Clinical Trial Protocol

	Document Number: **c42988075-04**
EU Trial No.	2023-510263-35-00
UTN	U1111-1301-9035
BI Trial No.	1479-0014
BI Investigational Medicinal Product	Zongertinib (BI 1810631)
Title	The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial)
Lay Title	A study in healthy men to test whether zongertinib affects how 3 other medicines (midazolam, omeprazole, and repaglinide) are taken up and processed in the body
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted], Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted], Fax: [redacted]
Current Version, Date	Version 4.0, 12 Jul 2024
Original Protocol Date	06 Mar 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	06 Mar 2024
Revision date	12 Jul 2024
BI trial number	1479-0014
Title of trial	The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial)
[redacted] **Investigator**	[redacted]
Trial site	
Clinical phase	I
Trial rationale	Based on in-vitro data zongertinib is a potential [redacted] as well as a time-dependent inhibitor of CYP3A4. Additionally, zongertinib may exhibit inductive effects on the three enzymes as well. This trial aims to investigate the in-vivo effect of zongertinib on the activity of CYP3A4, CYP2C8 and CYP2C19 using the recommended in-vivo probes midazolam (for CYP3A4), repaglinide (for CYP2C8) and omeprazole (for CYP2C19).
Trial objective	To assess the effect of multiple oral doses of zongertinib on the pharmacokinetics of midazolam, omeprazole and repaglinide.
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of midazolam, omeprazole and repaglinide Secondary endpoints: AUC_{0-tz} of midazolam, omeprazole and repaglinide
Trial design	Non-randomised, open-label, 2-period, fixed-sequence trial
Number of subjects **total entered** **on each treatment**	 16 16
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Trial product 1 **dose** **mode of admin.**	zongertinib, 60 mg film-coated tablets 1 x 2 tablets (=120 mg zongertinib) qd for 15 days (in period 2 only) Oral with 240 mL of water

Trial product 2	NovoNorm® 0.5 mg Tabletten
dose	1 x 1 tablet (= 0.5 mg repaglinide), 1 single dose in period 1 and 2 single doses in period 2
mode of admin.	Oral with 240 mL of water
Trial product 3	Omeprazol STADA® protect 20 mg magensaftresistente Tabletten
dose	1 x 1 tablet (=20 mg omeprazole), 1 single dose in period 1 and 2 single doses in period 2
mode of admin.	Oral with 240 mL of water
Trial product 4	Midazolam ratiopharm® 2 mg/ml orale Lösung
dose	1 x 0.5 ml (= 1 mg midazolam), 1 single dose in period 1 and 2 single doses in period 2
mode of admin.	Oral with 240 mL of water
Duration of treatment	Treatment Reference 1 (R1): 1 x 1 tablet repaglinide on Day 1 of period 1 Treatment Reference 2 (R2): 1 x 0.5 mL midazolam solution together with 1 x 1 tablet omeprazole on Day 2 of period 1 Treatment Test 1 (T1 – investigation of CYP2C8 inhibition): 1 x 1 tablet repaglinide together with 1 x 2 tablets zongertinib on Day 1 of period 2 Treatment Test 2 (T2 – investigation of CYP3A4 & CYP2C19 inhibition): 1 x 0.5 mL midazolam solution together with 1 x 1 tablet of omeprazole and 1 x 2 tablets zongertinib on Day 2 of period 2 (following predosing with zongertinib on Day 1 of period 2) Treatment Test 3 (T3 – investigation of CYP2C8 induction): 1 x 1 tablet of repaglinide together with 1 x 2 tablets zongertinib on Day 14 of period 2 (following predosing with zongertinib over 13 days) Treatment Test 4 (T4 – investigation of CYP3A4 and CYP2C19 induction): 1 x [redacted] midazolam solution together with 1 x 1 tablet of omeprazole and 1 x 2 tablets zongertinib on Day 15 of period 2 (following predosing with zongertinib over 14 days)

Statistical methods	Relative bioavailability of midazolam, omeprazole and repaglinide will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subject' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART – PERIOD 1 (R1, R2)

Period	Visit	Day	Planned time (relative to the first drug intake [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[11]	PK $_{blood}$ midazolam/omeprazole	PK $_{blood}$ repaglinide	ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -2			Screening (SCR)[1]	A			x	x	
Period 1	2	-1	-12:00	20:00	Admission to trial site[7]	x[5,7]					x[7]
		1	-1:00	07:00	Allocation to subject number[2]			x[2]		x[2]	x[2]
			0:00	08:00	Repaglinide dosing						
			0:15	08:15				x			
			0:30	08:30		x[10]		x			
			0:45	08:45				x			
			1:00	09:00		x[10]		x			
			1:30	09:30		x[10]		x			
			2:00	10:00	240 mL fluid intake + snack[3]			x			x
			2:30	10:30				x			
			3:00	11:00				x			
			4:00	12:00	240 mL fluid intake, lunch[3]			x			x
			6:00	14:00				x			
			8:00	16:00	Snack (voluntary)[3], all subjects together						
			11:00	19:00	Dinner[3], all subjects together						
		2	24:00	08:00	Midazolam & Omeprazole dosing		x[8]	x[8]		x[2]	x[2]
			24:15	08:15			x				
			24:30	08:30			x				
			24:45	08:45			x				
			25:00	09:00			x				
			25:30	09:30			x				
			26:00	10:00	240 mL fluid intake + snack[3]		x				x
			28:00	12:00	240 mL fluid intake, lunch[3]		x				x
			30:00	14:00			x				
			32:00	16:00	Snack (voluntary)[3]		x				
			34:00	18:00			x				
			35:00	19:00	Dinner[3], all subjects together						
			36:00	20:00			x				x
		3	48:00	08:00	Breakfast (voluntary), discharge from trial site						x
			Wash-out of at least 3 days (following last medication)								

FLOW CHART – PERIOD 2 (T1, T2, T3, T4)

Period	Visit	Day	Planned time (relative to the first drug intake [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[11]	PK blood midazolam/omeprazole	PK blood repaglinide	PK blood zongertinib	Liquid biopsy	[redacted]	ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
Period 2	3	-1	-12:00	20:00	Admission to trial site[7]	x[5,7]								x[7]
		1	-01:00	07:00		B[2]		x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
			0:00	08:00	Zongertinib + Repaglinide dosing									
			0:15	08:15				x						
			0:30	08:30		x[10]		x	x					
			0:45	08:45				x						
			1:00	09:00		x[10]		x	x					
			1:30	09:30		x[10]		x	x					
			2:00	10:00	240 mL fluid intake + snack[3]			x	x			x	x	x
			2:30	10:30				x	x					
			3:00	11:00				x	x					
			4:00	12:00	240 mL fluid intake, Lunch[3]			x	x			x	x	x
			6:00	14:00				x	x					
			8:00	16:00	Snack (voluntary)[3]				x					
			10:00	18:00					x					
			11:00	19:00	Dinner[3], all subjects together									
			12:00	20:00					x					x
		2	24:00	08:00	Zongertinib + Midazolam + Omeprazole dosing		x[8]	x[8]	x[8]			x[2]	x[2]	x[2]
			24:15	08:15			x							
			24:30	08:30			x							
			24:45	08:45			x							
			25:00	09:00			x							
			25:30	09:30			x							
			26:00	10:00	240 mL fluid intake + snack[3]		x					x	x	x
			28:00	12:00	240 mL fluid intake, Lunch[3]		x					x	x	x
			30:00	14:00			x							
			32:00	16:00	Snack (voluntary)[3]		x							
			34:00	18:00			x							
			35:00	19:00	Dinner[3], all subjects together									
			36:00	20:00			x							x
		3	48:00	08:00	Zongertinib dosing[12], followed by discharge from trial site		x[12]		x[12]				x[2]	x[2]
		4	72:00	08:00	Zongertinib dosing[9]	B[8]								x[2]
		5	96:00	08:00	Zongertinib dosing[9]				x[8]		x[2]	x[2]		x[2]
		6	120:00	08:00	Zongertinib dosing[9]									x[2]
		7	144:00	08:00	Zongertinib dosing[9]	B[8]			x[8]					x[2]
		8	168:00	08:00	Zongertinib dosing[9]									x[2]
		9	192:00	08:00	Zongertinib dosing[9]				x[8]					x[2]
		10	216:00	08:00	Zongertinib dosing[9]	B[8]			x[8]		x[2]	x[2]		x[2]
		11	240:00	08:00	Zongertinib dosing[9]				x[8]					x[2]
		12	264:00	08:00	Zongertinib dosing[9]									x[2]
		13	288:00	08:00	Zongertinib dosing[9]	B[8]			x[8]					x[2]
			300:00	20:00	Admission to trial site[7]	x[5,7]								x[7]

