Clinical Trial Protocol

Document Number:	**c43424163-02**
EU Trial No.	2024-510628-38-00
UTN	U1111-1302-1171
BI Trial No.	1479-0015
BI Investigational Medicinal Product	Zongertinib (BI 1810631)
Title	The effect of zongertinib on the pharmacokinetics of dabigatran (part 1) and rosuvastatin, metformin and furosemide administered as a cocktail (part 2) in healthy male subjects (a 2-part, open-label, 2-period, fixed-sequence cross-over trial)
Lay Title	A study in healthy men to test whether zongertinib influences the amount of 4 other medicines (dabigatran, rosuvastatin, metformin, and furosemide) in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted], Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 2.0, 17 Jun 2024
Original Protocol Date	09 Apr 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	09 April 2024
Revision date	17 June 2024
BI trial number	1479-0015
Title of trial	The effect of zongertinib on the pharmacokinetics of dabigatran (part 1) and rosuvastatin, metformin and furosemide administered as a cocktail (part 2) in healthy male subjects (a 2-part, open-label, 2-period, fixed-sequence cross-over trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	Evaluation of in-vivo effects of zongertinib on drug transporter probe substrates
Trial objective	To assess the effect of zongertinib on the pharmacokinetics of dabigatran, rosuvastatin, metformin and furosemide
Trial endpoints	Part 1 Primary endpoints: $AUC_{0-\infty}$ and C_{max} of dabigatran Secondary endpoint: AUC_{0-tz} of dabigatran Part 2 Primary endpoints: $AUC_{0-\infty}$ and C_{max} of rosuvastatin, metformin and furosemide Secondary endpoints: AUC_{0-tz} of rosuvastatin, metformin and furosemide
Trial design	Part 1: Open-label, 2-period, fixed-sequence cross-over trial Part 2: Open-label, 2-period, fixed-sequence cross-over trial
Number of subjects **total entered** **on each treatment**	 32 Trial Part 1: 16 Trial Part 2: 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	Zongertinib, 60 mg film-coated tablets
dose	1 x 2 tablets (=120 mg zongertinib)
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 2	Pradaxa® 150 mg hard capsule
dose	1 capsule (= 150 mg dabigatran-etexilate)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 3	Crestor® 10 mg film-coated tablets
dose	1 tablet (= 10 mg rosuvastatin)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 4	MetfoLiquid GeriaSan®, 1000 mg / 5 mL oral solution
dose	1 x 0.05 mL oral solution (= 10 mg metformin)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 5	Lasix® liquidum 10 mg/mL oral solution
dose	1 x 0.1 mL oral solution (= 1 mg furosemide)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	<u>Part 1</u> Period 1: 1 hard capsule Pradaxa® (= 150 mg dabigatran-etexilate) Period 2: 2 tablets zongertinib (2 x 60 mg = 120 mg) followed by 1 hard capsule Pradaxa® (= 150 mg dabigatran-etexilate) [redacted] The treatment periods are separated by a wash-out interval of at least 7 days between study drug administrations. <u>Part 2</u> Cocktail: rosuvastatin (10 mg), metformin (10 mg) and furosemide (1 mg) are administered together as a cocktail (referred to as 'cocktail') Period 1: cocktail *(see above)* Period 2: 2 tablets zongertinib QD (2 x 60 mg = 120 mg of zongertinib daily) from Day -9 to Day 3 (total of 12 days); on Day 1 cocktail *(see above)* will be administered together with zongertinib

Statistical methods	The same analyses will be performed for both parts of the study: Relative bioavailability 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 – PART 1 REFERENCE TREATMENT

Period	Visit	Day	Planned time (relative to dabigatran administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood dabigatran	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	-21 to -1			Screening (SCR)[1]	A		x	x	
1	2	-1	-12:30	20:00	Admission to trial site[8]	x[5,8]				x[8]
		1	-1:30	07:00	Allocation to subject number[2]		x[2]		x[2]	x[2]
			[redacted]		240 mL fluid intake					
					Dabigatran-etexilate administration					
			0:30	09:00			x			
			1:00	09:30			x			x
			1:30	10:00			x			
			2:00	10:30	240 mL fluid intake		x			x
			2:30	11:00			x			
			3:00	11:30			x			x
			3:30	12:00			x			
			4:00	12:30	240 mL fluid intake, thereafter lunch[3]		x		x	x
			5:00	13:30			x			
			6:00	14:30			x			x
			7:00	15:30			x			
			8:00	16:30	Snack (voluntary)[3]		x			x
			10:00	18:30			x			
			10:30	19:00	Dinner					
			12:00	20:30			x			x
		2	24:00	08:30	Breakfast (voluntary)[3], discharge from trial site		x		x	x
			34:00	18:30	Ambulatory visit		x			x
		3	48:00	08:30	Ambulatory visit		x			x
Wash-out of at least [redacted]										

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.
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. Letters indicate different sets of safety laboratory examinations (for details refer to Section 5.2.3).
8. The time is an approximate. The procedure is to be completed not later than 10 hours prior to first drug administration.

FLOW CHART – PART 1 TEST TREATMENT

Period	Visit	Day	Planned time (relative to dabigatran administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood dabigatran	PK blood zongertinib	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
		-1	-12:30	20:00	Admission to trial site[8]	x[5,8]					x[8]
		1	[redacted]		Zongertinib administration		x[2]	x[2]		x[2]	x[2]
					Dabigatran-etexilate administration[9]			x[9]			
			0:30	09:00			x				
			1:00	09:30			x	x			x
			1:30	10:00			x				
			2:00	10:30	240 mL fluid intake		x	x			x
			2:30	11:00			x				
			3:00	11:30			x	x			x
			3:30	12:00			x				
2	3		4:00	12:30	240 mL fluid intake, thereafter lunch[3]		x			x	x
			5:00	13:30			x				
			6:00	14:30			x				x
			7:00	15:30			x				
			8:00	16:30	Snack (voluntary)[3]		x				x
			10:00	18:30			x				
			10:30	19:00	Dinner						
			12:00	20:30			x				x
		2	24:00	08:30	Breakfast (voluntary)[3], discharge from trial site		x			x	x
			34:00	18:30	Ambulatory visit		x				x
		3	48:00	08:30	Ambulatory visit		x				x
FU	4	15 to 36			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.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to zongertinib 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. Letters indicate different sets of safety laboratory examinations (for details refer to Section 5.2.3).
8. The time is an approximate. The procedure is to be completed not later than 10 hours prior to first drug administration.
9. Dabigatran administration in time, immediately followed by zongertinib PK sample

FLOW CHART – PART 2 REFERENCE TREATMENT

Period	Visit	Day	Planned time (relative to cocktail administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK $_{blood}$ cocktail components	[redacted]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[4]
SCR	1	-21 to -1			Screening (SCR)[1]	A			x	x	x
1	2	-1	-12:00	20:00	Admission to trial site[8]	x[5,8]					x[8]
		1	-1:00	07:00	Allocation to subject number[2]		x[2]		x[2]	x[2]	x[2]
			0:00	08:00	Cocktail administration						
			0:20	08:20			x				
			0:40	08:40			x				
			1:00	09:00			x				x
			1:30	09:30			x				
			2:00	10:00	240 mL fluid intake		x			x	x
			2:30	10:30			x				
			3:00	11:00			x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x			x	x
			5:00	13:00			x				
			6:00	14:00			x			x	x
			8:00	16:00	Snack (voluntary)[3]		x				x
			10:00	18:00			x				x
			11:00	19:00	Dinner						
			12:00	20:00			x				x
		2	24:00	08:00			x			x	x
			25:00	09:00	Breakfast						
			28:00	12:00	Lunch[3]						x
			32:00	16:00	Snack (voluntary)						
			35:00	19:00	Dinner						
			36:00	20:00			x				x
		3	48:00	08:00	Discharge, Breakfast (voluntary)[3]		x			x	x
		4	72:00	08:00	Ambulatory visit		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.
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. 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.
5. Only urine drug screening and alcohol breath test will be done at this time

[redacted]

7. Letters indicate different sets of safety laboratory examinations (for details refer to Section 5.2.3).
8. The time is an approximate. The procedure is to be completed not later than 10 hours prior to cocktail administration.

FLOW CHART – PART 2 TEST TREATMENT

Period	Visit	Day	Planned time (relative to cocktail administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood cocktail components	PK blood zongertinib	[redacted]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[4]
2	3	-9	-216:00	08:00	Zongertinib administration[9]	B[2,12]		x[2]		x[2]	x[2]	x[2]
		-8	-192:00	08:00	Zongertinib administration[9]							x
		-7	-168:00	08:00	Zongertinib administration[9]							x
		-6	-144:00	08:00	Zongertinib administration[9]	B						x
		-5	-120:00	08:00	Zongertinib administration[9]							x
		-4	-96:00	08:00	Zongertinib administration[9]			x[10]				x
		-3	-72:00	08:00	Zongertinib administration[9]	B						x
		-2	-48:00	08:00	Zongertinib administration[9]							x
		-1	-24:00	08:00	Zongertinib administration[9]							x
			-12:00	20:00	Admission to trial site[8]	x[5,8]						x[8]
		1	-1:00	07:00		B[2]				x[2]	x[2]	x[2]
			0:00	08:00	Zongertinib & cocktail administration		x[10]	x[10]				
			0:20	08:20			x	x				
			0:40	08:40			x	x				
			1:00	09:00			x	x				x
			1:30	09:30			x	x				
			2:00	10:00	240 mL fluid intake		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, thereafter lunch[3]		x	x		x	x	x
			5:00	13:00			x	x				
			6:00	14:00			x	x		x	x	x
			8:00	16:00	Snack (voluntary)[3]		x	x				x
			10:00	18:00			x	x				x
			11:00	19:00	Dinner							
			12:00	20:00			x	x				x
		2	24:00	08:00	Zongertinib administration[11]		x[11]	x[11]		x[2]	x[2]	x[2]
			25:00	09:00	Breakfast							
			28:00	12:00	Lunch[3]							x
			32:00	16:00	Snack (voluntary)							
			35:00	19:00	Dinner							
			36:00	20:00			x	x				x
		3	48:00	08:00	Zongertinib administration[11]		x[11]	x[11]		x[2]	x[2]	x[2]
			49:00	09:00	Discharge, Breakfast (voluntary)[3]							
		4	72:00	08:00	Ambulatory visit		x	x				x
FU	4	17 to 30			End of study (EoS) examination[1]	C				x	x	x

1. 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.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to the next drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. 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.
5. Only urine drug screening and alcohol breath test will be done at this time

[redacted]

7. Letters indicate different sets of safety laboratory examinations (for details refer to Section 5.2.3).
8. The time is an approximate. The procedure is to be completed not later than 10 hours prior to cocktail administration.
9. Subjects are required to be fasted for at least 10 hours prior and 1 hour post ambulatory drug administration. In addition, the tolerance time for ambulatory dosing (and other scheduled procedures) from Day -9 to Day -1 in Period 2 is ± 2 hours.
10. To be performed within 15 min prior to drug dosing.
11. PK samples should be on planned time, followed by zongertinib administration. Tolerance for zongertinib administration: up to +15 minutes.
12. Including urine drug screening and alcohol breath test

TABLE OF CONTENTS

[redacted]

[redacted]

ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	
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
[redacted]	
$AUC_{\tau,ss}$	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
[redacted]	
[redacted]	
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
FAS	Full Analysis Set
[redacted]	
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
[redacted]	
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QTc interval	QT interval corrected for heart rate, using the method of Fridericia (QTcF)
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
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
[redacted]	
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	

1. INTRODUCTION

The trial will be performed to assess the influence of zongertinib on the pharmacokinetics of dabigatran, rosuvastatin, metformin and furosemide which are probe substrates of clinically relevant drug transporters. The in-vivo effect of zongertinib on the probe substrates will be used to predict potential transporter-based drug-drug interactions.

1.1 MEDICAL BACKGROUND

1.1.1 Human epidermal growth factor receptor 2 (HER2)

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.

1.1.2 Drug transporters

Drug transporters play an important role in drug absorption, distribution, and excretion. Inhibition of drug transporters by concomitantly administered drugs may cause clinically relevant drug-drug interactions (DDI) [P14-07656], [R10-1157]. With increasing recognition and understanding of the involvement of drug transporters in clinically relevant DDIs, thorough investigation of transporter-mediated DDI has become indispensable during drug development. Based on the recommendations of the International Transporter Consortium's (ITC) white paper [R10-1157], regulatory agencies explicitly state drug transporters that should be investigated in vitro for inhibition by new investigational drugs during drug development. The specific transporters explicitly referred to by both the EMA guideline [P15-06991] and the FDA guidance [R20-2271] are the ABC transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and the SLC transporters, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic cation transporter 2 (OCT2), organic anion transporter 1 (OAT1), and OAT3. If in vivo inhibition of a drug transporter known to be relevant for drug disposition cannot be excluded based on in vitro data, an in vivo study is recommended by regulatory agencies. A valuable approach to investigate several separate mechanisms underlying DDIs with the investigational product as the perpetrator in one single study is the "cocktail study". This method, in which a mixture of well-characterized probe drugs is administered together with the new investigational product, is well established for investigation of cytochrome P450 (CYP)-mediated DDIs. Both the EMA and FDA recommend the use of cocktail studies also for the investigation of transporter-mediated DDIs [P15-06991], [P12-05791]. A cocktail of drug transporter substrates has been developed by BI during the last years. This cocktail consists of 0.25 mg digoxin (substrate of P-gp), 10 mg rosuvastatin (substrate of OATP1B1, OATP1B3 and BCRP), 10 mg metformin (substrate of OCT2, MATE1 and MATE2-K) and 1 mg furosemide (substrate of OAT1 and OAT3), thus covering all transporters of potential clinical relevance recommended by EMA and FDA (see above). In the given doses the cocktail demonstrated no mutual interactions [R20-1915]. The metabolism of these drugs is minor facilitating the investigation of transporter-mediated DDIs without enzyme inhibition potentially confounding the results.

In this trial digoxin, which is the probe substrate for P-gp, will not be utilised. Instead, the effects of zongertinib on P-gp will be examined using dabigatran-etexilate in Part 1 of the trial. Similar to digoxin, dabigatran-etexilate is a recommended probe substrate for the evaluation of P-gp based interactions [P15-06991], [P12-05791]. In contrast to digoxin, which reflects interactions mediated by intestinal and systemic P-gp, the prodrug dabigatran-etexilate reflects only interactions mediated by intestinal P-gp, because only small amounts of dabigatran-etexilate become systemically available, while the active moiety dabigatran is not a substrate of P-gp (see Section 1.2.2). Investigating the inhibition of intestinal transporters allows a single dose administration of the inhibitor (single dose of zongertinib is used in Part 1), because the inhibitor concentrations in the intestinal lumen are decisive for the interaction, and high concentrations in the gut lumen can be reached by a single dose. Using digoxin as P-gp

substrate would require zongertinib dosing also during the long elimination phase of digoxin (half-life of about 40 hours).

In Part 2 of this trial potential transporter-mediated interactions between zongertinib and the remaining probe substrates rosuvastatin, metformin and furosemide (given as a cocktail) will be evaluated.

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 dabigatran-etexilate, rosuvastatin, metformin and furosemide to the respective SmPCs [R24-2285, R24-1169, R24-1152-R24-2284].

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 monotherapy administered using either a [redacted] as well as in the dose expansion phase with [redacted]. Overall, the median treatment duration was [redacted] and the exposure ranged [redacted] during the dose escalation at data cut-off; during the dose expansion, the median treatment duration was [redacted] and the exposure ranged from [redacted] days. Data cut

time point for the data described here is [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 (at [redacted] and platelet count decreased Grade 3 [redacted] 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 ([redacted]). 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 [redacted] zongertinib [redacted] One week later the patient was admitted to the hospital with hepatic failure and prolonged prothrombin time. During hospitalisation, study medication was interrupted, and the patient was treated with N-acetylcysteine and methylprednisolone over 7 days. After discharge from the hospital treatment continued with 50 mg prednisolone. The patient was recovering and restarted study drug on Day 63 [redacted] Liver enzymes and bilirubin were further normalising.

The patient had COVID-19 infection and was treated with Remdisivir starting on Day 25 of study treatment as possible confounding factors.
A second patient who was treated with [redacted] zongertinib [redacted] over 42 days developed, despite interruption of study drug due to ALT, AST Grade 2 and total bilirubin Grade 1, further increases of ALT and AST up to Grade 4 (>20.0x ULN), increased total bilirubin up to Grade 3 (>3x ULN), and coagulopathy Grade 3 on Day 55. On Day 57, the patient had developed subacute hepatic failure Grade 4, cholestasis Grade 4 and hypoalbuminaemia Grade 2. Treatment of the AEs included hepatoprotective and anticholestatic agents as well as dexamethasone. Liver enzymes and total bilirubin were improving between Days 66 and 76. During the further course the patient developed infection (on Day 81) and subsequent sepsis (on Day 86) with fatal outcome 7 days later. Further evaluations are ongoing. 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 [redacted] and investigated [redacted]. Thirteen healthy male volunteers were dosed with single doses of [redacted] 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 [redacted] 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 [redacted] 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 [redacted] in 1 subject (6.3%) and was the only significant AE in the trial,

according to ICH E3. The event was considered [redacted] and resolved without therapy. Overall, 7 out of 16 subjects (43.8%) while on treatment with zongertinib ([redacted]) 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 [redacted] and investigated absolute bioavailability of zongertinib [redacted] 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 [redacted] 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 [redacted] zongertinib following oral administration [redacted] 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 [redacted] 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, [redacted] 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 [redacted] 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 for [redacted] dosing (see Table 1.2.1.6: 2). The observed PK profile of zongertinib appears [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 multiple dosing on [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 Dabigatran

Following single dose administration of dabigatran-etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran is characterized by maximum plasma concentration at approximately 1-2 hours after oral administration of dabigatran-etexilate, a biexponential distribution phase and a terminal elimination half-life of about 8-10 hours. With BID dosing the steady state is attained within 3 days, and C_{max} at steady state is about 30% higher than after the first dose. Dabigatran plasma concentrations and the pharmacokinetic parameters C_{max} and AUC increased in a dose proportional manner after oral administration of the prodrug dabigatran etexilate and after intravenous infusion of dabigatran. The pharmacodynamic parameters aPTT, INR, ECT, and TT show close correlation with dabigatran plasma concentrations. The bioavailability of dabigatran in the capsule formulation is about 6.5%. After treatment with the proton pump inhibitor pantoprazole (increased gastric pH) bioavailability is reduced by approximately 20-30%. Co-administration with food results in delay of C_{max} from 2 to 4 hours; there is no consistent effect on total exposure. Neither dabigatran-etexilate nor dabigatran interact with CYPs. No drug-drug interactions based on CYP dependent pathways have been identified. Dabigatran-etexilate but not the active moiety, dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp). Accordingly, the bioavailability of dabigatran is increased when P-gp inhibitors such as verapamil, quinidine, amiodarone, dronedarone or ketoconazole are co-administered. However this effect could be significantly reduced by staggered administration of the P-gp inhibitor. Due to rapid hydrolisation only small amounts of dabigatran etexilate reach systemic circulation. Thus, modulators of P-gp can affect intestinal absorption of dabigatran-etexilate, but not its further disposition. Therefore, the staggered administration of a P-gp inhibitor at the time point of maximum dabigatran concentration (t_{max}) will cause a significantly lower increase in dabigatran bioavailability, because a great part of the compound has been already absorbed from the intestinal lumen. This effect has been proven for the P-gp inhibitors dronedarone [U11-2448-01] and verapamil [U09-1052-01], when given 2 h after dabigatran.
Co-administration of the suggested P-gp inhibitor clarithromycin did not meaningfully affect the PK of dabigatran. Rifampicin, an inducer of P-gp reduced the bioavailability of free and total dabigatran. Conversely, the PK of co-administered P-gp substrates like digoxin or the inhibitors (clarithromycin, verapamil, quinidine, ketoconazole, amiodarone) was not affected by dabigatran-etexilate confirming the in vitro results that neither dabigatran-etexilate nor its intermediate metabolites or the active moiety dabigatran are inhibitors of P-gp. In the RE-LY study, the effect of concomitant use of verapamil, amiodarone or all potent P-gp inhibitors on trough and 2 h dabigatran plasma concentrations was assessed descriptively. In RE-LY, a greater than 20% increase was not observed when amiodarone, verapamil, diltiazem or any strong P-gp inhibitor was co-administered. These findings were qualitatively in agreement to the results of the phase I studies though the magnitude of the effect was on average much lower in RE-LY. Accordingly, the difference in event rates (i.e., major or any bleeding) and efficacy endpoints (stroke, SEE) in patients receiving or not receiving verapamil, amiodarone or diltiazem were not pronounced and not clearly different from patients treated concomitantly with warfarin and a P-gp inhibitor [U09-3249-02].

Dabigatran and dabigatran-etexilate were well tolerated by healthy subjects. Overall, more than 1000 healthy volunteers have been included in phase I trials with dabigatran-etexilate. Adverse events were few, mild, and included primarily hematoma at the venipuncture site or need for

prolonged compression for hemostasis on venous catheter removal at higher doses. Major bleedings were not observed in the Phase I trials. At the highest dose of dabigatran-etexilate studied in humans, 400 mg three times daily as oral solution, 6 of 8 subjects reported mild bleeding such as hematoma or prolonged bleeding at a venous puncture site, or gingival bleeding [U00-1856]. In a further Phase I study [U06-1614-01] single doses of 600 mg, 750 mg, and 900 mg HPMC capsules were planned to be administered to find out the highest tolerable dose. After 600 mg a 2-fold to 3-fold increase in the main coagulation parameter aPTT was achieved at 2 to 4 h post dose. The only observed AEs were transient abdominal discomfort and a mild phlebitis at the puncture site in one subject each. The dose levels 750 mg and 900 mg were not performed because a full therapeutic effect was already achieved with 600 mg. For a more detailed description of the dabigatran profile, please refer to the current SmPC [R24-2285].

1.2.3 Rosuvastatin

Rosuvastatin is an HMG-CoA reductase inhibitor indicated for treatment of hypercholesterolemia and for prophylaxis of cardiovascular events. Inhibition of HMG-CoA decreases hepatic cholesterol production which, in turn, stimulates hepatocellular uptake of low-density lipoproteins [R24-1169]. After oral administration, maximal rosuvastatin plasma concentrations are reached at ~5 h. Oral bioavailability is ~20%, plasma protein binding is ~90%, and VZ/F is ~134 L. The liver is a principal compartment of distribution, with hepatocellular uptake being mediated mainly by OATP1B1 and, to a lesser degree, by OATP1B3. Elimination is mainly via faeces and to a lesser degree, via urine (principally via renal tubular secretion), with a t1/2 of 19 h [R24-1169], [P14-07833]. In therapy, the initial rosuvastatin dose is 5-10 mg once daily (QD), and during therapy, the daily dose may be increased to up to 40 mg [R24-1169].
Adverse reactions to rosuvastatin are normally mild and transient. Myalgia and myopathy with concomitant increase of creatine kinase, and, in rare cases, rhabdomyolysis have been observed during rosuvastatin therapy. Moreover, as for other HMG-CoA reductase inhibitors a dose-dependent increase of liver transaminases may be observed [R24-1169]. For a complete listing of adverse reactions, including frequency of occurrence, please refer to the current SmPC [R24-1169].

1.2.4 Metformin

Metformin is an oral antidiabetic that reduces plasma glucose concentrations by decreasing intestinal glucose absorption and hepatic glucose production and by enhancing glucose utilization in peripheral tissues. Thus, metformin reduces basal (fasting) and postprandial plasma glucose in patients with type 2 diabetes mellitus (T2DM). However, metformin does not stimulate insulin secretion and is not causally related to hypoglycaemia in patients with T2DM or in healthy volunteers. Metformin is used in patients with T2DM if sufficient reduction of plasma glucose is not reached by diet and exercise alone [R24-1152]. After oral administration, t_{max} is reached at ~2.5 h, and oral bioavailability (of 500-850 mg) is ~50 60%. Plasma protein binding is negligible, however, metformin enters erythrocytes which probably compose a deep distribution compartment. CLR of metformin is high (estimated population mean of 507 ± 129 mL/min) and the principal mode of elimination, with a $t_{1/2}$ of approximately 6.5 h [R24-1152], [P11-01873].

The initial metformin dose is normally 500-850 mg up to three times daily. The dose may be increased to up to 3000 mg per day [R24-1152]. Most frequent adverse reactions to metformin are gastrointestinal complaints such as nausea, vomiting, diarrhoea, abdominal pain, or appetite loss. Moreover, metformin may cause changed taste (e.g., metallic taste), and, very rarely or with unknown frequency, respectively, skin reactions or abnormal liver function tests. For a complete listing of adverse reactions, including frequency of occurrence, please refer to the current version of the SmPC [R24-1152]. In addition, metformin may, very rarely, cause lactic acidosis. This is a life-threatening disorder caused by metformin accumulation, principally in diabetic patients with severe renal insufficiency. In case of unspecific symptoms such as muscle cramps in combination with gastrointestinal disorder or severe asthenia, lactic acidosis needs to be taken into account. Other possible symptoms are dyspnoea, abdominal disorders, hypothermia, and coma [R24-1152]. To our knowledge, lactic acidosis has not been observed in healthy volunteers thus far. Doses of up to 850 g metformin did not cause hypoglycaemia. However, lactic acidosis has been observed with this severe overdosing [R24-1152]. For a more detailed description of metformin`s profile please refer to the current SmPC [R24-1152].

1.2.5 Furosemide

Furosemide is a loop diuretic indicated for treatment of oedema (cardiac, hepatic, renal, or due to burns), arterial hypertension, oliguria or pulmonary oedema. By inhibition of the $Na^+/2Cl^-/K^+$ carrier in the distal ascending limp of Henle's loop, furosemide increases diuresis and excretion of sodium, potassium, calcium, and magnesium [R24-2284]. After administration of furosemide as an oral solution, oral bioavailability is ~80%. Maximal plasma concentrations (t_{max}) are observed at ~1 h. Plasma protein binding is 95%, and VZ/F is 0.2 L/kg. Furosemide is eliminated principally as unchanged substance, to two thirds by the kidney (glomerular filtration and secretion) and to one third by excretion into bile [R24-2284]. In therapy, initial doses of oral furosemide are normally 40 mg, but higher doses of over 200 mg are possible in individual cases when diuresis with lower doses is not sufficient. Maintenance dose is normally 40-80 mg/day [R24-2284].
Adverse reactions include mainly electrolyte disorders including dehydration and hypovolemia, hearing disorders and allergic reactions including skin reactions. Symptoms of overdosing are characterized by excessive loss of electrolytes which may lead to hypotension, syncope, or delirium [R24-2284.
For a complete listing of furosemide adverse reactions, including frequency of occurrence, please refer to the current SmPC [R24-2284].

1.2.6 Residual Effect Period

The Residual Effect Period (REP) of zongertinib is [redacted]. 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 dabigatran is 3 days, the REP for rosuvastatin is 6 days, the REP for metformin is 2 days and the REP for furosemide is 2 days.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on non-clinical data, zongertinib is a potential [redacted].
This trial aims to investigate the in-vivo effect of zongertinib on these drug transporters by using the drug transporter model substrates. In Part 1 of the trial the effect of a single dose zongertinib on the kinetics of dabigatran (P-gp) will be investigated. In Part 2 of the trial the kinetics of rosuvastatin (OATP1, BCRP), metformin (MATE1, MATE2-K, OCT2) and furosemide (OAT1, OAT3) which are administered as a cocktail (see Section 1.1.2), will be investigated alone and together with zongertinib (dosed to steady state). The results of this trial will guide predictions on the DDI potential of zongertinib with respect to the inhibition of the investigated drug transporters.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

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

1.4.2 Risks

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

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: Zongertinib		
[redacted]		

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		

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
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.

1.4.2.1 Risks related to the administration of the probe substrates

Risk related to the administration of dabigatran-etexilate (Part 1)
In study 1160.60 a single dose of 600 mg dabigatran-etexilate was well tolerated by healthy subjects [U06-1614-01]. Taking into account the dose proportional kinetics of dabigatran the well tolerated single dose of 600 mg provides a safety margin of 4 to the therapeutic dose of 150 mg, which is used in Part 1 of this trial.
Dabigatran-etexilate is a sensitive substrate of intestinal P-glycoprotein (P-gp). The effect of several P-gp inhibitors has been tested in healthy subjects. The strongest effects have been seen with a single dose of verapamil (+180% in dabigatran C_{max}) and with multiple doses of ketoconazole (+150% in dabigatran C_{max} und AUC). The observed increase in dabigatran exposure has been well tolerated by healthy subjects (1160.74 and 1160.101), which is in line with the described safety margin of 4, that has not been exceeded by any P-gp inhibitor. Verapamil and ketoconazole are well characterized inhibitors of P-gp and therefore recommended for testing P-gp inhibition [P12-05791]. Considering that the potential effect of zongertinib on the P-gp substrate dabigatran-etexilate is not expected to exceed the observed strong effect of verapamil or ketoconazole on dabigatran exposure and taking into account the overall safety margin of 4, which has not been exceeded by any P-gp inhibitor, no undue risk to healthy subjects is expected from the combined administration of 150 mg dabigatran-etexilate and zongertinib in this trial.

Risk related to the administration of rosuvastatin (Part 2)
Rosuvastatin is a substrate of OATP1B1/OATP1B3 and BCRP. Rifampicin is a known strong inhibitor of OATP transporters. After combined administration of rifampin and rosuvastatin Lai et al. and Pruesaritanont et al. describe an about 10-13-fold increase of rosuvastatin C_{max} and a 5-fold increase of rosuvastatin AUC [R15-4771], [R17-1790]. This effect size could be confirmed by our cocktail validation trial 0352-2100, in which a dose of 10 mg rosuvastatin has been given together with rifampicin and was well tolerated [c23988236-01]. The administration of 10 mg rosuvastatin in the trial 0352-2082 resulted in a [redacted] In a DDI study

with itraconazole using single doses of 80 mg rosuvastatin Cooper et al report a rosuvastatin plasma exposure of AUC of 571 ng/mL*h and C_{max} of 61 ng/mL, that was well tolerated by healthy subjects [R13-4572] providing a safety margin of [redacted] compared to the exposure after 10 mg rosuvastatin seen in 0352-2082. Specific inhibition of BRCP through the use of fostamatinib caused an approximately 2-fold increase in rosuvastatin C_{max} and AUC [R16-2202s], both of which remains within the dose range of rosuvastatin, which was well tolerated by healthy volunteers.

Risk related to the administration of metformin (Part 2)
Metformin is a substrate of OCT2 and MATE transporters. Cimetidine is a known inhibitor of these transporters. The greatest effect of cimetidine on metformin exposure has been reported by Somogyi et al. The combined administration of cimetidine and metformin increased metformin C_{max} and AUC by 81% and 50%, respectively [R99-0743]. In this trial a very low dose of 10 mg metformin will be given. Considering that therapeutic doses of 1000 mg metformin have been well tolerated by healthy subjects [U13-2366-01], no undue risk is expected from combined administration of metformin and zongertinib in this study.

Risk related to the administration of furosemide (Part 2)
Furosemide is a substrate of OAT1 and OAT3. Probenecid is a known inhibitor of these drug transporters. Smith and Vree observed an approximately 3-fold increase of furosemide AUC after combined administration of probenecid and 40 mg [R17-1861] and 80 mg [R17-1859] furosemide. This effect size could be confirmed by our cocktail validation trial 0352-2100, in which a dose of 1 mg furosemide has been administered together with probenecid [c23988236-01]. In our cocktail validation study 0352-2082 a single dose of 20 mg furosemide has been well tolerated by healthy subjects [c03246006-01]. Assuming dose-proportional kinetics, this would provide a safety margin of 20 to the furosemide dose used in this study (1 mg), which is assessed to be sufficient to cover the potential inhibition of OAT1/ OAT3 by zongertinib.

1.4.3 Discussion

There is significant 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 and current version of the IB [c32836122]) that support multiple dosing of zongertinib as planned for the current trial. In particular, zongertinib has been administered at multiple doses of up to [redacted] 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 [redacted] 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 in-vivo effect of zongertinib on the activity of drug transporters in vivo. The data of this trial are required for an in-depth understanding of the pharmacokinetics of zongertinib. Considering the medical need for an effective and safe treatment of solid tumours with HER2 mutations, the benefit of this trial is assessed to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

For Part 1 of the trial, the main objective is to assess the effect of a single dose of zongertinib on the pharmacokinetics of a single dose of dabigatran-etexilate.

For Part 2 of the trial, the main objective is to assess the effect of zongertinib at steady-state on the pharmacokinetics of a single dose of rosuvastatin, metformin and furosemide (administered as a cocktail).

2.1.2 Primary endpoints

The following PK parameters will be determined for the probe drugs dabigatran, rosuvastatin, metformin and furosemide:

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

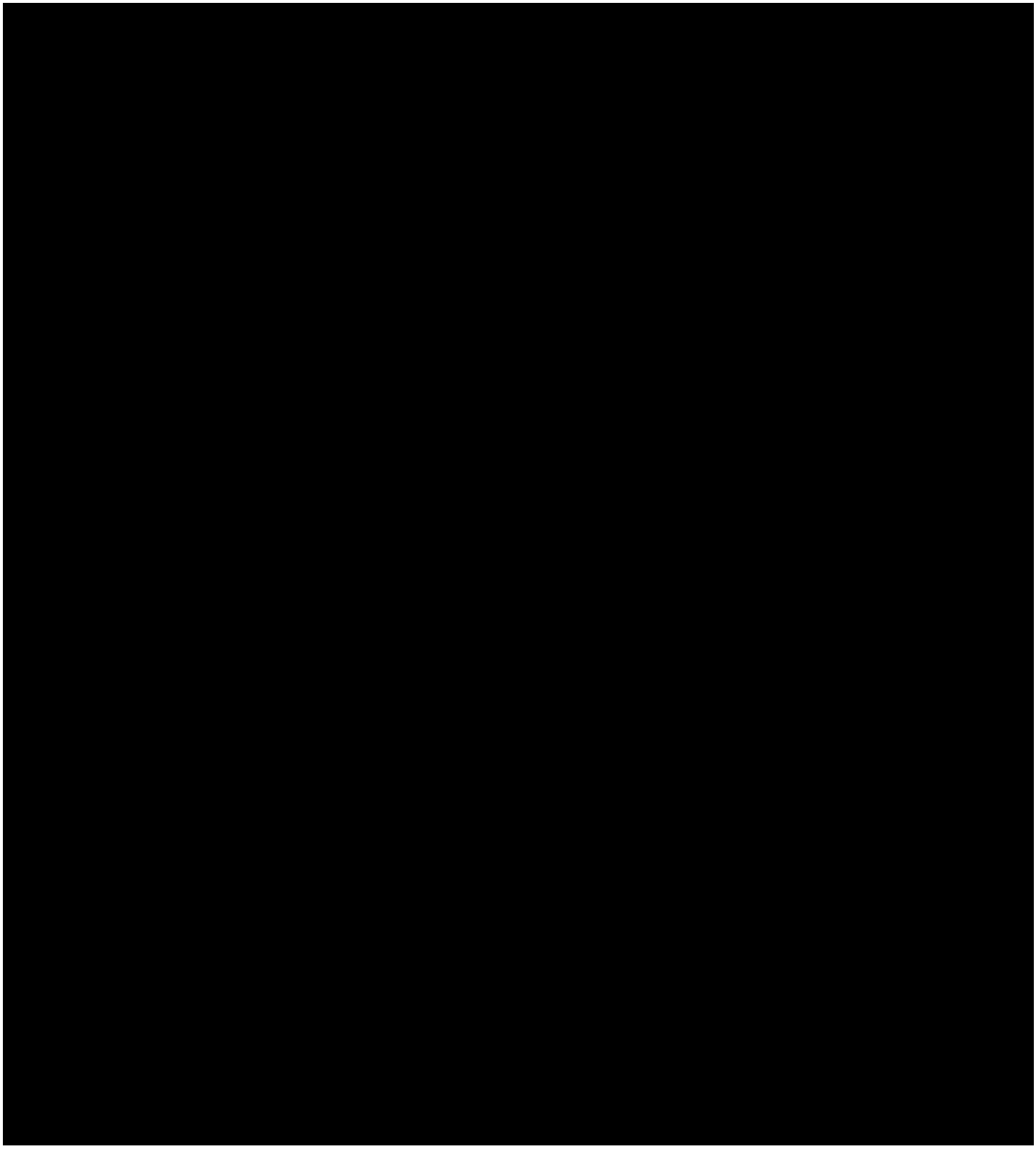
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following PK parameter will be determined for the probe drugs dabigatran, rosuvastatin, metformin and furosemide:

- 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]



2.2.2.2 Safety and tolerability

Safety and tolerability of zongertinib, dabigatran-etexilate, rosuvastatin, metformin and furosemide 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 activities of clinically relevant drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K) by utilizing FDA and EMA recommended probe drugs (P15-06991 and R20-2271). In Part 1 of the trial, the effect of a single dose zongertinib on the kinetics of dabigatran (P-gp) will be investigated. In Part 2 of the trial, the kinetics of rosuvastatin (OATP1B, BCRP), metformin (MATE1, MATE2-K, OCT2) and furosemide (OAT1, OAT3) which are administered as a cocktail (see Section 1.1.2), will be investigated alone and together with zongertinib (dosed to steady state).

The trial will be performed as a non-randomised, open-label, 2-period fixed-sequence crossover trial in healthy male subjects enrolled at a single site in order to compare the test treatments (T) to the reference treatments (R). An overview of the treatments is given below, for details, refer to Section 4.1:

Part 1

Treatment Reference (R)

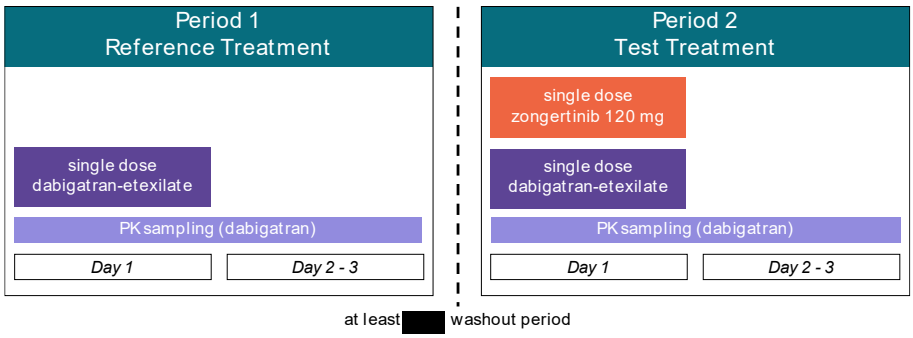
- Administration of 150 mg of dabigatran-etexilate on Day 1 of period 1

Treatment Test (T)

- Administration of 120 mg of zongertinib followed by administration of 150 mg dabigatran-etexilate 30 minutes later on Day 1 of period 2

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

Figure 3.1: 1



Part 2

Treatment Reference (R)

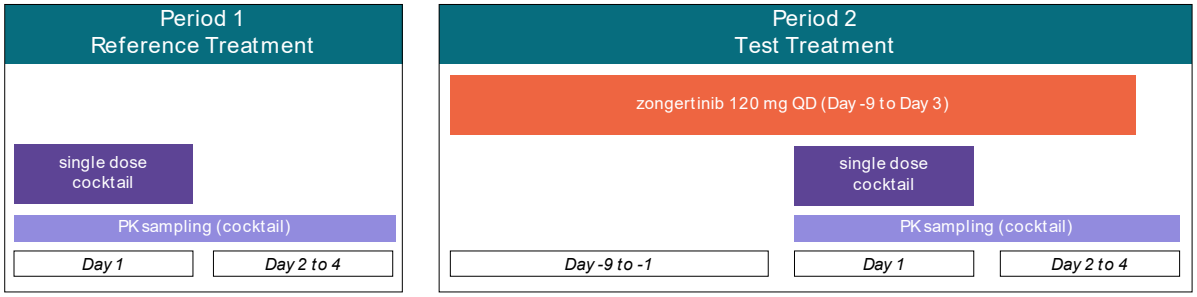
- Administration of cocktail (consisting of 10 mg of rosuvastatin, 10 mg metformin and 1 mg of furosemide) on Day 1 of period 1

Treatment Test (T)

- Administration of 120 mg zongertinib daily from Day -9 to Day 3 (12 days in total) of period 2 & simultaneous administration of cocktail (consisting of 10 mg of rosuvastatin, 10 mg metformin and 1 mg of furosemide) on Day 1 of period 2

A schematic diagram of the trial design is displayed in Figure 3.1: 2 below.

Figure 3.1: 2



Reference treatment will always be followed by the Test treatment in a fixed sequence. In Part 1, periods 1 and 2 are separated by a wash-out interval of at [redacted]. In Part 2, no wash-out interval between periods is required. Part 1 and Part 2 of the trial may be conducted in parallel. All subjects of the respective study part may be treated in one cohort (for discussion of study-associated risks see Section 1.4). In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required.

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 this trial, 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 formulations/treatments [R94-1529].

Because of the [redacted] 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 and urine concentrations of the analytes.

In Part 2, [redacted] by EMA and FDA guidance (P15-06991 and R20-2271).

3.3 SELECTION OF TRIAL POPULATION

It is planned that 32 healthy male subjects will enter the trial (16 subjects in Part 1 und 16 subjects in Part 2 of 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
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days (or within five half-lives, whichever is longer) of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 24 g per day)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTcF intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. 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

25. Subject is an employee of the trial site or financially dependent on the investigator
26. ALT (alanine transaminase), AST (aspartate transaminase), or serum creatinine above upper limit of normal range at screening examination, confirmed by a repeat test; eGFR (estimated glomerular filtration rate according to CKD EPI formula) lower than 80 mL/min/1.73 m^2, 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 1.2.6) the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
6. The subject shows a marked prolongation of the QT/QTc interval during treatment with the study drug(s). This is defined as an absolute increase of the QTcF interval >500 ms or a change from baseline (defined as last predose value) in the QTcF interval of >60 ms, confirmed by a repeat ECG
7. The subject exhibits an AE of severe intensity (CTCAE grade 3 or higher) or a serious adverse event (SAE)

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

For each part of the trial, 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. For each part of the trial, the total number of replacements may not exceed 4. A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Zongertinib will be provided by BI Pharma GmbH & Co. KG, Germany. Dabigatran-etexilate, rosuvastatin, metformin and furosemide will be obtained from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

Trial product 1

Substance:	Zongertinib
Pharmaceutical formulation:	Film-coated tablet ([redacted])
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	60 mg
Posology:	2-0-0
Mode of administration:	Oral
Duration of use:	Single dose in Part 1 period 2; multiple dose QD for 12 consecutive days in Part 2 period 2

Trial product 2

Name:	Pradaxa® 150 mg Hartkapseln
Substance:	Dabigatran-etexilate
Pharmaceutical formulation:	Hard capsule
Source:	Public pharmacy

Unit strength:	150 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	1 single dose treatment per period in Part 1

Trial product 3

Name:	Crestor® 10 mg Filmtabletten
Substance:	Rosuvastatin
Pharmaceutical formulation:	Film-coated tablet
Source:	Public pharmacy
Unit strength:	10 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	1 single dose treatment per period in Part 2

Trial product 4

Name:	MetfoLiquid GeriaSan® 1000mg/5ml Lösung zum Einnehmen
Substance:	Metformin hydrochloride
Pharmaceutical formulation:	Oral solution
Source:	Public pharmacy
Unit strength:	1000 mg / 5 mL
Posology:	0.05 mL – 0 – 0
Mode of administration:	Oral
Duration of use:	1 single dose treatment per period in Part 2

Trial product 5

Name:	Lasix® liquidum
Substance:	Furosemide
Pharmaceutical formulation:	Oral solution
Source:	Public pharmacy
Unit strength:	10 mg/mL
Posology:	0.1 mL – 0 – 0
Mode of administration:	Oral

Duration of use: 1 single dose treatment per period in Part 2

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. [redacted] was selected for the current trial.

Single doses of dabigatran-etexilate 150 mg, rosuvastatin 10 mg, metformin 10 mg and furosemide 1 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

For Part 1 and Part 2 of the trial, there is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The allocation of subjects to Part 1 or Part 2 of the trial will be based on the subjects' availability. Prior to first administration of trial medication the subjects will be allocated to a trial subject number by drawing lots. 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 is a two-period fixed-sequence trial. For Part 1 and Part 2 of the trial, all subjects will receive the reference and test treatment in a fixed order. The treatments to be evaluated are summarised in Table 4.1.4: 1 (for Part 1) and 4.1.4: 2 (for Part 2) below.

Part 1

Table 4.1.4: 1 Dosage and treatment schedule (Part 1)

Treatment	Substance	Formulation	Unit strength (mg)	Dosage	Total daily dose (mg)	Study Visit (V), Day (D)
Reference	Dabigatran-etexilate	tablet	150	1 tablet	150	V2, D1
Test	Zongertinib	tablet	60	2 tablets	120	V3, D1
	Dabigatran-etexilate	tablet	150	1 tablet	150	V3, D1

Administration of dabigatran-etexilate and zongertinib will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer all trial medication as an oral dose together with about 240 mL of non-sparkling 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 dabigatran-etexilate. During the first [redacted] after administration of zongertinib and [redacted] after administration of dabigatran-etexilate 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 [redacted].

Part 2

Table 4.1.4: 2 Dosage and treatment schedule (Part 2)

Treatment	Substance	Formulation	Unit strength (mg)	Dosage	Total daily dose (mg)	Study Visit (V), Day (D)
Reference	Rosuvastatin	film-coated tablet	10	1 tablet	10	V2, D1
	Metformin	oral solution	200/mL	0.05 mL	10	V2, D1
	Furosemide	oral solution	10/mL	0.1 mL	1	V2, D1
Test	Zongertinib	tablet	60	2 tablets	120	V3, D-9 – D3
	Rosuvastatin	film-coated tablet	10	1 tablet	10	V3, D1
	Metformin	oral solution	200/mL	0.05 mL	10	V3, D1
	Furosemide	oral solution	10/mL	0.1 mL	1	V3, D1

Administration of zongertinib 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 -9 to Day -1 in Period 2 subjects are required to fast for at least 10 hours prior and 1 hour post drug administration. Zongertinib will be administered together with about 240 mL of non-sparkling water to subjects who are in a standing position.

Similar to administration of zongertinib the administration of the drug transporter probe cocktail will be performed following on overnight fast (fasting is to start no later than 10 h before the scheduled dosing) and in a standing position. The cocktail will be administered as indicated below:

[redacted]

Thereafter, complete drug administration is assumed. [redacted]. Of note, on Day 1 in period 2 zongertinib is to be administered together with rosuvastatin (only 1 glass of about 240 mL of non-sparkling water is to be used).

The investigator (or authorised designee) will administer trial medication as outlined above. 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 48 h after administration of the cocktail. During the first 4 h after administration of cocktail 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.

Due to the long sampling duration in period 1 of the trial (sampling until Day 4) no wash-out interval between period 1 and period 2 is required in part 2 of the trial.

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.

Dabigatran-etexilate, rosuvastatin, metformin and furosemide

Dabigatran-etexilate, rosuvastatin, metformin and furosemide will be obtained as commercial products by the clinical trial site from a public pharmacy. 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

Dabigatran-etexilate, rosuvastatin, metformin and furosemide 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

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

[redacted] should be avoided from 24 h before each cocktail administration in Part 2 of the trial until the end of urine collection of the respective period.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after administration of dabigatran-etexilate (Part 1) or cocktail (Part 2).

On Day 1 of all periods in Part 1 and Part 2 of the trial from 1 h before (first) drug intake until lunch, fluid intake is restricted to the water administered with the drugs, and an additional 240 mL of water at 2 h and 4 h after latest trial medication administration (mandatory for all subjects). In addition, in part 1, period 1 of the trial, about 240 mL of water will be administered 60 min before dabigatran administration.

In all periods in Part 1 and Part 2, total fluid intake on Day 1 is restricted to 3000 mL from lunch until 24 h post-dose. In Part 2 of the trial on Day 2 of both trial periods (in-house confinement) the total fluid intake is restricted to 4000 mL. Of note, during the days of urine collection, total fluid intake should be at least 1500 mL.

[redacted]) are not

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

[redacted]) are not allowed during in-house stay.

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.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial.

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/or urinary excretion 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. Demographics information includes trial subject`s age on the day of informed consent, subject's sex at birth, and ethnicity and race in order to sufficiently characterize the trial population and [redacted]. 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 according 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] or comparable test system) will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

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

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.

5.2.6 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

A suspected unexpected serious adverse reaction (SUSAR) is an untoward, unexpected and unintended serious response to a study drug. A SUSAR should be considered as unexpected if the nature, seriousness, severity, or outcome of the reaction is not consistent with the reference safety information of the investigational drug (e.g. the investigator's brochure, or the corresponding defined local label such as the summary of product characteristics).

5.2.6.1.3 AEs considered ‘Always Serious’

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

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

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

5.2.6.1.4 Adverse events of special interest

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

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - 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 [redacted] samples will be collected at the time points / time intervals 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). Of note, back-up aliquots and left-over sample volumes from pre-specified analyses may be used for further investigations as outlined below (see Section 5.3.2.3 Further investigations). The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

Sampling and processing for dabigatran

For quantification of dabigatran concentrations in plasma, 2.7 mL of blood will be drawn into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube 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. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples 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. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.
At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, planned sampling time. Further information such as matrix may also be provided. Aliquot names are planned as follows:

- ‘A1 – dabi’ = primary for dabigatran
- ‘A2 – dabi’ = back-up for dabigatran

Sampling and processing for zongertinib

For quantification of zongertinib concentrations in plasma, 2.7 mL of blood will be drawn into a K_2-EDTA-anticoagulant blood drawing tube 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. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples 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. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.
At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, planned sampling time. Further information such as matrix may also be provided. Aliquot names are planned as follows:

- 'A1 – zong' = primary for zongertinib
- 'A2 – zong' = back-up for zongertinib

Sampling and processing for cocktail components

For quantification of rosuvastatin, metformin and furosemide concentrations in plasma 7.5 mL of blood will be drawn into a K_2-EDTA-anticoagulant blood drawing tube (one tube for all 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. [redacted] Six plasma aliquots, one primary for each analyte and three back-ups, will be obtained and stored in polypropylene tubes (back-up aliquots are to be stored in in brown/amber polypropylene tubes – e.g., Sarstedt Screw cap micro tube, 1.5 ml). All aliquots should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 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 three primary aliquots (one for each analyte) may be sent to the analytical laboratory simultaneously. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis. Once the bioanalyst has acknowledged safe arrival of the three primary aliquots, the first back-up aliquot will be transferred to the analytical laboratory. The remaining two back-up aliquots will be transferred to [redacted] to allow for potential analysis of biomarkers, if appropriate.
At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, planned sampling time. Further information such as matrix may also be provided. Aliquot names are planned as follows:

- 'A1 – rosu' = primary for rosuvastatin
- 'A2 – met' = primary for metformin
- 'A3 – furo' = primary for furosemide
- 'BU1' = back-up 1

- ‘BU2’ = back-up 2
- ‘BU3’ = back-up 3

[redacted]

5.3.2.3 Further investigations:

Plasma [redacted] samples (including back-ups and left-over sample volumes from pre-specified analyses) may be used as follows:

- Analysis of endogenous substances [redacted]),
- Further [redacted]

Results of further investigations are of exploratory nature only and are planned to be part of the trial report. The study samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

The tolerance time for ambulatory dosing (and other scheduled procedures) from Day -9 to Day -1 in period 2 of Part 2 of the trial is ± 120 minutes.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 60 min during in-house confinement. During ambulatory visits the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 120 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 [redacted], 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. Beyond the planned time of 48 hours after drug administration the tolerance time of ± 120 min will be allowed for blood sampling times.

In both parts of the trial all subjects may have their dinner together.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Part 1
Each subject is expected to participate in 2 treatment periods (Days -1, 1, 2 and 3 in each period). At least [redacted] will separate drug administrations in the first and second treatment periods.

Trial participants will be admitted to the trial site on Day -1 of each period and will remain under close medical surveillance at the trial site for at least 24 hours following administration of dabigatran-etexilate. 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.

Part 2
Each subject is expected to participate in 2 treatment periods (Days -1, 1, 2, 3 and 4 in period 1 and Days -9 to 4 in period 2). No wash-out between the two periods is required.

Trial participants will be admitted to the trial site on Day -1 of each period and will remain under close medical surveillance at the trial site for at least 48 h following administration of cocktail drugs. 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 [redacted] 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 the study 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

For Part 1 and Part 2 of the trial, the same analyses will be performed if applicable.

The relative bioavailability of probe substrates dabigatran (Part 1), and rosuvastatin, metformin, and furosemide (Part 2) administered alone compared with co-administered zongertinib will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for probe substrates dabigatran (Part 1), and rosuvastatin, metformin, and furosemide (Part 2) and zongertinib (Part 2) will be calculated according to the relevant BI internal procedures.

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

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

Descriptive statistics of PK parameters will be calculated if $N \geq 2$.

7.2.2 Primary endpoint analyses

Primary analyses

The primary endpoints (refer to Section 2.1.2) will be calculated according to the relevant BI internal procedures.

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: subject and treatment. The effect 'subject' 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

[redacted]

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

7.2.3 Secondary endpoint analyses

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

[redacted]

[redacted]

7.2.5 Safety analyses

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

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the 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 1.2.6) 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 group without consideration of time intervals and treatment periods.

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

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No 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 each part of the trial with the aim of ≥ 12 evaluable subjects per trial part, 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.

Part 1

The observed intra-individual coefficient of variation (gCV) for dabigatran-etexilate in previous trials [ ] was roughly for C_{max} and for $AUC_{0-\infty}$.

Part 2

The observed intra-individual coefficient of variation (gCV) for rosuvastatin in previous trials [ ] was roughly for C_{max} and for $AUC_{0-\infty}$.

The observed intra-individual coefficient of variation (gCV) for metformin in a previous trial] was roughly for C_{max} and for $AUC_{0-\infty}$.

The observed intra-individual coefficient of variation (gCV) for furosemide in a previous trial] was roughly for C_{max} and for $AUC_{0-\infty}$.

For various assumptions around the gCV of 17%, Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference) for both parts of the trial. 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 [%]
5	1.05	50	47.61	52.51
5	1.05	100	95.22	105.02
5	1.05	150	142.83	157.53
5	1.05	200	190.44	210.04
10	1.10	50	45.34	55.14
10	1.10	100	90.68	110.28
10	1.10	150	136.02	165.41
10	1.10	200	181.36	220.55
15	1.16	50	43.20	57.88
15	1.16	100	86.39	115.75
15	1.16	150	129.59	173.63
15	1.16	200	172.79	231.50
20	1.21	50	41.18	60.72
20	1.21	100	82.35	121.43
20	1.21	150	123.53	182.15
20	1.21	200	164.70	242.86
25	1.27	50	39.28	63.65
25	1.27	100	78.55	127.31
25	1.27	150	117.83	190.96
25	1.27	200	157.10	254.61

*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.

Assuming an intra-individual gCV of 20% and N≥12 PK evaluable subjects, the trial will achieve with probability 95% two-sided 90% confidence intervals that have a precision of at least 1.21. As an example, for the above stated assumptions and an expected ratio of geometric means (T/R) of 100%, the expected two-sided 90% confidence interval will range from (82.35, 121.43).

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

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU 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 according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

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

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

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

8.2 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 the [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.

SAEs are processed in the global Safety Database and assessed for the company causal relationship as well as the expectedness of the event according to the reference safety information. Individual Case Safety Reports (ICSR) are subsequently reported according to local Regulations. Reporting suspected unexpected serious adverse reactions (SUSARs) to the EMA will be performed via E2B transmission of Individual Case Safety Reports (ICSRs) to the Eudravigilance CT Module within the required timelines.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

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

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

8.6 TRIAL MILESTONES

The first act of recruitment represents the start of the trial and is defined as the date when the first 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 [redacted]

The trial will be conducted at [redacted], under the supervision of the [redacted] 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]. Dabigatran-etexilate, rosuvastatin, metformin and furosemide 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 dabigatran concentrations in plasma will be performed at [redacted].

Analyses of rosuvastatin, metformin and furosemide concentrations in plasma and urine (if applicable) will be performed at [redacted].

If appropriate, analysis of biomarkers in plasma and urine will be performed at [redacted].

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

Data management and statistical evaluation will be done by BI according to BI SOPs.

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

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		17 June 2024
EudraCT number **EU number**		2024-510628-38-00
BI Trial number		1479-0015
BI Investigational Medicinal Product(s)		Zongertinib (BI 1810631)
Title of protocol		The effect of zongertinib on the pharmacokinetics of dabigatran (part 1) and rosuvastatin, metformin and furosemide administered as a cocktail (part 2) in healthy male subjects (a 2-part, open-label, 2-period, fixed-sequence cross-over trial)

Substantial Global Amendment due to urgent safety reasons	☐
Substantial Global Amendment	☒
Non-substantial Global Amendment	☐

Section to be changed		1. Abbreviations and definitions 2. Flowchart 3. 3.1 4. 3.3.3 5. 3.3.4.1 6. 5.2.6.1.2 7. 5.3.2.3 8. 5.6. 9. 6.2.1 10. [redacted] 11. 8.1 12. 8.4 13. 9.1 14. 9.2
Description of change		1. Definition of QTc as QTcF 2. Deletion of references to pharmacogenomic sampling 3. Addition of diagram of trial design 4. Modification of exclusion criteria 10, 13, and 21 as well as addition of 2 new exclusion criteria (25 and 26) 5. Addition of 2 withdrawal criteria for individual subjects 6. Definition of SUSAR

		7. Results from further investigations included in the CTR 8. Deletion of section 'Pharmacogenomic evaluation' 9. Deletion of reference to pharmacogenomic sampling [redacted] 11. Omission of reference to subjects' legally accepted representatives 12. Addition of description of SUSAR reporting 13. Update of SmPC reference for furosemide and dabigatran-etexilate 14. Update of investigator's brochure reference
Rationale for change		1. Upon health authority / IEC request 2. Consideration of IEC (RFI part II) regarding the genotyping ICF could not be sufficiently addressed 3. Upon health authority / IEC request 4. Upon health authority / IEC request 5. Upon health authority / IEC request 6. Upon health authority / IEC request 7. Upon health authority / IEC request 8. Consideration of IEC (RFI part II) regarding the genotyping ICF could not be sufficiently addressed 9. Consideration of IEC (RFI part II) regarding the genotyping ICF could not be sufficiently addressed [redacted] 11. Upon health authority / IEC request 12. Upon health authority / IEC request 13. Upon health authority / IEC request 14. Upon health authority / IEC request

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	17 Jun 2024 16:33 CEST
Verification-Paper Signature Completion		17 Jun 2024 16:46 CEST
Approval-Clinical Program [redacted]		17 Jun 2024 18:23 CEST
Author-Trial Statistician		18 Jun 2024 14:54 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**