 48h after dosing. After the first 5 participants of Group 1 have been dosed, the first 2 participants of Group 2 will be enrolled, and Group 1 will be completed (3 additional participants) if no safety concerns are reported. Thereafter, a preliminary safety and PK analysis (i.e., AEs, medically relevant abnormalities in vital signs, ECG, and safety laboratory up to Day 4) will be performed for the subjects of Group 2. Additionally all already available safety information of subjects from Group 1 and Group 3 (as applicable) will be reviewed. The data will be reviewed by the Principal Investigator, the CTL, TCP and the Patient Safety and Pharmacovigilance (PSPV) representative (or authorised deputies respectively). The next 3 participants of Group 2 will only be dosed after the preliminary analysis if the following criteria are met:

- deemed safe by the Principal Investigator and sponsor team based on safety analysis and
- [redacted]

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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)

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. The single-dose individual-matches comparison is deemed appropriate to meet the objectives of the study. EMA and FDA guidance [R05-0337, R05-0340] recommend to assign matched control participants with normal hepatic function to control for other factors which may influence the PK in a hepatic impaired population such as age, sex and weight . The resulting sample sizes in each group (see Section 7.5) are considered to be sufficient for the exploratory evaluation of PK.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and up to 16 participants with normal hepatic function will enter the trial. They will be recruited from the volunteers' pool of the trial site.

Participants with hepatic impairment will be assigned to one of the hepatic impairment groups (mild or moderate), according to Child-Pugh score (see Table 3.3: 1 and 3.3: 2). The hepatic function assessment and assignment to the hepatic impairment groups will be conducted by the investigators at the screening examination.

Table 3.3:1 Child-Pugh scoring

Measures	**1 Point**	**2 Points**	**3 Points**
Total Bilirubin, µmol/L (mg/dL)	< 34 (< 2)	34 - 50 (2 - 3)	> 50 (> 3)
Serum albumin, g/dL	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time, prolongation (s) / or INR	< 4.0 < 1.7	4.0 - 6.0 1.7 - 2.3	> 6.0 > 2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 3.3:2 Child-Pugh scoring interpretation

Total Points	**Hepatic Impairment Class**
5-6	Child-Pugh A (mild hepatic impairment)
7-9	Child-Pugh B (moderate hepatic impairment)
10-15	Child-Pugh C (severe hepatic impairment)

Encephalopathy Grading System:

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behaviour, decerebrate, slow 2-3 cps delta activity

Participants with normal hepatic function will be matched individually by sex, age (±10 years) and weight (±15%) to the participants with hepatic impairment. One participant with normal hepatic function may match one participant in one or both groups of participants with hepatic impairment.

A log of all participants 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 participants with normal hepatic function and patients with hepatic impairment.

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3.3.2 Inclusion criteria

3.3.2.1 Inclusion criteria applicable to all participants

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

1. Male or female subjects of non-childbearing potential. Female subjects must be of non-childbearing potential either be a) postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 25 U/L and estradiol below 30 ng/L is confirmatory) or b) have proof of acceptable surgical sterilization. Subjects must use condom from time point of administration of trial medication until 30 days after drug administration.
2. Age of 18 to 80 years (inclusive)
3. BMI of 18.0 to 42 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Male subjects with WOCBP partner must be willing to use highly effective methods of contraception (condom in combination with other methods or sexual abstinence) from time point of administration of trial medication until 30 days thereafter. These include:

   - Subject uses condoms

   - Subject is sexually abstinent

   - Subject is vasectomized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and uses condom

Additionally female partners of male subjects must be willing to use any of the following criteria for a highly effective contraception from at least 30 days **before** the first administration of the male partner until 30 days thereafter:

- Use of intrauterine device or intrauterine hormone-releasing system by female partner plus use of condom

- Use of progestogen-only hormonal contraception by female partner that inhibits ovulation (injectables or implants) plus use of condom

- Use of combined (estrogen and progestogen containing) hormonal contraception by female partner that prevents ovulation (oral, intravaginal, or transdermal) plus use of condom

- Surgically sterilised (including hysterectomy or bilateral tubular occlusion) plus use of condom

- Postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 25 U/L and estradiol below 30 ng/L is confirmatory) plus use of condom

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

6. For group 1 and 2 only: Hepatic impairment classified as Child-Pugh A (score 5-6 points) or Child-Pugh B (score 7-9 points)
7. For group 1 and 2 only: Absence of clinically significant abnormalities, as based on a complete medical history including a full physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests at both screening and admission to trial site, with the exception of findings that in the opinion of the investigator are consistent with the participant's hepatic impairment
8. For group 1 and 2 only: Medication and/or treatment regimens must have been stable (i.e., no dose adjustments) for at least 4 weeks prior to the screening period and should be kept stable until study completion

   Fluctuating treatment regimens may be considered for inclusion on a case-by-case basis if the underlying disease is under control in the opinion of the investigator and must be agreed to by both the investigator and the sponsor's medical monitor
9. For group 3 only: Individually matched to participants with hepatic impairment according to age, sex and weight
10. For group 3 only: Absence of clinically significant abnormalities identified by a detailed medical history, full physical examination, vital signs and 12-lead ECG at screening. Absence of clinically significant abnormalities identified by a laboratory test at screening visit.

3.3.3 Exclusion criteria

3.3.3.1 Exclusion criteria for all participants:

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) assessed as clinically relevant by the investigator (apart from any non-severe hepatic impairment and associated underlying diseases)
2. Severe hepatic impairment (classified as Child-Pugh C or score 10-15)
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance (apart from values due to underlying disease)
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator (apart from underlying disease)
5. Severe gastrointestinal, renal (eGFR CKD-EPI <40 ml/min/1.73 m^2 for the hepatic impaired patients and eGFR CKD-EPI <90 ml/min/1.73 m^2 for matched controls), respiratory, cardiovascular, metabolic, immunological or hormonal disorders assessed as clinically relevant by the Investigator.
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

8. History of relevant orthostatic hypotension, repetitive fainting spells, or repetitive 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 or squamous cell carcinoma in situ of the skin or in situ carcinoma of uterine cervix
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 (or 5 of its half-lives, whichever is longer) 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 30 days for single dose studies or 60 days for multiple dose studies or 5 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. Current smoker or ex-smoker defined as having quit smoking for less than 3 months.
15. Use of e-cigarettes (vape)
16. Alcohol abuse (consumption of more than 24 g per day for men and 12g for women)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Sperm donation is not permitted until 30 days after last drug administration.
20. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
21. Inability to comply with the dietary regimen of the trial site
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. Intake of strong CYP3A inhibitors or inducers or any potentially hepatotoxic agents within 30 days or 5 half-life times (whichever is longer) to administration of trial medication.

Exclusion criteria applying to participants with normal hepatic function only (group 3)

25. Repeated measurement of systolic blood pressure outside the range of 90 to 150 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 100 bpm

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

26. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 470 ms) or any other relevant ECG finding at screening

27. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance

Exclusion criteria applying to participants with hepatic impairment only (group 1 and 2)

28. Repeated measurement of systolic blood pressure outside the range of 90 to 170 mmHg, diastolic blood pressure outside the range of 50 to 100 mmHg, or pulse rate outside the range of 50 to 100 bpm

29. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 480 ms) or any other relevant ECG finding at screening

30. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance, except for laboratory values outside the reference range due to underlying disease

31. Thrombocytes < 40.000 10^9/L

32. Gastrointestinal bleeding within 3 months prior to Visit 1

33. Encephalopathy > II

34. Oesophageal varices > stage 2

35. Severe ascites

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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Withdrawal from further drug administration of individuals is not feasible for single-dose studies after drug administration. Participants will be asked to complete an end-of-trial examination if for example:

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

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 moderate or severe intensity, 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
6. Participants with normal or mildly impaired hepatic function: the subject has a drug related elevation of AST and/or ALT ≥3-fold above ULN or ≥3x to elevated (not clinically significant) screening (if elevated at screening) or ≥3x baseline value (if elevated at baseline) (whichever was higher) and an elevation of total bilirubin ≥2-fold above ULN or ≥2x to elevated (not clinically significant) screening (if elevated at screening) or ≥2x baseline value (if elevated at baseline) (whichever was higher) measured in the same blood sample and confirmed by a repeat measurement

Additional discontinuation criterion for participants with moderately impaired hepatic function only.

1. Participants with moderately impaired hepatic function: drug related elevation of AST and/or ALT ≥3-fold above ULN or ≥3x to elevated screening (if elevated at screening) or ≥3x baseline value (if elevated at baseline) (whichever was higher) together with an increase in total bilirubin ≥2-fold to screening values (if elevated at screening) or ≥2x baseline values (if elevated at baseline) (whichever was higher) in the same blood sample and confirmed by a repeat measurement will lead to termination of Group 2 only.

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 2 subjects do not complete the trial in any group (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 1/3 of the total number of evaluable subjects anticipated to complete the trial. A replacement subject will be assigned a unique trial subject number.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	60 mg
Posology:	2-0-0
Mode of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

The dose selected for this trial is below the standard clinical dose used for further development of zongertinib (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment investigated in this trial. The participants with hepatic impairment and the matching participants with normal hepatic function will be assigned to treatment groups according to the Child-Pugh classification and as control groups as outlined in Table 4.1.3:1.

Table 4.1.3:1 Trial Treatment Groups

Treatment Group	Child-Pugh Classification	Child-Pugh Score (points)	Number of participants
Group 1	A	5-6	8
Group 2	B	7-9	8
Group 3	-	-	8-16*

* If a subject of Group 3 is matching to participants of Group 1 and Group 2, this participant will be considered as match to both subjects.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. For discussion of trial-associated risks and safety measures, see Section 1.4 and 3.1).

4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive the same treatment. The treatment 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)	Zongertinib (BI 1810631)	Film-coated Tablet	60 mg	2x tablets (60 mg) single dose for 1 day	120 mg

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

Subjects will be kept under close medical surveillance following drug administration at least until discharge on D6. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. The treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. 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.

No re-supply is planned.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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,

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 for participants with normal hepatic function. In participants with hepatic impairment medication for treatment of the hepatic or other concomitant diseases are allowed. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

Strong CYP3A inhibitors and inducers are restricted medication in all trial participants due to potential drug-drug interactions.

If necessary, short-term use of ibuprofen or acetylsalicylic acid is acceptable for symptomatic treatment of AEs. Paracetamol intake is not allowed.

Symptomatic treatment of adverse reactions is at the discretion of the investigator.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 5 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

[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 administration of trial medication.

[redacted] should be avoided as they tend to create false positive drug screening results.

Smoking is not allowed during the study.

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

For participants and their partners adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.3 for the definition of adequate measures).

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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).

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 including determination of body weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor 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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	X	X
	Prothrombin time	X	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	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
	Lactate dehydrogenase (LDH)	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	Follicle Stimulation Hormone (FSH)	X	--	--
	Estradiol	X	--	--

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Plasma)	X	--	X
	HbA1C (only for participants with diabetes mellitus)	X	--	--
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	--	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Bilirubin, Indirect	X	X	X
	Protein, Total	X	X	X
	Albumin	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 Visit 1 (screening examination)
B: parameters to be determined at Visit 2 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening and pregnancy test, it is planned to perform these tests during screening only. Drug screening and urine pregnancy test will be performed at screening and at admission to the site on Day -1.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to treatment 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 tests and urine pregnancy test. These tests will be performed at the trial site as per local procedure.

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 at the times provided in the Flow Chart.

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

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

All ECGs will be stored electronically. 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).

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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 that occur after drug administration:

  For participants with normal hepatic function and mildly impaired hepatic function:

1.) AST or ALT elevation ≥ 3x ULN or ≥300 U/L or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher) and total bilirubin ≥ 2 x ULN or ≥ 2 x screening value (if elevated at screening) or ≥ 2 x baseline value (if elevated at baseline) (whichever is higher) measured at the same visit and confirmed by repeat sample, or

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

2.) AST or ALT elevation ≥ 3x ULN or ≥300 U/L or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher) and INR ≥ 1.5 x ULN or ≥ 1.5 x screening value (if elevated at screening) or ≥ 1.5 x baseline value (if elevated at baseline) (whichever is higher) measured at the same visit and confirmed by repeat sample, or

3.) AST or ALT elevation ≥ 3x ULN or ≥300 U/L or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher) with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), or

4.) AST and ALT elevation ≥ 5 ULN or ≥300 U/L or ≥ 5 screening value (if elevated at screening) or ≥ 5 baseline value (if elevated at baseline) (whichever is higher)

These laboratory findings constitute a hepatic injury alert, and participants showing any of these abnormalities need to be followed up according to the DILI Checklist provided in the ISF.

Additionally, with participants having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥ 3x and < 5x ULN requires repeat testing within 72h. DILI Checklist is not required unless repeat testing triggers alerts 1,2,3, or 4.

For participants with moderately hepatic impaired function:

1.) AST or ALT elevation ≥ 2x ULN or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher), and total bilirubin >2x or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher)

2.) AST or ALT elevation ≥ 2x ULN or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher) and INR >1.2x or >1.2x screening (if elevated at screening) or baseline value (if elevated at baseline) (whichever is higher)

3.) AST or ALT elevation ≥ 2x ULN or ≥ 2x screening value (if elevated at screening) or ≥ 2x baseline value (if elevated at baseline) (whichever is higher) and any new onset, or worsening of signs and/or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), or

4.) AST or ALT ≥ 3x ULN or ≥ 3x screening value (if elevated at screening) or ≥ 3x baseline value (if elevated at baseline) (whichever is higher)

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Once a subject has been enrolled in the clinical trial and has taken trial medication, and/or if a partner of the male trial participant becomes pregnant 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.

This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations.

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

As 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 zongertinib concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an K2-EDTA (dipotassium

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 within 120 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.

5.3.2.2 Blood sampling for protein binding of zongertinib

Approximately 30 mL blood will be collected into a potassium ethylenediaminetetraacetic acid (K2-EDTA)-anticoagulant blood drawing tubes to enable determination of ex vivo plasma protein binding of zongertinib before drug administration. The blood samples will be stored on ice and centrifuged within 60 min after collection. Centrifugation will last for about 10 min (at about 2000 g to 4000 g) at about 4-8 °C. The total amount of the plasma (obtained from the 30 mL blood sample) will be divided into 2 appropriately pre-labelled cryo-tubes.

Date and time of the blood draw as well as date and time of drug intake of the respective subject must be documented in the eCRF. The plasma samples will be stored at about -20 °C or below until shipment.



Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

[redacted]

[redacted]

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. The pharmacokinetic parameters and measurements outlined in Section 5.3 are of exploratory nature only.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 for in-house visits and ± 2h for ambulatory visits.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

On Day -1 trial participants will be admitted to the trial site and kept under close medical surveillance following drug administration at least until discharge on D6. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, participants will come to the trial site for ambulatory visits.

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The effect of hepatic impairment on the PK endpoints of single dose of zongertinib will be estimated by the ratios of geometric means of the respective pairwise comparison of interest, i.e. for each hepatic impairment group (Child-Turcotte-Pugh class A and B) vs the respective matched control subjects, and their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified for any comparison.

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 participants who were treated with one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all participants in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and were 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 of the main PK parameter values 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 (BI 1810631) will be calculated according to the relevant BI internal procedures.

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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).

Descriptive statistics of PK parameters will be calculated if N≥2.

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 the effects ‘degree of hepatic impairment’ and ‘matched pair’ as fixed effects . The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response measured on subject m with degree of hepatic impairment k,

μ = the overall mean,

s_m = the effect of the m^{th} matched pair, m = 1, 2, ..., 8,

τ_k = the effect of k^{th} degree of hepatic impairment, k=1 for no impairment (healthy), k= 2 for either Child-Pugh class A or B,

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

e_{km} = the random error associated with the k^{th} degree of hepatic impairment for matched pair m,

where, $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and e_{km} is an independent random variable.

The model described above will be fitted separately for the two hepatic impaired groups, i.e., one model for the participants with mild hepatic impairment and their matched controls, and one model for the participants with moderate hepatic impairment and their matched controls.

For evaluation of each primary endpoint, the difference between the expected means for log response of hepatic impaired group ($\log(\tau_2)$) – log response of the respective control group ($\log(\tau_2)$ - $\log(\tau_1)$) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% CIs 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.

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 statistically using the same methods as described for the primary endpoints.

[redacted]

7.2.5 Safety analyses

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

Treatment groups 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 EoS examination date will be assigned to 'follow-up'. These assignments

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock of the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No formal interim analysis is planned.

A preliminary, exploratory analyses of all available or specific data (e.g. safety, PK) will be performed after dosing of 2 participants from Group 2, prior to final database lock, to inform the decision of dosing continuation in Group 2 (see Section 3.1). For the assessment of PK data, the PK parameters will be calculated according to the relevant Boehringer Ingelheim internal procedure. A quality check of the preliminary PK data will be performed. In contrast to the final PK calculations, the preliminary PK analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final PK results. The preliminary PK analysis will provide individual and gMean concentration profiles and summary statistics of PK parameters per group. No inferential statistical preliminary analysis is planned. No formal preliminary PK report will be written and results will not be reported in the CTR.

In case a second preliminary analysis will be performed after the next 3 participants from Group 2 have been dosed (see Section 3.1), the analysis will be conducted as described above for the first preliminary analysis.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

The trial will not be randomised, thus this section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include a maximum of 32 subjects in the trial: 8 patients with mild hepatic impaired function (Child-Pugh A), 8 patients with moderate hepatic impairment (Child-Pugh B), and up to 16 matched control subjects with normal hepatic function will be treated. Note, one subject with normal hepatic function may match a patient in only one or in both groups with hepatic impaired participants. The matching criteria for the matched control subjects are described in Section 3.1.

The planned sample size is not based on a power calculation but is considered as sufficient to detect major differences between the different groups of participants with hepatic impairment and the respective control group with participants with normal hepatic function. Furthermore, a sample size of 8 participants in each hepatic impairment and control group is considered sufficient for hepatic impairment trials [R05-0340].

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

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

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

SAE/AESI are processed in the global safety database and assessed for the sponsor causal relationship, as well as the expectedness of the event according to the reference safety information. Individual case safety reports are subsequently reported according to local regulations.

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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the American Research Corporation under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.
BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial activities, in order to

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

The trial will be managed by a FOT vendor based on a contract wich specifies the delegated responsibilities and duties. BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to:

- Oversee and manage the trial in accordance with applicable regulations and SOPs,
- Direct the clinical trial team and oversee the FOT vendor in the preparation, conduct, and reporting of the trial,
- Ensure appropriate training.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

In the participating country the trial will be performed by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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

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

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

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

Data management and statistical evaluation will be done by BI and/or a Contract Research Organization 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.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9. REFERENCES

9.1 PUBLISHED REFERENCES

P15-01211 Arteaga CL Engelman JA. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell; 25(3), p. 282-303; 2014.

P19-00456 Wang Y Jiang T Qin Z Jiang J Wang Q Yang S et al. HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. Ann Oncol; 30(3), p. 447-455; 2019.

P19-10412 Connell CM Doherty GJ. Activating HER2 mutations as emerging targets in multiple solid cancers. ESMO Open; 2, p. e000279; 2017.

P20-09250 Jebbink M Langen AJ de Boelens MC Monkhorst K Smit EF. The force of HER2 - a druggable target in NSCLC? Cancer Treat Rev; 86, p. 101996; 2020.

R05-0337 Guidance for industry: pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. http://www.fda.gov/cder/guidance/3625fnl.pdf; 2003.

R05-0340 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. London, 17 February 2005, CPMP/EWP/2339/02.

R09-6185 Hynes NE MacDonald G. ErbB receptors and signaling pathways in cancer. Curr Opin Cell Biol; 21, p. 177-184; 2009.

R18-1357 U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v 5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22 (access date: 2017-04-09); 2017.

R20-1872 Citri A Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol; 7, p. 505-516; 2006.

R20-1990 Wang Z. ErbB receptors and cancer. Methods Mol Biol; 1652, p. 3-35; 2017.

9.2 UNPUBLISHED REFERENCES

c32836122 [redacted] Investigator´s Brochure Zongertinib (BI 1810631). Current version.

c40238670 Relative bioavailability of BI 1810631 as two different oral formulations given as single doses and investigation of the effects of food and multiple-dose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial). 1479-0003. 11 Sep 2023.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

c40238724	Relative bioavailability of BI 1810631 as two different oral formulations given as single doses and investigation of the effects of food and multipledose rabeprazole on the pharmacokinetics of single-dose BI 1810631 following oral administration in healthy male subjects (an open-label, randomised, four-way crossover trial). 1479-0003.
c42362953	The effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two period, fixed-sequence trial).1479-0004. 30 Nov 2023.
c43437359	The effect of multiple doses of carbamazepine on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial).1479-0011.
c43542365	A phase I, open-label trial in two parallel parts to investigate mass balance, metabolism, and basic pharmacokinetics of BI 1810631 (C-14) administered as oral solution (Part A) and to investigate absolute bioavailability of BI 1810631 administered as film-coated tablet together with an intravenous microtracer dose of BI 1810631 (C-14) (Part B) in healthy male volunteers. 1479-0006.
c43722140	Relative bioavailability of BI 1810631 following oral administration under fed and fasted conditions in healthy male subjects (an open-label, randomised, single-dose, two-way crossover trail). 1479-0010.
n00282230	Identification of human cytochrome P450 isoforms responsible for the metabolism of BI 1810631

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10. APPENDICES

Not applicable.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		06 Dec 2024
Universal Trial No. (UTN)		**U1111-1307-9446**
BI Trial number		1479-0020
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		Pharmacokinetics, safety and tolerability of zongertinib following oral administration in male and female participants of non-childbearing potential with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants of non-childbearing potential with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		3.3
Description of change		Within deleted from text: “Participants with normal hepatic function will be matched individually by sex, age (±10 years) and weight (±15%) to the participants with hepatic impairment.”
Rationale for change		Typo corrected
Section to be changed		3.3.3
Description of change		eGFR for healthy volunteers corrected to <90 ml/min/1.73 m^2
Rationale for change		Typo corrected
Section to be changed		3.3.3
Description of change		Numbering corrected
Rationale for change		Numbering correct
Section to be changed		5.2.3
Description of change		GLDH measurement deleted
Rationale for change		GLDH measurement not needed

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11.2 GLOBAL AMENDMENT 2

Date of amendment		18 Dec 2024
Universal Trial No. (UTN)		**U1111-1307-9446**
BI Trial number		1479-0020
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		Pharmacokinetics, safety and tolerability of zongertinib following oral administration in male and female participants of non-childbearing potential with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants of non-childbearing potential with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		3.3
Description of change		Number Connection Test (NCT) deleted from protocol
Rationale for change		Number Connection Test deleted due to lack of specificity to detect hepatic encephalopathy.

Proprietary confidential information © 2025 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11.3 GLOBAL AMENDMEND 3

Date of amendment		17 Feb 2025
Universal Trial No. (UTN)		**U1111-1307-9446**
BI Trial number		1479-0020
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		Pharmacokinetics, safety and tolerability of zongertinib following oral administration in male and female participants of non-childbearing potential with different degrees of hepatic impairment (Child-Pugh classification A and B) compared with matched male and female participants of non-childbearing potential with normal hepatic function (an open-label, non-randomised, single-dose, parallel, individual-matched design trial)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		5.2.3
Description of change		Coagulation measurement added in panel B
Rationale for change		To be able to assess INR value for DILI criteria also on D1, D2, D4 and D8
Section to be changed		5.2.6.1.4
Description of change		DILI criteria specified more precisely
Rationale for change		DILI criteria specified more precisely
Section to be changed		Synopsis and 7.2.2
Description of change		Minor adaptation in primary analysis
Rationale for change		Adaptation according to new ICH M13A guideline (ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms Step 5).

Signature Page for VV-TMF-986386 v4.0

Reason for signing: Approved	Name: [redacted] Role: V[redacted]n-Paper Signature Completion Date of signature: 17-Feb-2025 15:16:28 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 17-Feb-2025 15:22:54 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 17-Feb-2025 16:23:24 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 17-Feb-2025 17:04:39 GMT+0000

Signature Page for VV-TMF-986386 v4.0