Period	Visit	Day	Planned time (relative to the first drug intake [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[11]	PK blood midazolam/omeprazole	PK blood repaglinide	PK blood zongertinib	Liquid biopsy	[redacted]	ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
		14	312:00	08:00	Zongertinib + Repaglinide dosing			x[8]	x[8]			x[2]	x[2]	x[2]
			312:15	08:15				x						
			312:30	08:30		x[10]		x	x					
			312:45	08:45				x						
			313:00	09:00		x[10]		x	x					
			313:30	09:30		x[10]		x	x					
			314:00	10:00	240 mL fluid intake + snack[3]			x	x			x	x	x
			314:30	10:30				x	x					
			315:00	11:00				x	x					
			316:00	12:00	240 mL fluid intake, Lunch[3]			x	x			x	x	x
			318:00	14:00				x	x					
			320:00	16:00	Snack (voluntary)[3]				x					
			322:00	18:00					x					
			323:00	19:00	Dinner[3], all subjects together									
			324:00	20:00					x					x
		15	336:00	08:00	Zongertinib + Midazolam + Omeprazole dosing	B[2]	x[8]	x[8]	x[8]	x[2]	x[2]	x[2]	x[2]	x[2]
			336:15	08:15			x							
			336:30	08:30			x							
			336:45	08:45			x							
			337:00	09:00			x							
			337:30	09:30			x							
			338:00	10:00	240 mL fluid intake + snack[3]		x					x	x	x
			340:00	12:00	240 mL fluid intake, Lunch[3]		x					x	x	x
			342:00	14:00			x							
			344:00	16:00	Snack (voluntary)[3]		x							
			346:00	18:00			x							
			347:00	19:00	Dinner[3], all subjects together									
			348:00	20:00			x							x
		16	360:00	08:00	Breakfast (voluntary), discharge from trial site									x
FU	4	29 - 50			End of study (EoS) Examination[4]	C						x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
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, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. The time is an approximate. The procedure is to be completed not later than 10 hours prior to drug administration.
8. To be performed within 15 min prior to drug dosing

9. Subjects are required to be fasted for at least 10 hours prior and 1 hour post planned ambulatory drug administration. In addition, the tolerance time for ambulatory dosing in period 2 from Day 4 to Day 13 in Period 2 is ± 2 hours.
10. Bedside glucose test only
11. Letters A, B and C describe different sets of safety laboratory examinations. For details see Section 5.2.3
12. PK samples to be taken on time and zongertinib to be given within 15 minutes afterwards

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
AMP	Auxiliary Medicinal Product
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
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)

EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FAS	Full Analysis Set
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
HPC	Human Pharmacology Centre
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	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
$MRT_{,po}$	Mean residence time of the analyte in the body after oral administration
$MRT_{,po,ss}$	Mean residence time of the analyte at steady state in the body after oral administration
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
PTF	Peak-trough fluctuation
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics

SOP	Standard operating procedure
ss	(at) steady state
T	Test product or treatment
$t_{1/2}$	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	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

This trial investigates the in-vivo effect of zongertinib on the activity of CYP3A4, CYP2C8 and CYP2C19 using the recommended in-vivo probes midazolam (for CYP3A4), repaglinide (for CYP2C8) and omeprazole (for CYP2C19).

1.1 MEDICAL BACKGROUND

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

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

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

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

toxicity. Therefore there is a clear unmet medical need for new treatment options for NSCLC patients with HER2 insertion mutations.

1.2 DRUG PROFILE

For a more detailed description of the zongertinib profile, please refer to the current version of the Investigator's Brochure (IB) [c32836122] and for midazolam, repaglinide and omeprazole to the respective SmPCs [R20-1699 + R24-2815 + R24-0703]

1.2.1 Zongertinib

1.2.1.1 Mode of action

Zongertinib is an EGFR wild type sparing, selective HER2 inhibitor with potent inhibitory activity on all major HER2 mutations including the HER2 YVMA insertion allele. It is intended to treat patients with advanced solid tumors with HER2 aberrations.

1.2.1.2 Data from non-clinical studies

[redacted]

[redacted]

1.2.1.3 Data from studies in humans

Prior to the current trial, zongertinib was administered in the ongoing first-in-man trial in patients with cancer 1479-0001 and in five PK studies in healthy volunteers (trial 1479-0003, 1479-0004, 1479-0006, 1479-0010, 1479-0011). A short summary of the trials and drug-related adverse events in these trials is provided here. For details on PK, safety, and efficacy refer to the current version of the IB [c32836122].

1.2.1.4 Data from studies in patients

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

1479-0001 is an open-label, Phase I dose escalation trial, with dose confirmation and expansion, of zongertinib as monotherapy in patients with advanced or metastatic solid tumors with HER2 aberrations. Patients are continuously treated in different dose groups with [redacted] PK, safety, and efficacy data are collected. Patients were treated in the dose escalation phase with escalating doses of zongertinib [redacted] administered using either [redacted] as well as in the dose expansion phase with [redacted] Overall, the median treatment duration was 147 days and the exposure ranged from 1 to 568 days during the dose escalation at data cut-off; during the dose expansion, the median treatment duration was [redacted] and the exposure [redacted]. Data cut time point for the data described [redacted]. For further information also refer to the current version of the IB [c32836122].

Preliminary safety and tolerability data of patient first-in-man trial 1479-0001

Overall, zongertinib was well tolerated in patients in trial 1479-0001 and the majority of drug-related AEs was manageable. The MTD has not been reached in both treatment schedules. AEs leading to dose reductions, treatment interruptions, and treatment discontinuations were infrequent. During dose escalation, the most frequent AEs were diarrhoea (24 patients, 39.3%), followed by anaemia (13 patients, 21.3%), ALT increased (11 patients, 18.0%), AST increased (11 patients, 18.0%), blood alkaline phosphatase increased (10 patients, 16.4%), blood creatinine increased (10 patients, 16.4%) and COVID-19 (7 patients, 11.5%). Dose limiting toxicities during the MTD evaluation period were diarrhoea Grade 3 (and platelet count decreased Grade 3). In total, 25 (41%) patients had an SAE, with 1 patient (1.6%) having SAEs that were considered drug-related by the investigator (Grade 3 ALT increased and Grade 3 AST increased). Reported fatal AEs were not drug-related.

During dose expansion, most frequent AEs were diarrhoea (28 patients, 35.4%), anaemia (15 patients, 19%), ALT increased (10 patients, 12.7%), AST increased (10 patients, 12.7%), decreased appetite (9 patients, 11.4%), lymphocyte count decreased (9 patients, 11.4%) and dysgeusia (8 patients, 10, 1%). Dose limiting toxicities during the MTD evaluation period were diarrhoea Grade 3, febrile neutropenia Grade 3 and immune thrombocytopenia Grade 4 (SAEs were reported in 9 (11.4%) of patients. SAEs assessed as drug-related by the investigator occurred in 5 patients (6.3%). These were ALT increased and AST increased (in 2 patients each, 2.5%), as well as hepatic failure, immune thrombocytopenia, intestinal obstruction and neutrophil count decreased (in 1patient each, 1.3%). Reported fatal AEs were not drug-related. For further information also refer to the current version of the IB [c32836122].

Hepatotoxicity

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

A patient had occasional right hypochondrium pain, choluria, progressive jaundice, and diarrhoea starting on Day 36 of treatment with 240 mg zongertinib QD. One week later the patient was admitted to the hospital with hepatic failure and prolonged prothrombin time. During hospitalisation, study medication was interrupted, and the patient was treated with N-acetylcysteine and methylprednisolone over 7 days. After discharge from the hospital treatment continued with 50 mg prednisolone. The patient was recovering and restarted study drug on Day 63 at reduced dose of 180 mg QD. Liver enzymes and bilirubin were further normalising. The patient had COVID-19 infection and was treated with Remdisivir starting on Day 25 of study treatment as possible confounding factors.

A second patient who was treated with 240 mg zongertinib QD over 42 days developed, despite interruption of study drug due to ALT, AST Grade 2 and total bilirubin Grade 1, further increases of ALT and AST up to Grade 4 (>20.0x ULN), increased total bilirubin up to Grade 3 (>3x ULN), and coagulopathy Grade 3 on Day 55. On Day 57, the patient had developed subacute hepatic failure Grade 4, cholestasis Grade 4 and hypoalbuminaemia Grade 2. Treatment of the AEs included hepatoprotective and anticholestatic agents as well as dexamethasone. Liver enzymes and total bilirubin were improving between Days 66 and 76. During the further course the patient developed infection (on Day 81) and subsequent sepsis (on Day 86) with fatal outcome 7 days later. Further evaluations are ongoing. For further information also refer to the current version of the IB [c32836122].

Diarrhoea

Diarrhoea was reported during treatment with zongertinib and was of mainly of Grade 1 and 2. Diarrhoea occurred in 24 patients (39.3%) during dose escalation and in 28 patients (35.4%) during dose expansion. Diarrhoea was Grade 3, in 3 patients (4.9%) during dose escalation, and in 2 patients (2.5%) during dose expansion. Due to observed long-lasting periods in some patients, a proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal agents should start at first signs of diarrhoea. For further information also refer to the current version of the IB [c32836122].

1.2.1.5 Data from studies in healthy volunteers

Safety and tolerability data of healthy volunteer trial 1479-0003

Trial 1479-0003 was an open-label, randomized, 4-way crossover Phase I trial. The trial investigated relative bioavailability of zongertinib after administration as two different formulations (trial formulation 1 [TF1] and new formulation [NF]). Additionally, the trial investigated the food effect on the pharmacokinetics of a single dose of zongertinib in plasma and investigated the effect of multiple-dose treatment with rabeprazole on the pharmacokinetics of a single dose of zongertinib. Thirteen healthy male volunteers were dosed with single doses of 30 mg zongertinib in 4 treatment periods in randomized order.

In trial 1479-0003 there were no SAEs, no adverse events of special interest (AESI), and no other significant AEs. All AEs were of CTCAE Grade 1 or 2 severity, and none of the AEs were assessed as drug-related. Available safety data including AEs, Electrocardiogram (ECGs), VS, and safety laboratory indicate that single doses of 30 mg zongertinib were safe and well tolerated in trial 1479-0003. For more details refer to the current version of the IB [c32836122].

Safety and tolerability data of healthy volunteer trial 1479-0004

In trial 1479-0004, the effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of zongertinib in 16 healthy male subjects (an open-label, two-period, fixed-sequence trial) was tested.

There were no deaths, no serious AEs, no CTCAE grade 3, 4, or 5 AEs, and no protocol-specified AEs of special interest reported. A grade 1 AE of diplopia led to the premature discontinuation 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. Overall, 7 out of 16 subjects (43.8%) while on treatment with zongertinib (with and without itraconazole) had drug-related AEs, the most frequent events being diarrhoea (5 subjects, 31.3%) and headache (2 subjects, 12.5%). All AEs were reported as resolved by the end of the trial, except an AE of hand fracture which was not considered related to trial drug. No relevant changes in laboratory values, vital signs, or ECGs were reported as AEs. For further information also refer to the current version of the IB [c32836122].

Preliminary Safety and tolerability data of healthy volunteer trial 1479-0006
In trial 1479-0006, a phase I, open-label trial in two parallel parts investigated mass balance, metabolism, and basic pharmacokinetics of zongertinib (C-14) administered as oral solution (part A) and investigated absolute bioavailability of zongertinib administered as film-coated tablet together with an intravenous microtracer dose of zongertinib (C-14) (part B) in 15 healthy male volunteers.
There were no SAEs, no AESIs, and no other significant AEs. All AEs were of CTCAE Grade 1 severity. In part A and B, only diarrhoea (in 2 HVs) and abdominal pain (all Grade 1) were assessed as drug-related. Available safety data including AEs, ECGs, VS, and safety laboratory indicate that single doses of 60 mg zongertinib were safe and well tolerated in trial 1479-0006. For further information also refer to the current version of the IB [c32836122].

Preliminary Safety and tolerability data of healthy volunteer trial 1479-0010
In trial 1479-0010, the relative bioavailability of 240 mg zongertinib following oral administration under fed and fasted conditions in 16 healthy male subjects (an open-label, randomised, single-dose, two-way crossover trial) was investigated.
There were no SAEs, no AESIs, and no CTCAE grade 3, 4 and 5 AEs. Based on the preliminary safety data, 7 drug-related adverse events were reported in this trial (4x headache, 1x nausea, 1x cough, 1x tiredness). Thus, available safety data including AEs, ECGs, VS, and safety laboratory indicate that single doses of 240 mg zongertinib were safe and well tolerated in trial 1479-0010. For further information also refer to the current version of the IB [c32836122].

Preliminary Safety and tolerability data of healthy volunteer trial 1479-0011
In trial 1479-0011, the effect of multiple doses of carbamazepine on the pharmacokinetics of a single oral dose of 60 mg zongertinib was tested in 16 healthy male subjects (an open-label, two-period, fixed-sequence trial).
There were no SAEs, no AESIs, and no other significant AEs. All AEs were of CTCAE Grade 1 severity. During the treatment period with zongertinib alone a case of grade I fatigue was reported as the sole drug-related AE (as assessed by the investigator). Available safety data including AEs, ECGs, VS, and safety laboratory indicate that single doses of 60 mg zongertinib were safe and well tolerated in trial 1479-0011. For further information also refer to the current version of the IB [c32836122].

1.2.1.6 Clinical Pharmacology

Preliminary, exploratory PK analysis in trial 1479-0001 indicated [redacted] (see Table 1.2.1.6: 1). PK analysis of the Phase Ib extension by and large confirmed the data obtained in the previous analysis [redacted] (see Table 1.2.1.6.: 2). The observed PK profile of zongertinib appears to [redacted] to achieve efficacious plasma exposure, which is also suggested by the [redacted]

Table 1.2.1.6: 1 gMean (gCV%) PK parameters of zongertinib after [redacted] in trial 1479-0001 Phase 1a

Treatment (N)	$t_{max,ss}$ [1] (h)	$C_{max,ss}$ (nM)	$AUC_{\tau,ss}$ (nM*h)
[redacted]			

[1] Median (min -max)

Table 1.2.1.6: 2 gMean (gCV%) PK parameters of [redacted] zongertinib dose cohorts after [redacted] in trial 1479-0001 Phase Ib

Treatment (N)	$t_{max,ss}$[1] (h)	$C_{max,ss}$ (nM)	$AUC_{0-6,ss}$ (nM*h)
[redacted]			

[1] Median (min -max)

1.2.2 Repaglinide

Potential inducing and inhibitory effects of zongertinib on CYP2C8 will be investigated using the probe substrate repaglinide.
Repaglinide is indicated for therapy of type-2 diabetes mellitus alone or in combination with metformin. It is a short-acting stimulator of pancreatic insulin secretion. It causes depolarisation of pancreatic beta-cells which, in turn, enhances calcium influx, followed by insulin release.
After oral administration, repaglinide is rapidly absorbed with plasma t_{max} values within one hour and an absolute bioavailability of 63%. Volume of distribution is low (30 L), and plasma protein binding is high (>98%). Repaglinide is eliminated within 4-6 hours; plasma $t_{1/2}$ is around one hour. Elimination is principally via metabolism, mainly by CYP2C8 and to a lesser extent by CYP3A4 [R20-1699]. The drug transporter OATP1B1 has been shown to contribute to hepatocellular uptake of repaglinide [P13-07476]. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend the use of repaglinide as in vivo probe drug for CYP2C8 in DDI trials (FDA guidance [R20-2271] and EMA guideline [P12-10638]).
Repaglinide should be taken within 30 min before a meal. The recommended initial dose of repaglinide is 0.5 mg, the recommended maximal single dose is 4 mg, and the recommended maximal daily dose is 16 mg [R20-1699].
The most frequent side effect of repaglinide is hypoglycaemia. Niemi et al. reported a clinical trial in 12 healthy volunteers that were dosed with repaglinide (0.25 mg single dose followed by breakfast, snacks and a meal within 3 h after repaglinide dosing) with or without concomitant treatment with gemfibrozil, itraconazole, or both. Concomitant treatment with both gemfibrozil and itraconazole increased repaglinide AUC and C_{max} by 19.4- and 2.8-fold and prolonged repaglinide $t_{1/2}$ from 1.3 to 6.1 h [R14-3624]. In this trial, gemfibrozil and itraconazole enhanced and prolonged the effects of repaglinide on blood glucose concentrations, and two subjects required carbohydrate supplementation because of symptomatic hypoglycemia. In another trial in 24 healthy volunteers, 4 mg repaglinide was given with or without concomitant administration of flucloxacillin in the morning as oral single dose in fasted state followed by fasting for another 3 h [R14-3583]. Administration of repaglinide was followed by a decrease in plasma glucose concentrations (with plasma glucose concentrations in the range of 3.26-5.61 mM), but no symptoms of hypoglycemia were reported. In another trial in 29 healthy volunteers, oral single doses of 2 mg repaglinide were

administered after a 9 h fasting period and followed by a 6 h fasting period after repaglinide dosing [R14-3626]. In this trial, transient symptoms of hypoglycaemia such as dizziness, sweating, and tremor were observed but quickly disappeared after administration of apple juice. Otherwise repaglinide was well tolerated.

Repaglinide may be given to healthy subjects at fasted state, before a breakfast, or with sugar-containing drinks (e.g., apple juice or glucose-water solution). However, intake of carbohydrate-containing solution may relevantly slow gastric emptying and could therefore affect repaglinide oral absorption. Therefore repaglinide will be administered at fasted state in this trial. In order to prevent hypoglycemic episodes, carbohydrate-containing snacks will be handed out two hours after repaglinide intake. Moreover, to allow for timely detection of hypoglycaemic episodes and in order to ensure subject safety, blood glucose will be determined in 30 minute intervals until the subjects receive a carbohydrate-containing snack 2 hours after dosing (see Flow Chart). Additionally, subjects are hospitalized at the trial site and are under close medical surveillance for at least 12 hours after dosing with repaglinide. In addition, subjects are frequently asked for AEs after repaglinide. In case of clinical signs of hypoglycemia or blood glucose concentrations below 45 mg/dL (<2.5 mmol/L), oral glucose will be administered (see Section 4.2.1).

For further details see the current version of SmPC for repaglinide (R20-1699).

1.2.3 Midazolam

Potential inducing and inhibitory effects of zongertinib on CYP3A4 will be investigated using the probe substrate midazolam.
Midazolam is a short acting benzodiazepine which is used for the treatment of insomnia and as sedative premedication before surgical or diagnostic procedures. It has a volume of distribution of 0.7 to 1.2 L/kg at steady state. Its elimination half-life in young healthy volunteers ranges from 1.5 to 2.5 hours. The plasma clearance was determined to be 300 to 500 mL/min. Midazolam is almost completely eliminated by biotransformation to 1-hydroxymidazolam, and this process is mediated by CYP3A enzymes [R19-1961, R06-0294]. In contrast to testosterone or erythromycin, which have also been proposed as probes to monitor CYP3A activity, midazolam is metabolised specifically by CYP3A, and does not serve as a substrate for other CYP450 isoenzymes or the drug transporter P-glycoprotein (P-gp). Intravenous midazolam is a sensitive *in vivo* probe of hepatic CYP3A activity, whereas orally-administered midazolam is metabolised by both intestinal and hepatic CYP3A.
The administration of an oral dose of 1 mg midazolam is without a major sedative effect [P10-00100]. The therapeutic dose of midazolam is 7.5 mg to 15 mg. Thus, the chosen dose of 1 mg provides a sufficient safety margin. The subjects will be kept in-house at the trial site for 24 hours after dosing, covering the t_{max} and more than 5 half-lives of midazolam.

For further details see the current version of SmPC for midazolam (R24-0703).

1.2.4 Omeprazole

Potential inducing and inhibitory effects of zongertinib on CYP2C19 activity will be investigated using the probe substrate omeprazole.
Omeprazole is a proton pump inhibitor applied to treat ulcers, heartburn, gastroesophageal reflux, and Zollinger-Ellison syndrome [R24-0704, R24-2815]. The formation of 5-hydroxyomeprazole, the major primary metabolite of omeprazole, is dependent on CYP2C19 activity. In addition, omeprazole is metabolised by CYP3A to omeprazole sulphone. Since the affinity of omeprazole to CYP2C19 is 10 times higher than to CYP3A, omeprazole interferes with the metabolism of substrates for CYP2C19 but not of substrates for CYP3A [P96-3991]. Omeprazole has a small volume of distribution (0.3 L/kg). The plasma half-life is approximately 40 min. Plasma clearance was determined to be 0.3 to 0.6 L/min.
The therapeutic standard dose of omeprazole is 20 mg to 40 mg daily. In the treatment of Zollinger-Ellison syndrome, daily doses of up to 80 mg may be required. Omeprazole has a large therapeutic window. Fluvoxamin, a potent inhibitor of CYP2C19, caused a 4.5 fold increase of omeprazole exposure in healthy subjects (P14-11944). No side effects attributed to the intake of omeprazole have been reported by the authors. Similar to the trial described herein, a dose of 20 mg omeprazole was utilized.

For further details see the current version of SmPC for omeprazole (R24-2815).

1.2.5 Residual Effect Period

The Residual Effect Period (REP) 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.

The REP for omeprazole is 48 hours, the REP for repaglinide is 12 hours, the REP for midazolam is 24 hours.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Drug-drug interactions (DDI) are complex and have proven to be a major challenge for health care providers. One of the questions that must be addressed before new drugs can be safely administered is whether there is a drug interaction with other medications taken by the patient for the treatment of co-morbidities. Therefore, the interaction potential of a new compound is regularly evaluated during clinical drug development. [redacted]

Therefore, this trial is aimed to investigate the in-vivo effect of zongertinib on the activity of CYP3A4, CYP2C8 and CYP2C19 using the in-vivo probe drugs midazolam (for CYP3A4), repaglinide (for CYP2C8) and omeprazole (for CYP2C19) recommended by both the FDA and EMA as sensitive substrates for the respective CYP enzymes.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

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

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medications. An overview of trial-related risks is given in Table 1.4.2: 1.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: zongertinib (BI 1810631)		
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 in trial 1479-0001. AEs in the SMQ liver related investigations, signs and symptoms occurred in 20 patients (32.8%) during dose escalation and in 19 patients (24.1%) during dose expansion. This included AEs ≥ Grade 3, treatment interruptions, dose reductions and permanent discontinuations of trial medication. First onset of the liver related investigations was within 30 days in around 20% of patients. For further details see Section 1.2.	Short treatment duration (15 days) 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.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Intestinal toxicity	Reversible intestinal effects in dogs after multiple dosing (fecal alterations, Goblet cell hyperplasia) [c32836122]. Reported diarrhoea during treatment with zongertinib in trial 1479-0001, was mainly of Grade 1 and 2. Grade 3 diarrhoea occurred in few patients (see Section 1.2).	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Discontinuation of subject if diarrhoea CTCAE Grade 3 or higher. • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.
QT prolongation	Preclinical data indicate a low proarrhythmic potential of zongertinib. In trial 1479.0001, ECG QT prolongation was reported as AE in 3 patients (4.9%) during dose escalation and in no patient during dose expansion. 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.
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
Dysgeusia	Reported dysgeusia during treatment with zongertinib in trial 1479-0001, was mainly of Grade 1 and 2. Dysgeusia was reported as AE in 11 patients (7.9%) during dose escalation and dose expansion (c42938800).	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Reproductive and developmental toxicity	Embryo-fetal toxicity was observed in dose-range finding study in rats [c32836122]. Through the ejaculate, zongertinib 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 zongertinib until 30 days after the last dosing with zongertinib (see also exclusion criteria in Section 3.3.3)
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 • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.
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 • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
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 one patient each during dose escalation (1.6%) and dose expansion (1.3%). The AEs were Grade 2 and occurred at dose levels 240 mg qd and 300 mg qd) [c40238724].	• Only healthy volunteers will be included in the trial. • ECGs will be performed as defined in the Flow Chart • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.
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 • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.
Uncertainties due to the early stage of development	Comparatively very high plasma exposures were explored in humans (see current version of the IB [c32836122]) and showed a well tolerable and manageable safety profile so far (see Section 1.2.2 and current versoion of the IB [c32836122]). However, zongertinib is currently in early development and there may be unknown risks of treatment with zongertinib.	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Monitoring of safety laboratories, vital signs and ECGs during dosing (see Flow Chart) • Implementation of a sentinel cohort of max. 4 subjects to undergo treatment with zongertinib prior to main cohort.

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: repaglinide		
Hypoglycemia	Increased insulin release from pancreatic β-cells and subsequent decrease in blood glucose concentrations (pharmacodynamic effect).	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Glucose testing 30, 60 and 90 minutes post repaglinide dosing • Mandatory snack 120 minutes post repaglinide dosing
Investigational Medicinal Product: midazolam		
Sedation	Enhanced effect of the neurotransmitter GABA on $GABA_A$ receptors resulting in neural inhibition and subsequent sedation (pharmacodynamic effect)	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Subjects are confined to in-house stay at trial site and remain under close observation for at least 24 hours following midazolam administration. • Low dose of midazolam of 1mg (recommended dose for clinical use: 7.5 – 15mg)
Investigational Medicinal Product: omeprazole		
None		
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site

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

1.4.3 Discussion

There is significant unmet medical need in cancer patients harbouring HER2 mutations for effective, safe and well-tolerated therapies. zongertinib is an EGFR wild-type sparing selective HER2 inhibitor with potent inhibitory activity on all major HER2 mutations. It provides a unique opportunity for the treatment of NSCLC patients harbouring HER2 mutations, and data further suggest that zongertinib could be efficacious in all HER2-dependent cancers.

Zongertinib has been adequately characterized in preclinical studies and identified toxicities are addressed by appropriate mitigation (see section 1.4.2.). Moreover, data from 6 clinical trials are available (see section 1.2.1) that support multiple dosing of zongertinib as planned for the current trial. In particular, zongertinib has been administered at multiple doses of up to 360 mg q.d. and of up to 150 mg b.i.d. to patients in first-in-man trial 1479-0001. Furthermore, zongertinib has been administered to 66 healthy volunteers thus far with an acceptable safety profile. Specifically, 16 healthy volunteers received a single dose of 240 mg as part of the food-effect trial 1479-0010 (see section 1.2.1). Based on the preliminary safety data, 7 drug-related adverse events were reported in this trial (4x headache, 1x nausea, 1x cough, 1x tiredness) and all reported adverse events were of CTCAE grade 1 and 2.
Overall, in both patients and healthy volunteers, zongertinib showed acceptable safety and tolerability and reported AEs were manageable in the context of the respective trial.

The current study is necessary to support the development of zongertinib: The trial investigates the effect of zongertinib on the activity of CYP3A4, CYP2C8 and CYP2C19 in vivo. The data of this trial are required for an in-depth understanding of the pharmacokinetics of zongertinib. Considering the unmet medical need for an effective and safe treatment of solid tumours with HER2 mutations, the benefit of this trial is assessed to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to assess the influence of multiple doses of zongertinib on single dose kinetics of cytochrome P450 (CYP) probe substrates, as a means of predicting drug-drug interactions. These probe drug substrates are midazolam (for CYP3A4), repaglinide (for CYP2C8) and omeprazole (for CYP2C19).

2.1.2 Primary endpoint(s)

The following pharmacokinetic parameters will be determined for the probe drugs midazolam, repaglinide and omeprazole:

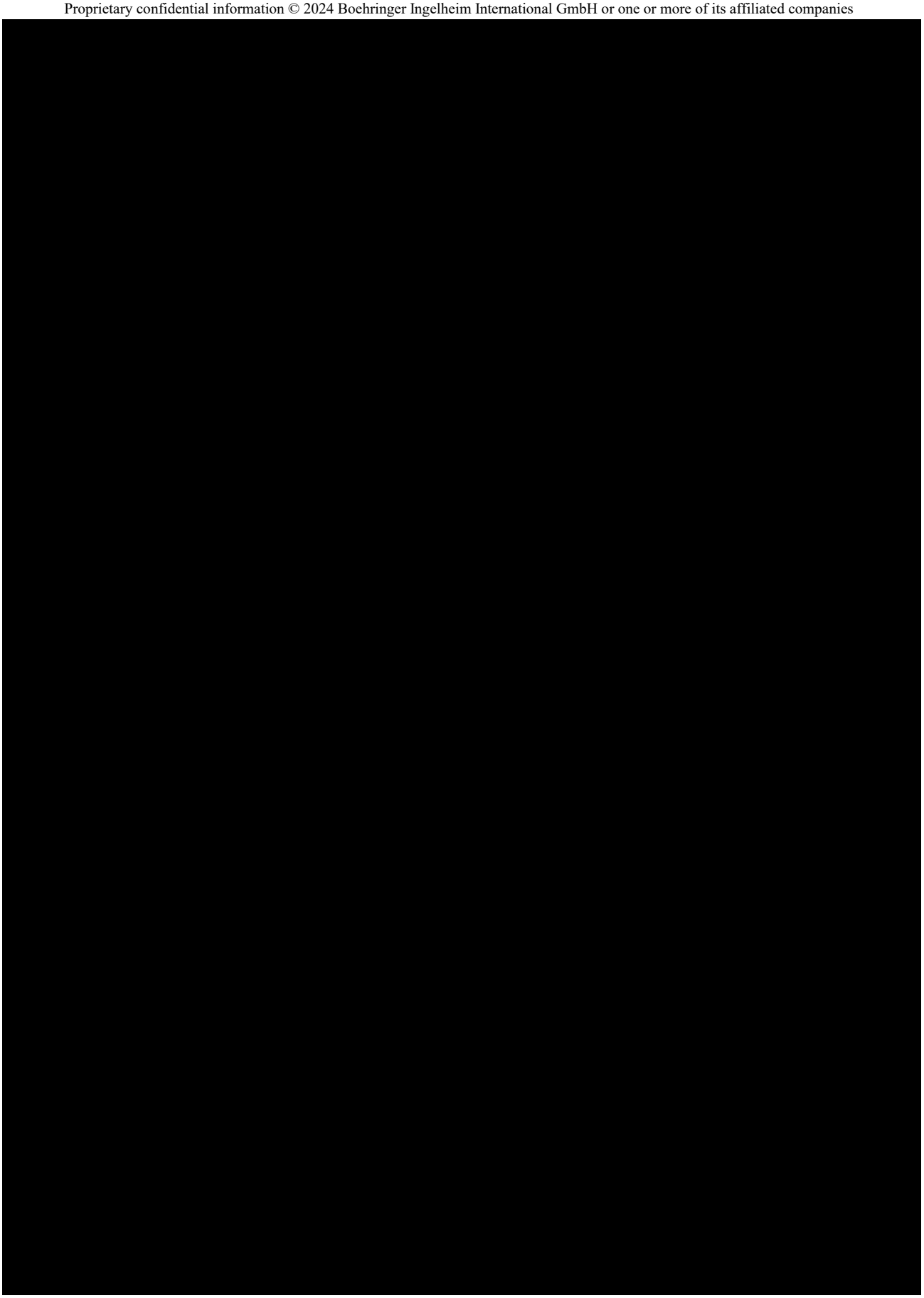
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

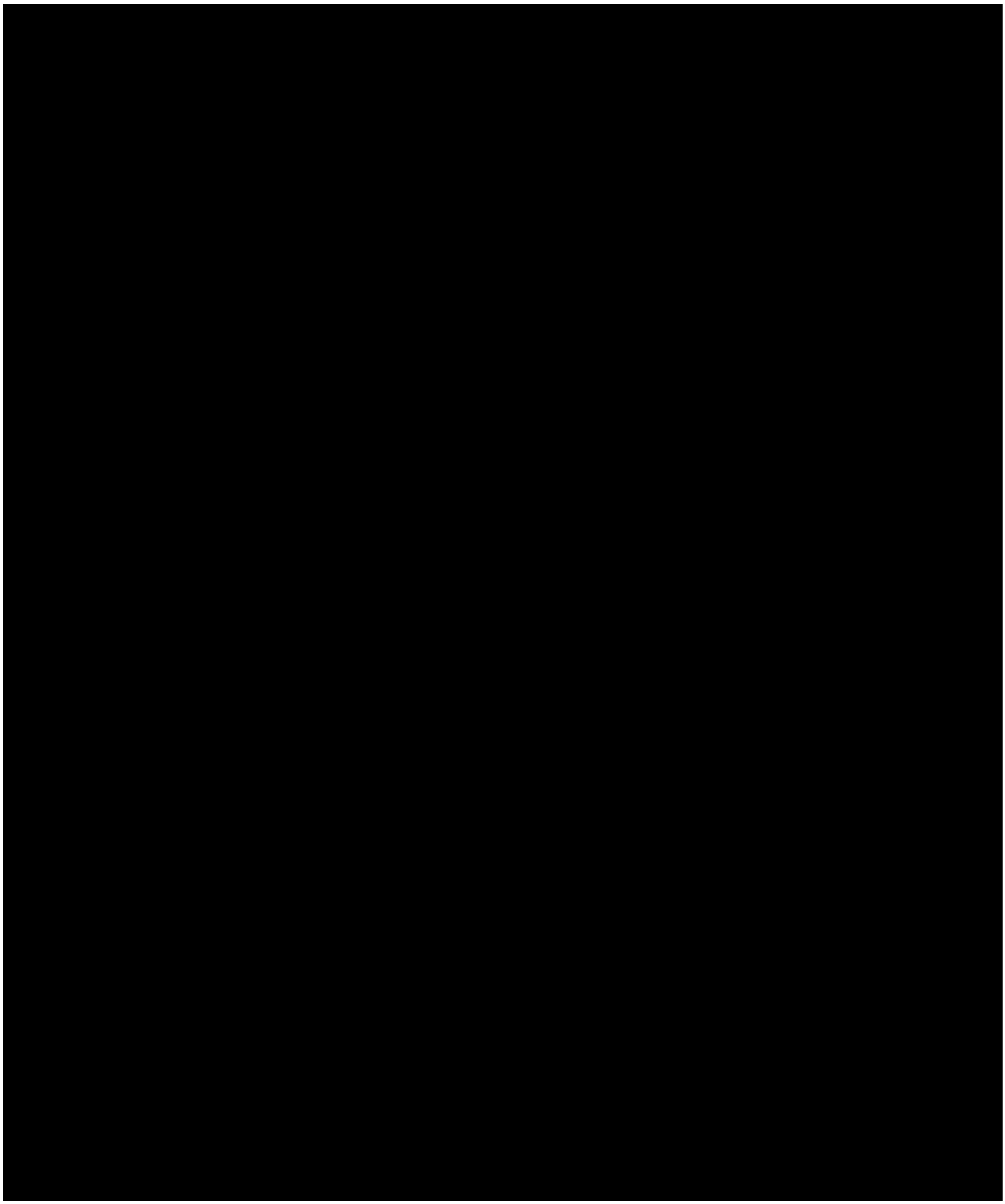
2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for the probe drugs midazolam, repaglinide and omeprazole:

- 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)

[redacted]





2.2.2.3 Safety and tolerability

Safety and tolerability of zongertinib and probe drugs will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial is designed to assess the effects of zongertinib on the activity of CYP3A4, CYP2C8 and CYP2C19 by utilizing specific probe drugs for the three CYP enzymes. The trial will assess the immediate inhibitory effects of zongertinib on CYP3A4 (probe drug: midazolam), CYP2C8 (probe drug: repaglinide) and CYP2C19 (probe drug: omeprazole) as well as the long-term inducing effects of zongertinib on the three CYP enzymes after achievement of steady-state levels of zongertinib and adaptation of CYP enzyme levels. Of note, the effects of zongertinib on CYP3A4 and CYP2C19 will be examined in a cocktail approach, i.e. midazolam (as a probe substrate for CYP3A4) and omeprazole (as a probe substrate for CYP2C19) will be administered simultaneously. Both drugs are part of the well-established [redacted] probe cocktail (P10-00100). The cocktail approach is especially valuable for drugs that may affect more than one metabolic pathway as it reduces the number of subjects required to attain valuable information on drug-drug-interactions [P04-02212]. In these cases the performance of cocktail studies is accepted by regulatory authorities (R20-2271 ; P12-10638).

Since the interaction potential of the components of the CYP cocktail and repaglinide has not yet been established, the administration of repaglinide is scheduled 24 hours prior to dosing of the two cocktail drugs (midazolam and omeprazole). Due to the short half-life of repaglinide ($t_{1/2}$ = approx. 1 hour), no specific wash-out period above and beyond 24 hours is required.

The trial will be performed as an open-label, two-period fixed sequence design trial in healthy male subjects enrolled at a single site. Sixteen subjects will receive the following oral treatments (for details, refer to Section 4.1.).

Reference Treatments

- R1: 0.5 mg of repaglinide in the morning of Day 1 of Visit 2
- R2: 1 mg of midazolam and 20 mg of omeprazole in the morning of Day 2 of Visit 2

Test Treatments

- T1 120 mg of zongertinib, 0.5 mg of repaglinide in the morning of Day 1 of Visit 3
- T2: 120 mg of zongertinib, 1 mg of midazolam and 20 mg of omeprazole in the morning of Day 2 of Visit 3 (following predosing with zongertinib on Day 1 of period 2)
- T3: 120 mg of zongertinib, 0.5 mg of repaglinide in the morning of Day 14 of Visit 3 (following predosing with zongertinib over 13 days)
- T4: 120 mg of zongertinib, 1 mg of midazolam and 20 mg of omeprazole in the morning of Day 15 of Visit 3 (following predosing of zongertinib over 14 days)

A schematic diagram of the trial design is displayed in Figure 3.1: 1 below.

Figure 3.1: 1 Trial design

Considering the flexible time frame for screening and follow-up examination the expected total trial duration for a single subject is about 10 weeks. The trial population will be divided into at least 2 cohorts. The first cohort should not contain more than 4 subjects. The dosing of the 2nd cohort with zongertinib will start at the earliest when the 1st cohort has completed Visit 3 (i.e. Period 2). Of note, in Visit 2 (Period 1), all cohorts may be treated together.

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

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

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

Because of the long half-life of zongertinib, a fixed-sequence design was selected, in which zongertinib is administered in the second trial period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since non-specific time-effects are unlikely due to the short trial duration.

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analytes (PK endpoints).

The dosing duration for zongertinib is [redacted] Due to the short half-lives of the three probe drugs ($t_{1/2}$ repaglinide: approx. 1 hour;

$t_{1/2}$ midazolam: 1.5 – 2.5 hours; $t_{1/2}$ omeprazole: < 1 hour) dosing of zongertinib past Day 15 of Period 2 is not considered necessary.

All three probe drugs used in this trial are listed as sensitive in vivo probes for drug-drug interaction trials by both the FDA [R20-2271] and EMA [P12-10638].

3.3 SELECTION OF TRIAL POPULATION

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

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

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

3.3.3 Exclusion criteria

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

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

5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs (including vaccinations) within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Use of nelfinavir, gemfibrozil, amprenavir, indinavir, ritonavir, itraconazole or ketoconazole within 30 days of planned administration of trial medication.
15. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
16. Inability to refrain from smoking on specified trial days
17. Alcohol abuse (consumption of more 24 g per day)
18. Drug abuse or positive drug screening
19. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
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 marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
23. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
24. 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

25. Subjects with WOCBP partner who are unwilling to use highly effective contraception from time point of first administration of zongertinib until 30 days after the last administration of zongertinib. Highly effective methods of contraception are:

    - Subject is sexually abstinent

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

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

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

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

    - Bilateral tubal occlusion in the female partner plus use of condom

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

26. ALT (alanine transaminase), AST (aspartate transaminase), or serum creatinine above upper limit of normal range at screening examination, confirmed by a repeat test; [redacted] confirmed by a repeat test

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.4) the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer.
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases)
5. The subject exhibits an AE of CTCAE grade 3 or a serious AE (SAE)
6. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF.

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Trial product 1

Substance:	zongertinib
Pharmaceutical formulation:	Film-coated tablet (SDD-iCF)
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	60 mg
Posology:	2-0-0
Mode of administration:	Oral
Duration of use:	q.d. for 15 consecutive days in Period 2

Trial product 2

Name:	NovoNorm® 0.5 mg Tabletten
Substance:	Repaglinide
Pharmaceutical formulation:	Tablet
Source:	Public pharmacy
Unit strength:	0.5 mg
Posology:	1 – 0 – 0
Mode of administration:	Oral
Duration of use:	1 single dose treatment in period 1 & 2 single dose treatments in period 2

Trial product 3

Name:	Omeprazol STADA® protect 20 mg magensaftresistente Tabletten
Substance:	Omeprazole
Pharmaceutical formulation:	Tablet
Source:	Public pharmacy
Unit strength:	20 mg
Posology:	1 – 0 – 0
Mode of administration:	Oral
Duration of use:	1 single dose treatment in period 1 & 2 single dose treatments in period 2

Trial product 4

Name:	Midazolam ratiopharm® 2 mg/ml orale Lösung
Substance:	Midazolam
Pharmaceutical formulation:	Oral solution
Source:	Public pharmacy
Unit strength:	2 mg/ml
Posology:	0.5 mL – 0 – 0
Mode of administration:	Oral
Duration of use:	1 single dose treatment in period 1 & 2 single dose treatments in period 2

Commercially available drug products (i.e. trial products 2, 3 and 4) may be substituted for commercially available and approved (in Germany) alternatives containing the same active pharmaceutical ingredient (termed “substance” above) via non-substantial amendment. This may be necessary e.g. in case of drug supply shortage on the German market. Of note, the dose received and duration of use will not be altered.

4.1.2 Selection of doses in the trial

According to DDI-guidelines, the exposure of the offender drug (in this case zongertinib) should be similar to the exposure seen under clinical conditions in patients. In the planned

[redacted]

Single doses of repaglinide 0.5 mg, midazolam 1 mg and omeprazole 20 mg are standard doses used in clinical drug-drug-interaction trials. Generally, the doses were selected based on their tolerability and their ability to reliably show PK interactions if indeed present (see Sections 1.2 and 1.4.2).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence. The subjects will be allocated to a trial subject number by drawing lots prior to first administration of trial medication. Once a subject number has been assigned, it cannot be reassigned to any other subject. Reference and test treatments will be administered in the sequence specified in the Flow Chart.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a two-period fixed sequence design trial. All subjects will receive zongertinib and probe drugs in a fixed order. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength (mg)	Dosage	Total daily dose (mg)	Study Visit (V), Day (D)
Reference	Repaglinide	tablet	[redacted]			V2, D1
	Midazolam	oral solution				V2, D2
	Omeprazole	tablet				V2, D2
Test	Zongertinib	tablet				V3, D1- D15
	Repaglinide	tablet				V3, D1
	Midazolam	oral solution				V3, D2
	Omeprazole	tablet				V3, D2
	Repaglinide	tablet				V3, D14
	Midazolam	oral solution				V3, D15
	Omeprazole	tablet				V3, D15

Administration of repaglinide, midazolam and omeprazole will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. During ambulatory dosing of zongertinib from Day 4 to Day 13 in Period 2 subjects are required to fast for at least 10 hours prior and 1 hour post planned drug administration. If several drug administrations are to take place simultaneously (for example V3 D2: midazolam, omeprazole and zongertinib), the drug in liquid form (i.e. midazolam) is to be administered first; additionally, zongertinib is to administered last, when scheduled simultaneously with other trial medication. The investigator (or authorised designee) will administer all trial medication as an

oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until at least 24 h after administration of repaglinide, midazolam and omeprazole. During the first 4 h after administration of repaglinide, midazolam and omeprazole, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), except for medical reasons or for recording of 12-lead ECG and vital sign measurements.

The last dose of medication in Period 1 and the first dose of medication in Period 2 are to be separated by a washout period of at least 3 days.

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. The open-label conduct is considered acceptable because the potential for bias is low and does not outweigh practical considerations. Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

4.1.6 Packaging, labelling, and re-supply

Zongertinib

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

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

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

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

No re-supply is planned.

Repaglinide, midazolam & omeprazole

Repaglinide, midazolam and omeprazole will be obtained as commercial products by the clinical trial site from a public pharmacy. Alternatively, the drug products may be obtained from wholesale and sent to the trial site. The drugs will be dispensed out of the original, unmodified packages.

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 Trial Manager (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
- 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

Midazolam, omeprazole and repaglinid may be obtained by the trial site at any time prior first dose.

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

In case of clinical signs of hypoglycemia or blood glucose concentrations below 45 mg/dL (<2.5 mmol/L) in the glucose bedside test, oral glucose will be administered in a stepwise manner in defined amounts of about 10 g carbohydrates (e.g., two glucose tablets "Dextro Energy classic" ([redacted]).

Otherwise, there are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator may authorise symptomatic therapy (e.g. administration of ibuprofen in case of headache). In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

[redacted] should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug screen.

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 other than the snack provided at 2 h post-dose is allowed for at least 4 h after drug intake during in-house confinement.

On in-house days with dosing of probe drugs (repaglinide or midazolam and omeprazole), 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 during in-house stays.

On Day 3 of period 2, subjects are required to be fasted for at least 10 h prior as well as 1 h post planned drug administration.

During ambulatory dosing of zongertinib from Day 4 to Day 13 of Period 2 subjects are required to be fasted for at least 10 h prior as well as 1 h post planned drug administration.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not

permitted from 7 days before the first administration of trial medication in the respective trial period until after the last PK sample of each trial period is collected.

[redacted] are not allowed during in-house stays at the trial site.

Smoking is not allowed during in-house confinement.

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.

[redacted]

4.2.2.3 Contraception requirements

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

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (Dinamap Pro 100, [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

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

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

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

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	X	X	X
	ALT [Alanine aminotransferase] /GPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	Free T3 - Triiodothyronine	X	--	--
	Free T4 – Thyroxine	X	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Albumin	X	X	X
	C-Reactive Protein (Quant)	X	--	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium (total)	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 HGB (qual)	X	--	X
	Urine leukocyte esterase (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)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 3 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 4 (end of trial examination)

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

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. It is planned to perform these tests during screening only with the exception of drug screening, which will be performed at screening and prior to each trial site admission.

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 A antibodies (qualitative) Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, [redacted]) will be performed prior to each trial site admission, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted], with the exception of drug screening tests. These tests will be performed at the trial site using Surestep™ Urine Drug Test or comparable test systems. Confirmatory drug screen may be performed at [redacted].

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).

Glucose bedside test

A glucose bedside test out of venous blood will be performed for safety reasons at predefined time points after each repaglinide administration (see Flow Chart). For quantification of blood glucose one drop (approximately 50 µL) of blood taken from a vein will be sufficient. The tests will be performed at the trial site using an Accu-Chek™ Aviva device or comparable test

system. The results will not be entered in the CRF/database and will not be reported in the CTR.

5.2.4 Electrocardiogram

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

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

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality (except blood drawing from an intravenous cannula which is already in place).

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

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 may be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable.

5.2.5.1 Suicidality assessment

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered ‘Always Serious’

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

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

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

5.2.6.1.4 Adverse events of special interest

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

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

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

5.2.6.1.5 Intensity (severity) of AEs

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

5.2.6.1.6 Causal relationship of AEs

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

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced

- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):

- All AEs (serious and non-serious) and all AESIs
- The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Pregnancy

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

General aspects
Blood samples for PK analyses will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle into blood drawing tubes (as outlined below).

After completion of the trial, the plasma samples, the left-over, and/or back-up aliquots may be used for further investigations related to trial IMPs (e.g., for stability testing or assessment of metabolites including, if applicable, re-analysis of parent compound and/or assessments of biomarkers). The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived. The results of any further investigations are not planned to be part of the CTR, but may be included into the CTR if necessary.

Sampling and processing for zongertinib, repaglinide, midazolam and omeprazole
For quantification of zongertinib and repaglinide (and its metabolites) concentrations in plasma, 2.7 mL of blood will be drawn into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube for each analyte at the times indicated in the Flow Chart.

For quantification of midazolam (and its metabolites) and omeprazole (and its metabolites) concentrations in plasma, 2.7 mL of blood will be drawn into a single K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube for both analytes at the times indicated in the Flow Chart.

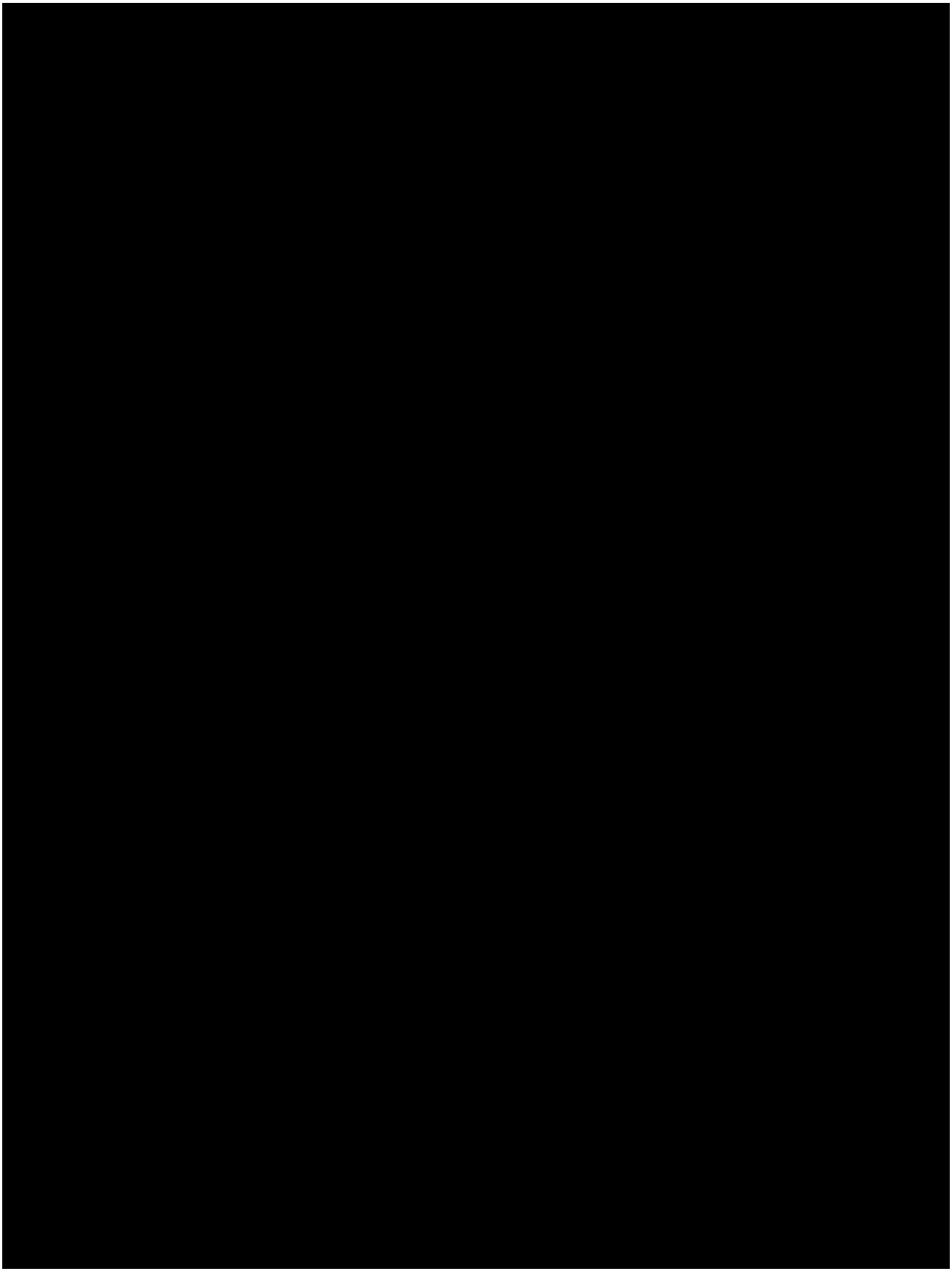
The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Three plasma aliquots will be obtained and stored in polypropylene tubes. All three aliquots should contain at least 0.3 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min , with interim storage of blood samples in ice water or on ice. 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. The third aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the second aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

Labelling
At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, planned sampling time, and the analyte (see table).

Table 5.3.2.1: 1 Labelling of PK sample aliquots

	Analyte		
Aliquot	zongertinib	repaglinide	midazolam/omeprazole
1	A1 zonger	A1 repa	A1 mid/om
2	A2 zonger	A2 repa	A2 mid/om
3	BU zonger	BU repa	BU mid/om

[redacted]



5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination or Visit 2 from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

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

5.6.2 Liquid Biopsy

For the exploration of individual variability of PK related proteins and activities through small extracellular vesicles in plasma by proteomics, RNA profiling and enzyme assay (liquid biopsy), approximately 15 mL of blood will be collected at the time points indicated in the Flow Chart. Changes to conditions of sample processing described in the CTP may be implemented via non-substantial amendement.

Approximately 2 x 7.5 mL of blood ([redacted]) will be drawn from a vein into a potassium ethylenediaminetetraacetic acid (K2-EDTA)-anticoagulant blood drawing tube at the timepoint indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture. The EDTA-anticoagulated blood samples will be centrifuged for approximately 15 min at approximately 2500x g at room temperature. Plasma will be extracted leaving a 5 mm buffer volume to ensure integrity of the buffy coat or clot. Plasma will be transferred from both EDTA collection tubes into two new 5 mL Eppendorf Protein LoBind tubes. Then, within 60 min minutes of collection, the 5 mL Eppendorf Protein LoBind tubes will be centrifuged at 2500 x g for 15 minutes at room temperature. Leaving a small buffer volume in the LoBind tubes, plasma samples will be aliquoted at a volume of 1 mL into new 5 mL Eppendorf Protein LoBind tubes labelled as 'Ali 1' to 'Ali 4' until all available plasma is transferred, any remaining plasma is to be transferred in the 5th aliquot labelled 'Ali 5'. All aliquots are subsequently frozen at approximately -70 °C or below until shipment of plasma samples. Until transfer on dry ice to analytical laboratory, the aliquots will be stored upright at approximately -70 °C or below at the trial site. At the analytical laboratory, the plasma samples will be stored at approximately -70 °C or below until analysis. The results of exploratory [redacted] will be described in the report separately from the trial CTR. After analysis the plasma samples may be used for further PK and/or biomarker methodological investigations, e.g., for stability

testing, enrichment of liver derived exosome, or exploration of shedding factor. The samples will be discarded after completion of the additional investigations but no later than 5 years upon the final trial report has been signed.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 and Day 2 of Visit 2 as well as Day 1, Day 2, Day 3, Day 14 and Day 15 of Visit 3 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.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, safety laboratory tests (excluding blood glucose testing) and ECG will be ± 30 min. For glucose testing the acceptable deviation from the scheduled time is ± 10 min.

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

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

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.

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

6.2.2 Treatment period(s)

Each subject is expected to participate in 2 treatment periods (Period 1: Day -1 to Day 3 and Period 2: Day -1 to Day 16). At least 3 days will separate drug administrations in the first and second treatment periods.

Trial participants will be admitted to the trial site on Day -1 of Period 1 and will remain under close medical surveillance for the entirety of Period 1 (Day -1 to Day 3). In Period 2 trial

participants will be admitted to the trial site twice on Day -1 and Day 13 and will remain under close medical surveillance for at least 48 h. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion.

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

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

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

6.2.3 Follow-up period and trial completion

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of probe drugs, midazolam, omeprazole and repaglinide, administered alone compared with co-administered with zongertinib will be estimated by the ratios of the geometric means (T1/R1, T2/R2, T3/R1, T4/R2), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.
- Biomarker parameter analysis set (BMS): This set includes all subjects in the treated set (TS) who provide at least one evaluable measure of the [redacted] without protocol deviations relevant to the evaluation of the biomarker (as specified in the subsection 'Biomarkers'). Listing of the biomarker will be based on the BMS.

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 the probe drugs (and metabolites) will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation

relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

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

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

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

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

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

7.2.1.3 Biomarkers

Biomarker endpoints are outlined in Section 2.2.2.2. Only [redacted] will be reported as listing in the CTR.

Biomarker data and parameters of a subject will be included in the biomarker listing if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of the biomarker (to be decided no later than in the Report Planning Meeting) or due to non-evaluability (as revealed during data analysis). Protocol deviations maybe similar to those listed for pharmacokinetics in Section 7.2.1.2.

Exclusion of a subject's data will be documented in the CTR. Biomarker data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the listing.

7.2.2 Primary endpoint analyses

Primary analyses

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

μ = the overall mean,

s_m = the effect associated with the m^{th} subject,
m = 1, 2, ..., n

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

e_{km} = the random error associated with the m^{th} subject who received treatment k.

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

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

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

Further exploratory analyses

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

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

7.2.3 Secondary endpoint analyses

The secondary endpoint (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.

7.2.5 Safety analyses

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

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the

screening period, those between first trial medication intake and end of REP (see Section 1.2.4) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings. Additionally, differences from baseline will be evaluated.
Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

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

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects in the trial with the aim of ≥ 12 evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for midazolam in previous trials [redacted]

The observed intra-individual coefficient of variation for repaglinide in the previous trial [redacted]

The observed intra-individual coefficient of variation for omeprazole in previous trials [redacted]

With these results two scenarios are considered in this trial: a scenario with the gCV around 25% and a scenario with the gCV roughly close to the highest observed value, 85%. Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.5: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2-period fixed sequence trial (N=12)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
20	1.214	80	65.88	97.15
20	1.214	100	82.35	121.43
20	1.214	125	102.94	151.79
25	1.273	80	62.84	101.85
25	1.273	100	78.55	127.31
25	1.273	125	98.19	159.13
30	1.334	80	59.99	106.68
30	1.334	100	74.99	133.36
30	1.334	125	93.73	166.69
80	1.993	80	40.14	159.44
80	1.993	100	50.17	199.30
80	1.993	125	62.72	249.13
85	2.061	80	38.82	164.86
85	2.061	100	48.53	206.07
85	2.061	125	60.66	257.59
90	2.128	80	37.59	170.26
90	2.128	100	46.99	212.82
90	2.128	125	58.73	266.03

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

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 4.2.1.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

Electronic Study Documentation System:
In [redacted] a validated electronic study documentation system (ClinBase™ or successor Trial Complete Early Phase (TCEP)) is used for processing information and controlling data collected in clinical trials. In addition to its function as a procedure control system, the study documentation system serves as databases. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

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

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

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

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

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place

- A fit for the purpose documentation (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim International GmbH, [redacted].

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

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial

- Ensure appropriate training and information of local Clinical Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

Zongertinib will be provided by the [redacted]. Repaglinide, midazolam and omeprazole will be obtained by the trial site from a public pharmacy.

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

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

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

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

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

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

Analyses of the Liquid Biopsy will be performed under the responsibility Boehringer Ingelheim Pharma GmbH & Co. KG, [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 according to BI SOPs or a contract research organisation appointed by BI.

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

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		18 Mar 2024
EudraCT number **EU number**		2023-510263-35-00
BI Trial number		1479-0014
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		1) 4.1.1 2) 4.1.6 [redacted]
Description of change		1) Substitution of commercially available drug products (i.e. trial products 2,3, and 4) by approved alternatives containing the same active pharmaceutical ingredient via non-substantial amendment. 2) Permission for trial site to obtain commercially available drug products from public pharmacies or wholesale. [redacted]
Rationale for change		1) Potential drug supply shortages for commercially available drug products. 2) Potential drug supply shortages for commercially available drug products.

		[redacted]

11.2 GLOBAL AMENDMENT 2

Date of amendment		17 May 2024
EudraCT number **EU number**		2023-510263-35-00
BI Trial number		1479-0014
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1) Title page, Lay title 2) Flowchart Period 1, Visit 2, Day 3 3) Flowchart Period 2, Visit 4, Day 3 and Day 16 4) 1.2.3. 5) 1.4.2, Table 1.4.2: 1 6) 3.3.3 7) 3.3.4.1 8) 4.1.4 9) 4.2.2.2 10) 6.1 11) 6.2.2
Description of change		1) Lay title was changed to: *A study in healthy men to test whether zongertinib affects how 3 other medicines (midazolam, omeprazole, and repaglinide) are taken up and processed in the body*

		2 - 5) Extension of in-house confinement following administration of midazolam from 12 to 24 hours 6) Addition of exclusion criterion 26: *ALT (alanine transaminase), AST (aspartate transaminase), or serum creatinine above upper limit of normal range at screening examination, confirmed by a repeat test;* [redacted] *confirmed by a repeat test* 7) Addition of withdrawal criterion for individual subjects from treatment: *The subject exhibits an AE of CTCAE grade 3 or a serious AE (SAE)* 8 - 9) Change in ambulatory dosing days following extension of in-house confinement following administration of midazolam from 12 to 24 hours; adjustment of wording regarding fasting in Section 4.2.2.2 to the change of ambulatory/in-house time intervals; actual fasting intervals remain unchanged 10) Change in in-house dosing days following extension of in-house confinement following administration of midazolam from 12 to 24 hours 11) Extension of treatment periods 1 & 2 by one day following extension of in-house confinement following administration of midazolam from 12 to 24 hours
Rationale for change		1 - 5) Upon request by ethics committee (RFI part II) 6 - 7) Upon health authority / ethics committee request (RFI part I) 8 - 11) Upon request by ethics committee (RFI part II)

11.3 GLOBAL AMENDMENT 3

Date of amendment		12 Jul 2024
EudraCT number **EU number**		2023-510263-35-00
BI Trial number		1479-0014
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		1. Synopsis (Trial product 3) 2. 4.1.1 (Trial product 3) 3. 5.4.1.1
Description of change		1-2. Change of Antra MUPS® 20 mg magensaftresistente Tabletten to Omeprazol STADA® protect 20 mg magensaftresistente Tabletten 3. Deletion of the reference to the shipment of the third aliquot for [redacted].
Rationale for change		1-2. Drug supply shortage of Antra MUPS® 20 mg magensaftresistente Tabletten on the German market 3. Clarification regarding the sample collection for [redacted]: there is no third : aliquot, thus the deleted sentence should be omitted.

APPROVAL / SIGNATURE PAGE

Document Number: c42988075 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-04

Title: The effect of multiple doses of zongertinib on the single-dose pharmacokinetics of midazolam, omeprazole and repaglinide in healthy male subjects (an open-label, 2-period, fixed-sequence trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	12 Jul 2024 16:17 CEST
Verification-Paper Signature Completion		15 Jul 2024 06:29 CEST
Author-Clinical Trial Leader		15 Jul 2024 09:46 CEST
Approval-Clinical Program [redacted]		15 Jul 2024 11:21 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed