Clinical Trial Protocol

	Document Number:	**c29490951-02**
EudraCT No.	2019-004245-33	
BI Trial No.	1405-0015	
BI Investigational Medicinal Product	BI 1323495	
Title	Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1323495 in healthy male subjects (open, single-dose, randomised, two-period crossover design in each trial part)	
Lay Title	A study in healthy men to test the influence of BI 1323495 on the amount of the medicines rosuvastatin and dabigatran in the blood	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: Fax: [redacted]	
Principal Investigator	[redacted] Phone: Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 1))	
Version and Date	Version: 2.0	Date: 22 June 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	22 June 2020
Revision date	Not applicable
BI trial number	1405-0015
Title of trial	Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1323495 in healthy male subjects (open, single-dose, randomised, two-period crossover design in each trial part)
Principal Investigator:	[redacted]
Trial site	
Clinical phase	I
Trial rationale	BI 1323495 has been characterised to be an inhibitor of P-gp, OATP1B1 and BCRP *in-vitro*. This trial will be performed to test the inhibitory effect of BI 1323495 on these drug transporters *in-vivo*. Dabigatran will be used as model substrate for P-gp, rosuvastatin as model substrate for BCRP and OATP1B1.
Trial objectives	To investigate the relative bioavailability of 10 mg rosuvastatin (Part 1) and 150 mg dabigatran (Part 2) given alone and together with [redacted] BI 1323495
Trial design	Randomised, open-label, two period crossover design in each trial part
Trial endpoints:	Part 1 Primary endpoints: $AUC_{0-\infty}$ and C_{max} of rosuvastatin Secondary endpoint: AUC_{0-tz} of rosuvastatin Part 2 Primary endpoints: $AUC_{0-\infty}$ and C_{max} of dabigatran Secondary endpoint: AUC_{0-tz} of dabigatran
Number of subjects **total entered** **each treatment**	 28: 14 in Part 1 and 14 in Part 2 14
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive) genotyped as UGT2B17 extensive metabolizers
Test product 1 **dose** **mode of admin.**	Rosuvastatin (Crestor® 10 mg Filmtabletten) 10 mg (1 tablet) Oral with 240 mL of water after a standardised breakfast

Test product 2	Dabigatran etexilate (Pradaxa® 75 mg Hartkapseln)
dose	75 mg (1 capsule)
mode of admin.	Oral with 240 mL of water after a standardised breakfast
Test product 3	BI 1323495 [redacted]
dose	[redacted]
mode of admin.	Oral with 240 mL of water after a standardised breakfast
Duration of treatment	Part 1 Treatment R1: 10 mg rosuvastatin as single dose on study day 1 of period 1 or 2 Treatment T1: 10 mg rosuvastatin + [redacted] g BI 1323495 as single dose on study day 1 of period 1 or 2 Drug administrations in period 1 and 2 are separated by a wash-out period of at least 7 days. Part 2 Treatment R2: 75 mg dabigatran as single dose on study day 1 of period 1 or 2 Treatment T2: 75 mg dabigatran + [redacted] BI 1323495 as single dose on study day 1 of period 1 or 2 Drug administrations in period 1 and 2 are separated by a wash-out period of at least 7 days.
Statistical methods	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 sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

FLOW CHART PART 1 (ROSUVASTATIN)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[5]	PK blood, Rosuvastatin	PK blood, BI 1323495	[redacted]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[7]
SCR	1	-21 to -1			Screening (SCR)[1]	x[A]				x	x	
1/2 (two identical periods separated by a wash-out of at least 7 days	2/3	1	-2:00	06:00	Admission to trial site[2]	x[B,2,3]	x[2]	x[2,8]		x[2]	x[2]	x[2]
			-0:30	07:30	Standardised breakfast							
			0:00	08:00	Drug administration							
			0:30	08:30				x[8]				
			1:00	09:00			x	x[8]				
			2:00	10:00	240 mL fluid intake		x	x[8]				
			3:00	11:00			x	x[8]				
			3:30	11:30			x					
			4:00	12:00	240 mL fluid intake		x	x[8]				
			4:30	12:30			x					
			5:00	13:00	Lunch[4]		x	x[8]				x
			5:30	13:30			x					
			6:00	14:00			x	x[8]				
			7:00	15:00			x					
			8:00	16:00	Snack (voluntary)[4]		x	x[8]				
			10:00	18:00			x					
			11:00	19:00	Dinner							
			12:00	20:00			x	x[8]				x
		2	24:00	08:00	Breakfast (voluntary)[4]	x[B]	x	x[8]		x	x	X
			28:30	12:30	Lunch (voluntary)[4]							X
			32:00	16:00	Snack (voluntary)							
			34:00	18:00	Discharge from trial site		x					x
		3	47:00	07:00	Ambulatory visit		x					x
		4	71:00	07:00	Ambulatory visit		x					x
		5	95:00	07:00	Ambulatory visit		x					x
FU	4	8 to 15			End of trial (EoTrial) examination[6]	x[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), [redacted] demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. [redacted]
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. Includes urine drug screening and alcohol breath test
4. If several actions are indicated at the same time, the intake of meals will be the last action.
5. Letters A, B, and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3)
6. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
7. 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.
8. Period with administration of test treatment (rosuvastatin + BI 1323495) only

FLOW CHART PART 2 (DABIGATRAN)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[5]	PK blood, Dabigatran	PK blood, BI 1323495	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[7]
SCR	1	-21 to -1			Screening (SCR)[1]	x[A]			x	x	
1/2 (two identical periods separated by a wash-out of at least 7 days	2/3	1	-2:00	06:00	Admission to trial site[2]	x[B,2,3]	x[2]	x[2,8]	x[2]	x[2]	x[2]
			-0:30	07:30	Standardised breakfast						
			0:00	08:00	Drug administration						
			0:30	08:30			x	x[8]			
			1:00	09:00			x	x[8]			
			1:30	09:30			x				
			2:00	10:00	240 mL fluid intake		x	x[8]			
			2:30	10:30			x				
			3:00	11:00			x	x[8]			
			3:30	11:30			x				
			4:00	12:00	240 mL fluid intake		x	x[8]			
			5:00	13:00	Lunch[4]		x	x[8]			x
			6:00	14:00			x	x[8]			
			8:00	16:00	Snack (voluntary)[4]		x	x[8]			
			10:00	18:00			x				
			11:00	19:00	Dinner						
			12:00	20:00			x	x[8]			x
		2	24:00	08:00	Breakfast (voluntary)[4]	x[B]	x	x[8]	x	x	x
			28:30	12:30	Lunch (voluntary)[4]						x
			32:00	16:00	Snack (voluntary)						
			34:00	18:00	Discharge from trial site		x				x
		3	47:00	07:00	Ambulatory visit		x				x
		4	71:00	07:00	Ambulatory visit		x				x
FU	4	8 to 15			End of trial (EoTrial) examination[6]	x[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 and faecal occult blood test), [redacted] demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. [redacted]
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. Includes urine drug screening and alcohol breath test
4. If several actions are indicated at the same time, the intake of meals will be the last action.
5. Letters A, B, and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3)
6. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory (including faecal occult blood test), recording of AEs and concomitant therapies.
7. 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.
8. Period with administration of test treatment (dabigatran + BI 1323495) only

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
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_{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
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after drug administration
BA	Bioavailability
BCRP	Breast cancer resistance protein
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
COPD	Chronic obstructive pulmonary disease
[redacted]	
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450 system
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial

EudraCT	European Clinical Trials Database
FOB	Faecal occult blood
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HMG-CoA	Hydroxymethylglutaryl coenzyme A
HPC	Human Pharmacology Centre
IB	Investigator's brochure
IC	Inhibitory concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
OATP	Organic anion transporting polypeptide
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose
T	Test treatment
[redacted]	

t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
[redacted]	
ULN	Upper limit of normal
[redacted]	
XTC	Ecstasy

1. INTRODUCTION

[redacted]

BI 1323495 has been characterised to be an inhibitor of P-glycoprotein (P-gp), Breast cancer resistance protein (BCRP) and of the Organic anion transporting polypeptide (OATP) 1B1 *in-vitro*. This trial will be performed to investigate whether, and to which extent, BI 1323495 is also *in-vivo* an inhibitor of these drug transporters.

1.1 MEDICAL BACKGROUND

[redacted]

[redacted]

1.2 DRUG PROFILE

1.2.1 BI 1323495

[redacted]

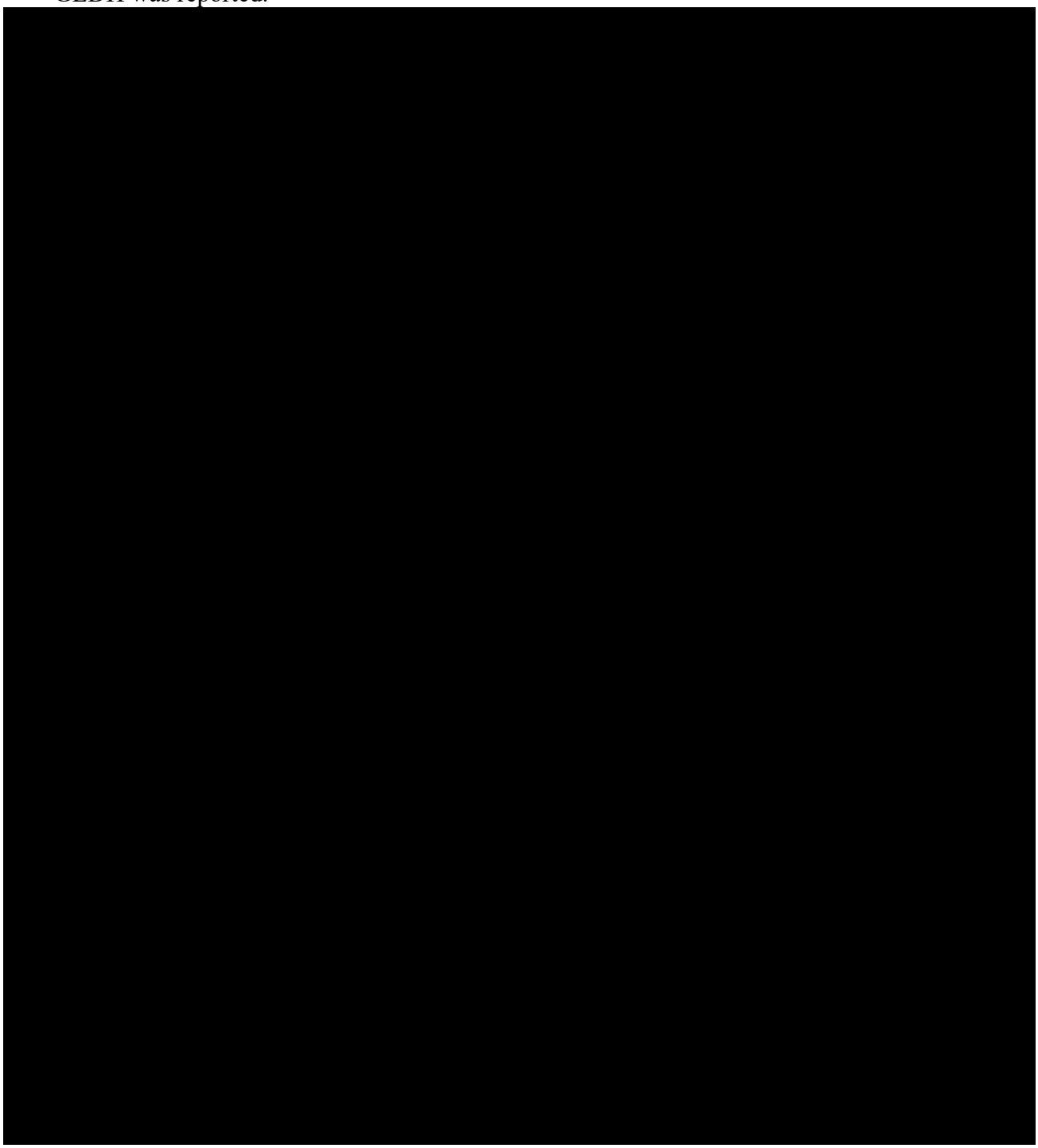
For a detailed description of the BI 1323495 profile, please refer to the current Investigator's Brochure [c21238478-02].

Clinical experience

At the time of preparing this trial protocol, three Phase I studies with administration of single doses of BI 1323495 to healthy male volunteers have been completed, trials 1405-0001 (first-in-man trial), 1405-0007 (relative BA/food effect), and 1405-0009 (drug interaction with itraconazole).

In the single rising dose (SRD) trial 1405-0001, single-dose treatment with up to 600 mg BI 1323495 or placebo was safe and well tolerated. There was no relationship between the occurrence of AEs and dose. Three AEs in subjects receiving BI 1323495 were judged as moderate in intensity, all other AEs were classified as mild. No severe or serious AEs were

reported. The most frequently reported treatment-emergent AE was headache, reported for 6 out of 48 subjects (12.5%) receiving BI 1323495 and 2 out of 15 subjects (13.3%) receiving placebo. The next-most frequently reported treatment-emergent AEs were fatigue and diarrhea, each reported for 2 out of 48 subjects (4.2%) receiving BI 1323495. In one subject receiving 300 mg BI 1323495, a mild (<2-fold ULN) and transient elevation of ALT and GLDH was reported.



For further details on safety and tolerability as well as on pharmacokinetics and biomarker data of the SRD trial refer to the IB (c21238478-02).

In the food effect trial 1405-0007, a randomised 2-way crossover study to compare the relative bioavailability of a single dose of [redacted] BI 1323495 [redacted] administered in the fasted state versus fed state (high-fat), [redacted]

Treatment-emergent AEs were reported for 5 out of the 12 treated subjects (41.7%). Adverse events were reported for 3 out of 12 subjects (25.0%) in the BI 1323495 fasted treatment period and for 2 out of 11 subjects (18.2%) in the BI 1323495 fed treatment period. No subjects were reported with AEs in both treatment periods.

Infections and infestations occurred in 2 of the 12 subjects (16.7%): influenza in 1 subject in the BI 1323495 fasted treatment period, and otitis externa in 1 subject in the BI 1323495 fed treatment period. Headache was reported in 2 of the 12 subjects (16.7%), one in each treatment period. Mouth injury was reported in 1 of the 12 subjects (8.3%) in the BI 1323495 fasted treatment period. The only investigator-defined drug-related AE was mild headache reported for 1 subject [c27223001-01].

Trial 1405-0009, a two-period fixed sequence study in healthy male subjects [redacted] investigated the effects of multiple doses of itraconazole – a strong CYP3A4 and P-gp inhibitor - on the relative bioavailability of a single dose of [redacted] BI 1323495. The clinical part has been completed and data are currently being evaluated. [redacted]

Treatment-emergent AEs were reported for 6 out of the 14 treated subjects (42.9%). Investigator defined drug-related AEs were reported for 3 subjects (21.4%), all of them mild or moderate diarrhea under treatment with itraconazole alone or itraconazole + BI 1323495. No relevant changes in vital signs, ECG, or laboratory parameters were reported.

In summary, single doses of BI 1323495 investigated so far in clinical trials with healthy subjects were safe and well tolerated.

1.2.2 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. In therapy, the initial rosuvastatin dose is 5-10 mg once daily. The daily dose may be increased to up to 40 mg [R19-3033].

After oral administration, maximal rosuvastatin plasma concentrations are reached at ~5 h. Oral bioavailability is ~20%, plasma protein binding is ~90%, and volume of distribution 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 the feces and to a lesser degree, via urine (principally via renal tubular secretion), with a $t_{1/2}$ of 19 h [R19-3033, P14-07833].

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 [R19-3033].

For a more detailed description of the rosuvastatin profile, please refer to the current SmPC for Crestor® 10 mg tablets [R19-3033].

1.2.3 Dabigatran

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Dabigatran is indicated for primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, and for the prevention of ischaemic stroke in patients with atrial fibrillation. The recommended daily dose for primary prevention of venous thromboembolism in orthopaedic surgery is 220 mg with an initial dose of 110 mg prior to the surgery. In patients with moderately impaired renal clearance (30-50 mL/min) the dose should be reduced to 150 mg daily (1 capsule of 75 mg bid) [R18-3151].

The absolute bioavailability of dabigatran following oral administration was approximately 6.5 %. After oral administration in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration, a bi-exponential distribution phase and a terminal elimination half-life of about 11 hours in healthy elderly subjects. Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours. Neither dabigatran etexilate nor dabigatran interacts 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 [R18-3151].

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].

[redacted]

For a more detailed description of the dabigatran profile, please refer to the current SmPC for Pradaxa® 75 mg hard capsules [R19-3343].

1.2.4 Residual Effect Period

The Residual Effect Period (REP) of BI 1323495, rosuvastatin, and dabigatran, i.e. the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present, will be defined as 7 days for each of the 3 products.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on *in-vitro* data BI 1323495 is an inhibitor of P-gp, BCRP, OATP1B1. This trial will be performed to test the inhibitory effect of BI 1323495 on these drug transporters *in-vivo*. Rosuvastatin will be used as a model substrate of BCRP and OATP1B1 (trial Part 1) and dabigatran as a model substrate of P-gp (Part 2).

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the clinical development of BI 1323495. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

Procedure-related risks

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

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

Drug-related risks

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.4, adverse events of special interest.

BI 1323495

[redacted]

In the SRD, food effect, and itraconazole drug interaction trial, single dose administration of up to 600 mg BI 1323495 was well tolerated, with no clinically relevant changes in any safety laboratory parameter, ECG, and vital signs observed (ref. Section 1.2.1). The occurrence of AEs did not appear to be related to BI 1323495 plasma exposure.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when BI 1323495 is administered.

Rosuvastatin

A single dose of 10 mg rosuvastatin has been well tolerated by healthy subjects in several clinical trials [c03246006-01, c08983809-01, c13060859-01].

The combined administration of 10 mg rosuvastatin with the OATP1B1/1B3-inhibitor rifampin in trial 352.2100 increased the rosuvastatin exposure from 6.8 to 77 nmol/L (C_{max}) and from 94 to 321 nmol/L*h ($AUC_{0-\infty}$.). This increase was well tolerated by healthy subjects [c23988236-01]. Comparable effects of rifampin on rosuvastatin exposure have been also described by Lai et al [R17-1790] and by Prueksaritanont et al [R15-4771].

Rifampin is a strong and well characterised inhibitor of OATP1B1/1B3 and is therefore recommended for testing OATP inhibition [R18-0241]. Considering this, it is assumed that the potential effect of BI 1323495 on the OATP-substrate rosuvastatin does not exceed the strong effect of rifampin on rosuvastatin exposure described above. Based on the good tolerability observed in trial 352.2100, no undue risk to healthy subjects is expected from the combined administration of 10 mg rosuvastatin and BI 1323495 in this trial.

Dabigatran

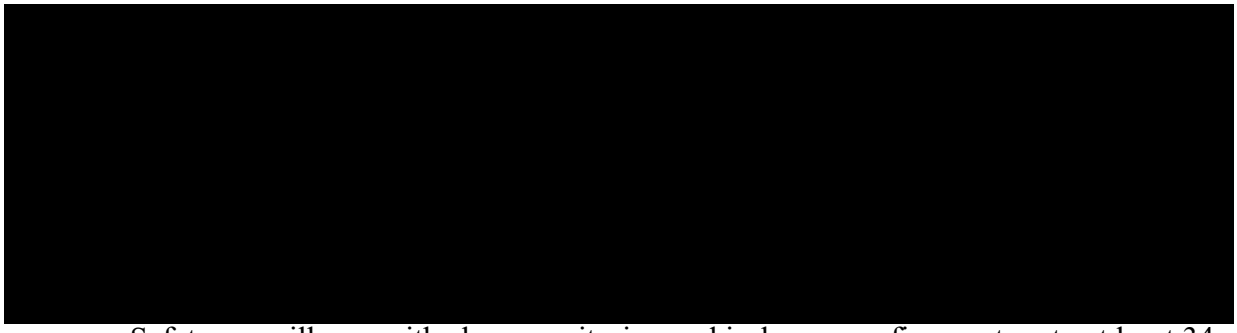
In trial 1160.60 a single dose of 600 mg dabigatran etexilate was well tolerated by healthy subjects [U06-1614-01]. Taking into account the dose-proportional kinetics of dabigatran, the well tolerated single dose of 600 mg provides a safety margin of 4 to the therapeutic dose of 150 mg daily and of 8 to the dose being used in Part 2 of this trial (75 mg).

Dabigatran etexilate is a sensitive substrate of intestinal 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 given 1 hour before dabigatran intake (2.8 fold increase of dabigatran C_{max}) and with multiple doses of ketoconazole (2.5 fold increase of dabigatran C_{max} und AUC) [R19-3343]. The observed increase in dabigatran exposure has been well tolerated by healthy subjects, which is in line with the described safety margin of 4 at a dose of 150 mg, that has not been exceeded by any P-gp inhibitor.

No undue risk to healthy subjects is expected from the combined administration of 75 mg dabigatran etexilate and BI 1323495 in this trial.

Risk mitigation and monitoring

- Careful selection of trial population with compound-specific exclusion criteria (see Section 3.3.3)
- Only healthy subjects will be included in this trial not requiring concomitant medications that could – in principle – trigger combined effects on the pharmacokinetics and / or safety of the investigational drugs.
- Although relevant alterations are not specifically expected, liver function tests including total and direct bilirubin, serum creatinine, urea, electrolyte levels, glomerular filtration rate, and blood coagulation parameters will be monitored as part of the standard safety laboratory assessments (see Section 5.2.3). Subjects with impaired liver, kidney or blood coagulation function will be excluded from participation in this trial. Furthermore, monitoring will be done for any signs of bleeding or bleeding-related adverse events.



- Safety surveillance with close monitoring and in-house confinement up to at least 34 hours after drug administration

Overall assessment

In summary, BI 1323495 has the potential to become an oral treatment for patients with COPD or CF. Based upon preclinical and clinical data with BI 1323495 and clinical information from competitor compounds as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound.

Healthy volunteers are not expected to have any direct benefit from participation in this drug-drug-interaction (DDI) trial.

Considering the medical need of the development of an effective treatment to slow the progression of COPD for patients with this disease and reduce exacerbations in patients with CF, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy male volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate the relative bioavailabilities of 10 mg rosuvastatin (Reference 1, Part 1) and 75 mg dabigatran (Reference 2, Part 2) given alone and together with 300 mg BI 1358894 (Test 1, Test 2) following oral administration.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for rosuvastatin (Part 1) and dabigatran (Part 2):

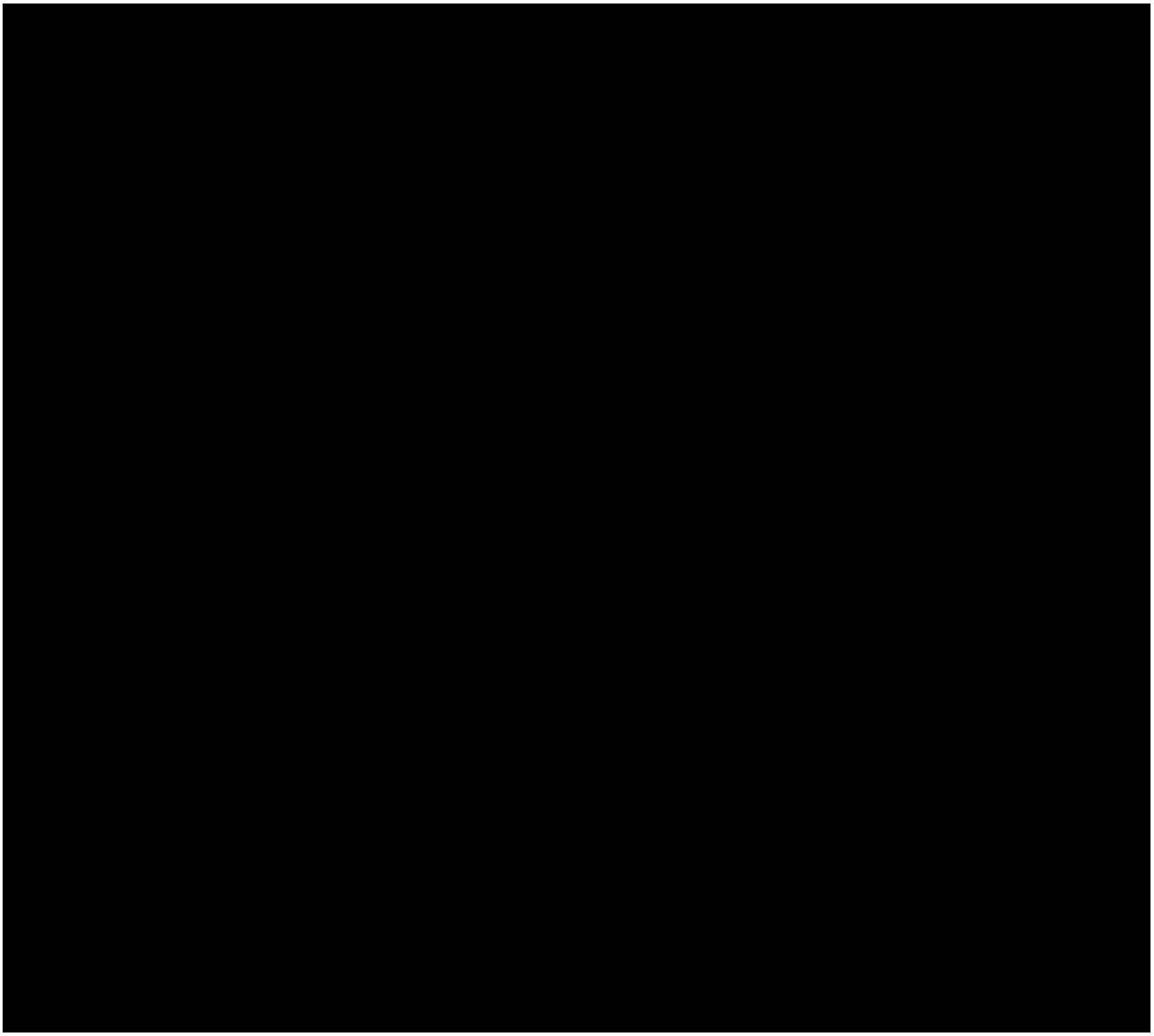
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for rosuvastatin (Part 1) and dabigatran (Part 2):

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

[redacted]



2.2.2.4 Safety and tolerability

Safety and tolerability of the investigational medicinal products will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study comprises two trial parts. Each part follows a randomised, open-label, two-period crossover design in healthy male subjects in order to compare the following test and reference treatments:

Treatments in Part 1

- Reference (R1): 10 mg rosuvastatin as single dose on study day 1 of period 1 or 2
- Test (T1): 10 mg rosuvastatin together with [redacted] BI 1323495 as single dose on study day 1 of period 1 or 2

Treatments in Part 2

- Reference (R2): 75 mg dabigatran etexilate as single dose on study day 1 of period 1 or 2
- Test (T2): 75 mg dabigatran etexilate together with [redacted] BI 1323495 as single dose on study day 1 of period 1 or 2

All treatments will be given after a standardised meal. Drug administrations in period 1 and 2 will be separated by at least 7 days. For details refer to Section 4.1.

An overview of all relevant trial activities is provided in the Flow Chart for Part 1 and Part 2. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

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

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that within each of Parts 1 and 2 of the study, 14 healthy male subjects will enter. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the study because no data on reproductive toxicology of BI 1323495 are available at this time.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

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 prior to admission to the study, in accordance with GCP and local legislation

[redacted]

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 (including positive or missing faecal occult blood test in Part 2)
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. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medications or their excipients)

11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial or compromise the subject's safety by participation in the trial (e. g. use of any drug that could reasonably inhibit platelet aggregation or coagulation, concomitant treatment with systemic cyclosporine, ketoconazole, itraconazole and dronedarone, use of fibrates or drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 24 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. 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
23. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of administration of trial medication until 30 days thereafter. Sperm donation is not allowed from the time point of drug administration until 30 days thereafter.
24. Active clinically relevant bleeding or subjects who in the investigator's judgement are perceived as having an increased risk of bleeding, for example because of blood coagulation disorders, current or recent gastrointestinal ulceration, presence of malignant neoplasms, recent brain or spinal injury, recent brain/spinal/ophthalmic surgery, recent intracranial hemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, major intraspinal or intracerebral vascular abnormalities
25. For Part 1 only: known myopathy, personal or family history of hereditary muscular disorders, or history of muscular toxicity with statins or fibrate; Asian ancestry; hypothyroidism
26. Subjects with any other condition that would preclude administration of rosuvastatin or dabigatran (i.e. contraindicated as per SmPC), such as active liver disease including elevations of serum transaminases exceeding 2 times the upper limit of normal, moderate

or severe renal impairment (creatinine clearance < 60 ml/min based on estimated GFR according to CKD-EPI formula), prosthetic heart valves requiring anticoagulant treatment

27. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or 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, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.4), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
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, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.

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:

1. Failure to meet expected enrolment goals
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated or suspended if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity. Furthermore a trial part will terminated or suspended, if more than two subjects in the respective trial part have drug-related non-serious adverse events of severe intensity or if at least 1 drug-related serious adverse event is reported.
3. Violation of GCP or the CTP impairing the appropriate conduct of the trial-
4. The sponsor decides to discontinue the further development of the investigational product

3.3.5 Replacement of subjects

Subjects withdrawn due to drug related adverse events will not be replaced.

Subjects not completing the trial for other reasons (including non PK evaluable subjects) may be replaced if considered necessary to reach the aim of the trial. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 1323495 has been manufactured by BI Pharma GmbH & Co. KG. Rosuvastatin and dabigatran etexilate will be obtained from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below.

Test product 1:

Name:	Crestor® 10 mg Filmtabletten
Substance:	Rosuvastatin
Pharmaceutical formulation:	Tablet, film-coated
Source:	Public pharmacy
Holder of marketing authorisation:	[redacted]
Unit strength:	10 mg
Posology:	1-0-0
Route of administration:	oral
Duration of use:	2 single doses in Part 1

Test product 2:

Name:	Pradaxa® 75 mg Hartkapseln
Substance:	Dabigatran etexilate
Pharmaceutical formulation:	Hard capsule
Source:	Public pharmacy
Holder of marketing authorisation:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	75 mg
Posology:	1-0-0
Route of administration:	oral
Duration of use:	2 single doses in Part 2

Test product 3:

Substance:	BI 1323495
Pharmaceutical formulation:	Tablet, film-coated
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]-0-0
Route of administration:	oral
Duration of use:	1 single dose in Part 1 and 2

4.1.2 Selection of doses in the trial

Rosuvastatin and dabigatran are used in the low range of standard clinical doses.

As regards BI 1323495, a single dose has been chosen that is expected to cover and potentially exceed the expected therapeutic exposure to investigate the inhibitory effects in a worst-case scenario and to account for potential uncertainties in the prediction of the expected therapeutic exposure.

Trial medication will be administered in the fed state, as this is the expected mode of drug administration for BI 1323495 in the planned indication of CF where a high proportion of patients are on continuous treatment with the CFTR modulator drug ivacaftor that needs to be taken together with a fat containing meal.

[redacted]

4.1.3 Method of assigning subjects to treatment groups

Prior to the start of the study, subjects willing to participate will be recruited to the trial parts according to their temporal availability.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation list will be provided to the trial site in advance. The randomisation procedure is described in Section 7.6.

All subjects of the respective trial part may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical

or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable (for discussion of study-associated risks see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

Each part of this trial follows a two period, two-way crossover design. All subjects will receive the 2 treatments in randomised order (R-T or T-R). The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
Part 1					
Reference (R1)	Rosuvastatin	Tablet	10 mg	1 tablet, single dose	10 mg
Test (T1)	Rosuvastatin	Tablet	10 mg	1 tablet, single dose, together with	10 mg
	BI 1323495	Tablet	[redacted]	[redacted] tablets, single dose	[redacted]
Part 2					
Reference (R2)	Dabigatran etexilate	Capsule	75 mg	1 capsule, single dose	75 mg
Test 2 (T2)	Dabigatran etexilate	Capsule	75 mg	1 capsule, single dose, together with	75 mg
	BI 1323495	Tablet	[redacted]	[redacted] tablets, single dose	[redacted]

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting or 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.

In each treatment, a standardised normal caloric breakfast (e.g., a roll with cheese, ham, and butter) will be served approximately 30 min before drug administration. The subjects must completely consume the meal prior to drug intake and consume no other food.

For restrictions with regard to diet, see Section 4.2.2.2.

Subjects will be kept under close medical surveillance until at least 34 h after drug administration. During the first 5 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The treatments will be separated by a wash-out phase of at least 7 days.

4.1.5 Blinding and procedures for unblinding

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

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

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

4.1.6 Packaging, labelling, and re-supply

BI 1323495

BI 1323495 tablets will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice. 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 EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

Rosuvastatin and dabigatran etexilate

Rosuvastatin tablets and dabigatran etexilate capsules will be obtained by the clinical trial site from a public pharmacy (European commercial goods). The medication 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 local clinical monitor (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the BI 1323495 investigational drugs delivered from the sponsor, provided 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

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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 trial clinical monitor. 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 study days) on the appropriate pages of the CRF.

For Part 1: Drugs which are contraindicated to be co-administered with rosuvastatin (ref. R19-3033), as well as acetylsalicylic acid or other drugs that may inhibit platelet aggregation or coagulation should be avoided during the entire study.

For Part 2: The intake of analgesics known to inhibit cyclooxygenase (e.g. acetylsalicylic acid, ibuprofen and diclofenac) is strongly forbidden starting from 1 week prior to first study drug administration until last PK-sampling. The same refers to the use of anticoagulants such as heparins, heparin ointment, oral anticoagulants (warfarin, rivaroxaban, etc.). Furthermore, concomitant systemic administration of strong P-gp inhibitors such as ketoconazole, itraconazole, cyclosporine, and dronedarone must be avoided during the entire trial.

4.2.2.2 Restrictions on diet and life style

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of each study period is collected.

Alcoholic beverages are not permitted from 24 hours before the first administration of trial medication in Period 1 until the end of trial examination after the last PK sample in Period 2 is collected.

Poppy-seeds containing foods should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug-screen.

Consumption of methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) and smoking are not allowed during in-house confinement.

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

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

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 study.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including.

5.2.2 Vital signs

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

5.2.3 Safety laboratory parameters

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

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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.

Faecal occult blood testing, using an immunochemical test kit for hemoglobin, will be performed by the laboratory at the time points indicated in the Flow Chart for Part 2.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]
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
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	X	X
	Prothrombin time	X	X	X
	INR (International Normalization Ratio)	X	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	--	X
	Creatinine	X	X	X
	GFR/ CKD-EPI[2]	X	X	X
	Bilirubin, Total	X	--	X
	Bilirubin, Direct	X	--	X
	Protein, Total	X	--	X
	C-Reactive Protein (Quant)	X	--	X
Electrolytes	Sodium	X	--	X
	Potassium	X	--	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	X
	Urine Protein (qual)	X	X	X
	Urine Glucose (qual)	X	X	X
	Urine Ketone (qual)	X	X	X
	Urobilinogen (qual)	X	X	X
	Urine Bilirubin (qual)	X	X	X
	Urine RBC/Erythrocytes (qual)	X	X	X
	Urine WBC/Leucocytes (qual)	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

[1] A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 and 3 (for study days and time points refer to Flow Chart)
C: parameters to be determined at Visit 4 (end of trial examination)

[2] Estimated glomerular filtration rate according to CKD-EPI formula (R12-1392)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted], with the exception of drug screening tests. These tests will be performed at the trial site using AccuSign® DOA 10 test or comparable test systems.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (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 study procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the method [redacted] 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 (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

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

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

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

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site.
These events should always be reported as SAEs as described above.

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:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should

make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine the relationship, 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
- Additional arguments amongst those stated before, like 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 as well as the time of onset, end time, and intensity of these events. 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:
  - All AEs (serious and non-serious) and all AESIs
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In 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.

5.2.6.2.3 Information required

All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently assessed as 'chronic' or 'stable', or no further information can be obtained.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis of BI 1323495, rosuvastatin and dabigatran

For quantification of rosuvastatin (Part 1), dabigatran (Part 2), and BI 1323495 concentrations in plasma, 2.7 mL of blood will be drawn for each analyte from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots per analyte 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 90 min, with interim storage of blood samples on ice-bath or refrigerated. 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, subject number, visit, and planned sampling time.

[redacted]

[redacted]

5.5 BIOBANKING

Not applicable.

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

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

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for the assessment of safety (e.g. vital signs, ECG, laboratory tests) will be ± 60 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 venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

[redacted]

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Part 1: Days 1-5 in each period, Part 2: Day 1-4 in each period). In both trial parts at least 7 days will separate drug administrations in the first and second treatment period.

On Day 1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 34 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, assessments will be done in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK and biomarker analysis, refer to Flow Chart, Section 5.3.2 and 5.4.

The safety measurements performed during the treatment periods are specified in Section 5.2 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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 EoTrial Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the relative bioavailability of 10 mg rosuvastatin (Part 1) and 75 mg dabigatran (Part 2) in plasma when given as oral single dose together with a single dose of [redacted] BI 1323495 (Test, T1 and T2) as compared to when given alone as oral single dose (Reference, R1 and R2) on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. Each trial part will be conducted as a two-treatment, two-period, randomised cross-over design, which allows intra-subject comparisons. It will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of rosuvastatin (Part 1) / dabigatran (Part 2) given alone compared with a combined administration with BI 1323495 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.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for rosuvastatin, dabigatran, and BI 1323495 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

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

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

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

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

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

7.3.1 Primary endpoint analyses

Primary analyses

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

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

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

μ = the overall mean,

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

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

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

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

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

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

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

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

Further exploratory analyses

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

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

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.4. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.4) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-36-472).

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

7.6 RANDOMISATION

For each trial part, subjects will be randomised to one of the 2 treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

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

The randomisation list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter 14 subjects in each trial part (accounting for up to 2 dropouts or non PK evaluable subjects). The planned sample size is not based on a power calculation but is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for rosuvastatin ranged from from 9.0 to 19.7% for AUC and from 14.1 to 28.4% for C_{max}, whereas the observed intra-individual coefficient of variation (gCV) for dabigatran were ~20% for C_{max} as well as for AUC in previous trials [c08983809-01, c13060859-01, U09-3249-02].

For various assumptions around the gCV, Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals with 95% tolerance probability are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2x2 crossover trial *(N=12)*

gCV [%]	Precision upper CI limit / relative BA estimate	Ratio [%]*	Lower CI limit [%]	Upper CI limit [%]
10.0	1.105	100	90.50	110.50
10.0	1.105	150	135.74	165.75
10.0	1.105	200	180.99	221.00
20.0	1.219	100	82.01	121.93
20.0	1.219	150	123.02	182.89
20.0	1.219	200	164.03	243.86
30.0	1.342	100	74.54	134.16
30.0	1.342	150	111.80	201.25
30.0	1.342	200	149.07	268.33

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

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 3.5.1.

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.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

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

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

8.3.1 Source documents

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

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

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™ (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™ 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 must retain the source and essential documents (including ISF) according to the local requirements valid at the time of the end of the trial.

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

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

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

Samples and/or data may be transferred to third parties and other countries as specified in the ICF.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for 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 EC/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 patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] of [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Clinical Trial 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 Clinical Trial Managers, Clinical Research Associates, and investigators of participating trial sites

The trial medication BI 1323495 will be provided by the [redacted]. Rosuvastatin and dabigatran supplies will be obtained from a public pharmacy in Germany.

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

Analyses of BI 1323495, rosuvastatin and dabigatran concentrations in plasma will be done by [redacted].

[redacted]

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

Data management and statistical evaluation will be done by BI or a contract research organisation appointed 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		22 June 2020
EudraCT number **EU number**		2019-004245-33
BI Trial number		1405-0015
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1323495 in healthy male subjects (open, single-dose, randomised, two-period crossover design in each trial part)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1) Flow Chart Part 1 2) Section 3.3.3 Exclusion Criteria 3) Section 8.1 Trial Approval, Subject Information, Informed Consent
Description of change		1) Typo corrected 2) Exclusion criterion no. 27 introduced (exclude subjects with positive SARS-CoV-2 testing) 3) Specified that separate informed consent for SARS-CoV-2 testing will be used.
Rationale for change		Additional measures for risk reduction during COVID-19 pandemic described

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-02

Title: Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1323495 in healthy male subjects (open, single-dose, randomised, two-period crossover design in each trial part)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	23 Jun 2020 09:57 CEST
Approval-Team Member Medicine		23 Jun 2020 10:00 CEST
Approval-Clinical Pharmacokinetics		23 Jun 2020 10:11 CEST
Author-Trial Statistician		23 Jun 2020 12:30 CEST
Approval-Therapeutic Area [redacted]		23 Jun 2020 12:37 CEST
Verification-Paper Signature Completion		25 Jun 2020 10:38 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed