Clinical Trial Protocol

	Document Number:	**c27867536-02**
EudraCT No.	2019-002763-10	
BI Trial No.	1402-0009	
BI Investigational Medicinal Product	BI 1358894	
Title	Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1358894 in healthy male subjects (open, single-dose, fixed sequence, two-period crossover design in each trial part)	
Lay Title	A study in healthy men to test the influence of BI 1358894 on the amount of the medicines rosuvastatin and dabigatran in the blood	
Clinical Phase	I	
Clinical Trial Leader	Phone: / Fax:	
Principal Investigator	Phone: / Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 1))	
Version and Date	Version: 2.0	Date: 28 August 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	22 July 2019
Revision date	28 August 2019
BI trial number	1402-0009
Title of trial	Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1358894 in healthy male subjects (open, non-randomised, single-dose, two-period crossover design in each trial part)
Principal Investigator	
Trial site	
Clinical phase	I
Trial rationale	BI 1358894 has been characterised to be an inhibitor of P-gp, OATP1B1/1B3 and BCRP in-vitro. This trial will be performed to test the inhibitory effect of BI 1358894 on these drug transporters in-vivo. Dabigatran will be used as model substrate for P-gp, rosuvastatin as model substrate for BCRP and OATP1B1/1B3.
Trial objective	To investigate the relative bioavailability of 10 mg rosuvastatin (Part 1) and 150 mg dabigatran (Part 2) given alone and together with 200 mg BI 1358894
Trial design	Part 1: non-randomised, open-label, two period crossover design Part 2: non-randomised, open-label, two period crossover design
Trial endpoints:	Part 1 Primary endpoints: $AUC_{0-\infty}$ and C_{max} of rosuvastatin Secondary endpoints: AUC_{0-tz} of rosuvastatin Part 2 Primary endpoints: $AUC_{0-\infty}$ and C_{max} of dabigatran Secondary endpoints: AUC_{0-tz} of dabigatran
Number of subjects **total entered** **each treatment**	 28 14 in Part 1, 14 in Part 2 In case more than 2 subjects do not complete the respective trial part according to protocol, up to 6 replacement subjects may be included into each trial part. Thus, a maximum of 20 subjects may participate in each trial part.
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)
Trial product 1	Crestor® 10 mg Filmtabletten
dose	1 tablet (=10 mg rosuvastatin)
mode of admin.	Oral with 240 mL of water after a high-fat, high-calorie breakfast
Trial product 2	Pradaxa® 150 mg Hartkapseln
dose	1 capsule (= 150 mg dabigatran etexilate)
mode of admin.	Oral with 240 mL of water after a high-fat, high-calorie breakfast
Trial product 3	BI 1358894 film-coated tablets;
dose	
mode of admin.	Oral with 240 mL of water after a high-fat, high-calorie breakfast
Duration of treatment	Part 1 (all treatments are given as single dose) Period 1: 1 tablet Crestor® 10 mg Filmtabletten Period 2: 1 tablet Crestor® 10 mg Filmtabletten together with 2 tablets BI 1358894 Treatments are separated by a wash-out period of at least 7 days between study drug administrations. Part 2 (all treatments are given as single dose) Period 1: 1 capsule Pradaxa® 150 mg Hartkapseln Period 2: 1 capsule Pradaxa® 150 mg Hartkapseln with 2 tablets BI 1358894 Treatments are separated by a wash-out period of at least 7 days between study drug administrations.
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 subjects and treatment. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART – PART 1

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK rosuvastatin	PK BI 1358894 and metabolite[7]	PK	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	-21 to -1			Screening (SCR)[1]	x				x	
	2/3	1	-3:00	05:00	Admission to trial site	x[2,5]	x[2]	x[2]	x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast						
			0:00	08:00	Drug administration						
			1:00	09:00			x		x		
			2:00	10:00	240 mL fluid intake		x		x		
			3:00	11:00			x	x	x		
			3:30	11:30			x				
			4:00	12:00	240 mL fluid intake		x		x		
			4:30	12:30			x				
			5:00	13:00			x	x	x		
			5:30	13:30			x				
			6:00	14:00	240 mL fluid intake, lunch[3]		x		x		x
			7:00	15:00			x	x			
			8:00	16:00	Snack (voluntary)[3]		x		x		
			10:00	18:00			x				
			11:00	19:00	Dinner						
			12:00	20:00			x		x		x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site		x		x	x	x
			34:00	18:00	Ambulatory visit		x				x
		3	48:00	08:00	Ambulatory visit		x				x
		4	72:00	08:00	Ambulatory visit		x				x
		5	96:00	08:00	Ambulatory visit		x				x
FU	4	8 to 21			End of trial (EoTrial) examination[4]	x				x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of the trial the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Only in period 2 (Treatment Test)

FLOW CHART – PART 2

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK dabigatran	PK BI 1358894 and metabolite [7]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x			x	
	2/3	1	-3:00	05:00	Admission to trial site	x[2,5]	x[2]	x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast					
			0:00	08:00	Drug administration					
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x			
			2:30	10:30			x			
			3:00	11:00			x	x		
			3:30	11:30			x			
			4:00	12:00	240 mL fluid intake		x			
			5:00	13:00			x	x		
			6:00	14:00	240 mL fluid intake, lunch[3]		x		x	x
			7:00	15:00				x		
			8:00	16:00	Snack (voluntary) [3]		x			
			10:00	18:00			x			
			11:00	19:00	Dinner					
			12:00	20:00			x			x
		2	24:00	08:00	Breakfast (voluntary) [3], discharge from trial site		x		x	x
			34:00	18:00	Ambulatory visit		x			x
		3	48:00	08:00	Ambulatory visit		x			x
		4	72:00	08:00	Ambulatory visit		x			
FU	4	8 to 21			End of trial (EoTrial) examination[4]	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, fecal occult blood test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory (including fecal occult blood test), recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Only in period 2 (Treatment Test)

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism and Elimination/Excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	attributable, legible, contemporaneous, original, accurate
ALT	Alanine amino transferase
ANOVA	Analysis of variance
aPTT	Aktivierte partielle Thromboplastinzeit
AST	Aspartate amino transferase
AUC0-24	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24h
AUC0-∞	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC0-tz	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability/Bioanalysis
BCRP	Breast cancer resistance protein
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline personality disorder
CA	Competent authority
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450 system
DG	Dose group

DILI	Drug induced liver injury
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECT	Electro-convulsive therapy
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
FDA	Food and Drug Administration
FIM	First in man
FOB	Fecal Occult Blood test
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GFR	Glomerular Filtration Rate
GOT	Global Operation Team
GPT	Glutamic pyruvic transaminase
HMG-CoA	hydroxymethylglutaryl coenzyme A
HPMC	HydroxyPropyl Methocellulose
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
INR	International Normalization Ratio
IPD	Important protocol deviation
IQRM	Integrated Quality and Risk Management
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
OATP	Organic anion transporting polypeptide
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PR	Pulse rate
q.d.	Quaque die, once daily

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
RA	Accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval τ
REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SRD	Single-rising dose
T	Test product or treatment
TCPK	Trial Clinical Pharmakokineticist
TRPC	transient receptor potential cation channel
TS	Treated Set
TSAP	Trial statistical analysis plan
TT	Thromboplastin time
tz	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	women of child bearing potential

1. INTRODUCTION

Boehringer Ingelheim (BI) is developing BI 1358894, an oral, small-molecule inhibitor of a transient receptor potential cation channel, subfamily C, members 4 and 5 (TRPC 4/5) for major depressive disorder (MDD). BI 1358894 has been characterised to be an inhibitor of P-glycoprotein (P-gp), Breast cancer resistance protein (BCRP) and of the Organic anion transporting polypeptides (OATP) 1B1 and 1B3 in-vitro. This trial should investigate, whether BI 1358894 is also in-vivo an inhibitor of these drug transporters.

1.1 MEDICAL BACKGROUND

Major depressive disorder is a debilitating disease characterised by low mood and often by low self-esteem, low energy, and a loss of interest. It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the National Institute of Mental Health funded STAR*D trial of >4000 patients with nonpsychotic depression, about 30% of the patients did not reach remission after 4 different medications [P06-11895] and continued to experience residual symptoms [R16-5475] that significantly impacted the patients' quality of life [R06-2872]. When monotherapy is insufficient, clinicians employ different augmentation strategies including add-on treatment with lithium or atypical antipsychotics. When augmentation strategies also fail, convulsive therapies such as electro-convulsive therapy may be used.

Borderline personality disorder (BPD) is a chronic mental disorder with an estimated prevalence of around 2% in the general community [R16-5476] and severely impaired quality of life [R16-5474]. The main symptom clusters of BPD include impulsive-behavioural dyscontrol, cognitive-perceptual symptoms, disturbed interpersonal relations, and affective instability. Patients with BPD have high rates of deliberate self-harm and a rate of completed suicide that is 50 times higher than in the general population [R16-5477]. Even the presence of a single diagnostic feature of BPD is predictive for poor functioning and psychiatric illness burden [R16-5483]. Treatment guidelines recommend psychotherapy as the mainstay of treatment, but pharmacotherapy is commonly used as an adjunctive, symptom-targeted component of treatment. However, no drug is approved for the treatment of BPD.

TRPC4 and TRPC5 form ion channels that are involved in the regulation of neuronal excitability. They are most highly expressed in the amygdala, frontal cortex, hippocampus, and hypothalamus [R15-3888, R16-5350], which are involved in modulation and processing of emotion and affect.

It is hypothesized that in patients with affective disorders, an overactive amygdala is a major contributor to attentional bias to negative stimuli, pessimistic thoughts, and anxiety [R16-5473] and there is growing evidence supporting the role of amygdala in the emotion processing disturbances observed in patients with BPD [R16-5472].

1.2 DRUG PROFILE

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 [R17-2886].

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 [R17-2886], [P14-07833].

In therapy, the initial rosuvastatin dose is 5-10 mg once daily (q.d.). The daily dose may be increased to up to 40 mg [R17-2886].

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 [R17-2886].

For a more detailed description of the rosuvastatin profile, please refer to the current SmPC [R19-1574].

1.2.3 Dabigatran

Pharmacokinetics

Following single dose administration in healthy volunteers, the pharmacokinetic profile of dabigatran is characterized by maximum plasma concentration at approximately 1-2 hours after oral administration of dabigatran etexilate, a biexponential distribution phase and a terminal elimination half-life of about 8-10 hours. With b.i.d. dosing the steady state is attained within 3 days, and C_{max} at steady state is about 30% higher than after the first dose. Dabigatran plasma concentrations and the pharmacokinetic parameters C_{max} and AUC increased in a dose proportional manner after oral administration of the prodrug dabigatran etexilate and after intravenous infusion of dabigatran. The pharmacodynamic parameters aPTT, INR, ECT, and TT show close correlation with dabigatran plasma concentrations.

The bioavailability of the dabigatran in the capsule formulation is about 6.5%. After treatment with the proton pump inhibitor pantoprazole (increased gastric pH) bioavailability is reduced by approximately 20-30%. Co-administration with food results in delay of C_{max} from 2 to 4 hours; there is no consistent effect on total exposure.

Neither dabigatran etexilate nor dabigatran 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. However this effect could be significantly reduced by staggered administration of the P-gp inhibitor.

Due to rapid hydrolisation only small amounts of dabigatran etexilate reach systemic circulation. Thus, modulators of P-gp can affect intestinal absorption of dabigatran etexilate, but not its further disposition. Therefore, the staggered administration of a P-gp inhibitor at the time point of maximum dabigatran concentration (t_{max}) will cause a significantly lower increase in dabigatran bioavailability, because a great part of the compound has been already absorbed from the intestinal lumen. This effect has been proven for the P-gp inhibitors dronedarone [U11-2448-01] and verapamil [U09-1052-01], when given 2 h after dabigatran.

Co-administration of the suggested P-gp inhibitor clarithromycin did not meaningfully affect the PK of dabigatran. Rifampicin, an inducer of P-gp reduced the bioavailability of free and total dabigatran. Conversely, the PK of co-administered P-gp substrates like digoxin or the inhibitors (clarithromycin, verapamil, quinidine, ketoconazole, amiodarone) was not affected by dabigatran etexilate confirming the *in vitro* results that neither dabigatran etexilate nor its intermediate metabolites or the active moiety dabigatran are inhibitors of P-gp.
In the RE-LY study, the effect of concomitant use of verapamil, amiodarone or all potent P-gp inhibitors on trough and 2 h dabigatran plasma concentrations was assessed descriptively. In RE-LY, a greater than 20% increase was not observed when amiodarone, verapamil, diltiazem or any strong P-gp inhibitor was co-administered. These findings were qualitatively in agreement to the results of the phase I studies though the magnitude of the effect was on average much lower in RE-LY. Accordingly, the difference in event rates (i.e., major or any bleeding) and efficacy endpoints (stroke, SEE) in patients receiving or not receiving verapamil, amiodarone or diltiazem were not pronounced and not clearly different from patients treated concomitantly with warfarin and a P-gp inhibitor [U09-3249-02].

Safety

Dabigatran and dabigatran etexilate were well tolerated by healthy subjects. Overall, more than 1000 healthy volunteers have been included in phase I trials with dabigatran etexilate.

Adverse events were few, mild, and included primarily hematoma at the venipuncture site or need for prolonged compression for hemostasis on venous catheter removal at higher doses. Major bleedings were not observed in the Phase I trials. At the highest dose of dabigatran etexilate studied in humans, 400 mg three times daily as oral solution, 6 of 8 subjects reported mild bleeding such as hematoma or prolonged bleeding at a venous puncture site, or gingival bleeding [U00-1856].

In a further Phase I study [U06-1614-01] single doses of 600 mg, 750 mg, and 900 mg HPMC capsules were planned to be administered to find out the highest tolerable dose. After 600 mg a 2-fold to 3-fold increase in the main coagulation parameter aPTT was achieved at 2 to 4 h post dose. The only observed AEs were transient abdominal discomfort and a mild

phlebitis at the puncture site in one subject each. The dose levels 750 mg and 900 mg were not performed because a full therapeutic effect was already achieved with 600 mg.

For a more detailed description of the dabigatran profile, please refer to the current SmPC [R18-2734].

1.2.4 Residual Effect Period

Based on an effective half-life of 33 h the Residual Effect Period (REP) of BI 1358894 has been determined to be 7 days. The REP for rosuvastatin and dabigatran is approximately 6 and 3 days, respectively. This is the period after the last dose with relevant measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on *in-vitro* data BI 1358894 is an inhibitor of P-gp, BCRP, OATP1B1/1B3. This trial will be performed to test the inhibitory effect of BI 1358894 on these drug transporters *in-vivo*. Dabigatran will be used as a model substrate of P-gp (Part 2) and rosuvastatin as a model substrate of BCRP and OATP1B1/1B3 (Part 1).

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 successful clinical development of BI 1358894 to improve the treatment of patients with major depressive disorder and borderline personality disorder. 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.

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.

Risk related to the administration of rosuvastatin (Part 1)

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 study 352.2100 increased the rosuvastatin exposure from 6.8 to 77 nmol/L (C_{max}) and from 94 to 321 nmol/L*h ($AUC_{0-inf.}$). 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 [P12-05791]. Considering this it is assumed, that the potential effect of BI 1358894 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 study 352.2100 no undue risk to healthy subjects is expected from the combined administration of 10 mg rosuvastatin and BI 1358894 in this trial.

Risk related to the administration of dabigatran (Part 2)

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

Dabigatran etexilate is a sensitive substrate of intestinal P-glycoprotein (P-gp). The effect of several P-gp inhibitors has been tested in healthy subjects. The strongest effects have been seen with a single dose of verapamil (+180% in dabigatran C_{max}) and with multiple doses of ketoconazole (+150% in dabigatran C_{max} und AUC). The observed increase in dabigatran exposure has been well tolerated by healthy subjects (1160.74 and 1160.101), which is in line with the described safety margin of 4, that has not been exceeded by any P-gp inhibitor.

Verapamil and ketoconazole are well characterized inhibitors of P-gp and therefore recommended for testing P-gp inhibition [P12-05791]. Considering that the potential effect of BI 1358894 on the P-gp substrate dabigatran etexilate does not exceed the observed strong effect of verapamil or ketoconazole on dabigatran exposure and taking into account the overall safety margin of 4, which has not been exceeded by any P-gp inhibitor, no undue risk to healthy subjects is expected from the combined administration of 150 mg dabigatran etexilate and BI 1358894 in this trial.

Drug-induced liver injury (DILI)

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.

Overall assessment

Considering the well characterised safety profile of the marketed drugs dabigatran and rosuvastatin, the safety profile observed so far with BI 1358894 and taking into account the planned single dose administration of all compounds the sponsor feels that the risk to participating subjects are minimised and justified when compared to the potential benefit that a successful clinical development of BI 1358894 could provide to the treatment of major depressive disorder and borderline personality disorder.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of rosuvastatin (Reference 1, Part 1) and dabigatran (Reference 2, Part 2) given alone and together with BI 1358894 (Test 1, Test 2) following oral administration.

2.1.2 Primary endpoints

In Part 1 the following pharmacokinetic parameters will be determined for rosuvastatin:

- $AUC_{0-\infty}$ (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)

In Part 2 the following pharmacokinetic parameters will be determined for dabigatran:

- $AUC_{0-\infty}$ (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

In Part 1 the following pharmacokinetic parameter will be determined for rosuvastatin:

- 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)

In Part 2 the following pharmacokinetic parameter will be determined for dabigatran:

- 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)

2.2.2.4 Safety and tolerability

Safety and tolerability of rosuvastatin, dabigatran and BI 1358894 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 consists of 2 trial parts. Each part follows a non-randomised, open-label, two-period crossover design with a fixed sequence in healthy male subjects in order to compare the following test and reference treatments:

Treatments in Part 1

- Reference (R1): tablet Crestor® Filmtabletten [rosuvastatin]
- Test (T1): tablet Crestor® Filmtabletten together with tablet BI 1358894

Treatments in Part 2

- Reference (R2): capsule Pradaxa® Hartkapseln [dabigatran etexilate]
- Test (T2): capsule Pradaxa® Hartkapseln together with tablet BI 1358894

All treatments will be given after a high-fat high-calorie breakfast. In both trial parts the Reference treatment will always be followed by the Test treatment in a fixed sequence. The treatment periods are separated by a wash-out phase of at least 7 days between the two drug administrations.

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

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL 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].

Because of the long terminal half-life of BI 1358894 (> 100 h), a fixed-sequence design was selected, in which BI 1358894 will be administered in the second study period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration.

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 14 healthy male subjects each will enter either Part 1 or Part 2 of the study. They will be recruited from the volunteers' pool of the trial site. In case more than 2 subjects do not complete the respective trial part according to protocol, up to 6 replacement subjects may be included into each trial part. Thus, a maximum of 20 subjects might participate in each trial part.

Only male subjects will be included in the study because no data on reproductive toxicology 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

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, retest allowed)
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 medication or its excipients)

11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
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 prolongation of 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.

    The following study specific exclusion criteria apply:

24. Known hypersensitivity to rosuvastatin or dabigatran
25. Active liver disease including elevations of serum transaminases exceeding 2 times the upper limit of normal
26. Moderate or severe renal impairment (creatinine clearance < 60 ml/min based on estimated GFR according to CKD-EPI formula
27. Known myopathy
28. Concomitant treatment with systemic cyclosporine, ketoconazole, itraconazole and dronedarone or use of fibrates
29. Hypothyroidism
30. Personal or family history of hereditary muscular disorders
31. History of muscular toxicity with another statin or fibrate
32. Asian ancestry
33. Known active bleeding

34. Concomitant treatment with other anticoagulants (e.g. unfractionated heparin, low molecular weight heparins, heparin derivatives, oral anticoagulants)
35. Prosthetic heart valves
36. Subjects who in the investigator's judgement are perceived as having an increased risk of bleeding, for example because of: 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

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

3.3.5 Replacement of subjects

In case more than 2 subjects do not complete the respective trial part according protocol for any reason (including non PK evaluable subjects), the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. The maximum number of replacement subjects is 6 per trial part. Thus the total number of exposed subjects will not exceed 20 in each trial part. A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 1358894 has been manufactured, packed and labelled by BI Pharma GmbH & Co. KG. Rosuvastatin and dabigatran will be obtained from a public pharmacy.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the trial product 1 are given below:

Name:	Crestor® Filmtabletten
Substance:	rosuvastatin
Pharmaceutical formulation:	tablet
Source:	
Unit strength:	
Posology:	
Route of administration:	oral
Duration of use:	2 single doses in Part 1

The characteristics of the trial product 2 are given below:

Name:	Pradaxa® Hartkapseln
Substance:	dabigatran etexilate
Pharmaceutical formulation:	hard capsule
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Posology:	
Route of administration:	oral
Duration of use:	2 single doses in Part 2

The characteristics of the trial product 3 are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Posology:	
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 standard clinical doses.

In the FIM study 1402-0001 the administration of BI 1358894 (fed conditions) resulted in an exposure of C_{max} = and AUC_{0-24} = (see 1.2.1). For the current trial this dose has been chosen to cover and to exceed the expected therapeutic exposure ($C_{max,ss}$ of and an AUC_{ss} of [c10354149]) to investigate the inhibitory effects in a worst-case scenario and to account for potential uncertainties in the prediction of the expected therapeutic exposure.

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in each trial part, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a study subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2. Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects of the respective study 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 trial part follows a two period crossover design. All subjects will receive the 2 treatments in a fixed sequence (with treatment Reference is always followed by treatment Test). The treatments to be evaluated are outlined in the tables below:

Table 4.1.4: 1 Dosage and treatment schedule in Part 1

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R1 (Reference)	rosuvastatin	tablet		tablet, single dose	
T1 (Test)	rosuvastatin	tablet		tablet, together with	
	BI 1358894	tablet		tablet	

Table 4.1.4: 2 Dosage and treatment schedule in Part 2

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R2 (Reference)	dabigatran	hard capsule		capsule, single dose	
T2 (Test)	dabigatran	hard capsule		capsule, together with	
	BI 1358894	tablet		tablets	

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 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 period, a high-fat, high-calorie breakfast has to be consumed by the subjects within 30 min prior to the planned study drug administration. The composition of the standard high-fat, high-calorie breakfast is detailed in Table 4.1.4: 3; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 3 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 6 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.

4.1.6 Packaging, labelling, and re-supply

Rosuvastatin and dabigatran will be obtained from a public pharmacy. Both drugs will be dispensed out of the original, unmodified packages.

BI 1358894 will be provided by BI. It 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.

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 investigational drugs delivered from the sponsor 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 given 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 all unused or partially used drug supplies have been returned by the clinical trial subject and 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.

Part 2 only: 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 (heparins, heparin ointment).

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 6 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (see Table 4.1.4: 3), the water administered with the drug, and an additional 240 mL of water at 2 h , 4 h and 6 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 2500 mL.

Green tea, 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 last PK sampling of the trial.

Poppy-seeds containing products should not be consumed starting 3 days before trial drug administration until last PK sampling of the respective treatment period.

Alcoholic beverages are not permitted starting 48 h before trial drug administration until the last PK sampling of the respective treatment period.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during the in-house confinement at the trial site.

Smoking is not allowed during in-house confinement.

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

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

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (Dinamap Pro 100,) 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.

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.

Fecal 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]
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	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
	Prothrombin time	X	X
	INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate transaminase] /GOT	X	X
	ALT [Alanine transaminase] /GPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
Hormones	Thyroid Stimulating Hormone	X	-
Substrates	Glucose (Plasma)	X	-
	Creatinine	X	X
	GFR/ CKD-EPI[3]	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
	Calcium	X	X
Urinalysis[2] (Stix)	Urine Nitrite (qual)	X	-
	Urine Protein (qual)	X	-
	Urine Glucose (qual)	X	-
	Urine Ketone (qual)	X	-
	Urobilinogen (qual)	X	-
	Urine Bilirubin (qual)	X	-
	Urine RBC/Erythrocytes (qual)	X	-
	Urine WBC/Leucocytes (qual)	X	-
	Urine pH	X	-
Urine sediment[2]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

1 A to be done at screening examination, B at Follow-up examination.
2 Microscopic examination if erythrocytes, leukocytes, or protein are abnormal in urine
3 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 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. Alcotest® 7410, or comparable test system) 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 , with the exception of drug screening tests. These tests will be performed at the trial site using the Multidrogen-Pipettiertest M-10/14-PDT, or comparable test systems.

FOB plus® test (Part 2 only): The subjects will receive a test tube with an integrated bar for stool sampling. On the next occasion they will take three samples from the stool with the collection bar and give it into the test tube. The test tubes should be closed carefully to not destroy the collection bar. These samples will be analysed for occult blood in faeces by immunological reaction according to the manufacturers instruction. As subjects may not be able to defecate at the trial site in the morning of the respective visit they may collect the specimen at home and bring the test specimen to the trial site.

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,) 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 (Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (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 via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details 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 fax 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 rosuvastatin and dabigatran

For quantification of rosuvastatin (Part 1) and dabigatran (Part 2) concentrations in plasma, 2.7 mL of blood will be drawn 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 will be obtained per analyte and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 90 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. 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.

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived. It is planned to use the back-up samples (2^{nd} aliquots of rosuvastatin and dabigatran samples) to get a profile of BI 1358894. Therefore, the second aliquot will be transferred to the analytical laboratory for BI 1358894 analytics after confirmation of TCPK.

5.3.2.2 Blood sampling for pharmacokinetic analysis of BI 1358894 and BI 1361608

For quantification of BI 1358894 and BI 1361608 (Part 1 and 2) concentrations in plasma, 2.7 mL of blood will be drawn 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 will be obtained per analyte and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 90 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

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

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

5.3.2.3 Blood sampling for pharmacokinetic analysis

For quantification concentrations in plasma, approx. 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA-anticoagulant blood drawing tube at the times indicated in the Flow Chart of Trial Part 1. 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 at least 15 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Centrifugation should be done within 60 minutes after sampling. One plasma aliquot will be obtained and stored in polypropylene tubes. The aliquot should contain at least 1.0 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 90 min, with interim storage of blood samples and aliquots on ice-bath or refrigerated.

The time each sample 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. 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.

After completion of the trial, the plasma samples may be used for further methodological investigations. However, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of rosuvastatin plasma concentration

Rosuvastatin concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

Plasma samples dedicated to the analysis of rosuvastatin are transferred to:

5.3.3.2 Analytical determination of dabigatran plasma concentration

Dabigatran concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

Plasma samples dedicated to the analysis of dabigatran are transferred to:

5.3.3.3 Analytical determination of BI 1358894 and BI 1361608 plasma concentration

BI 1358894 and BI 1361608 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

Plasma samples dedicated to the analysis of BI 1358894 and BI 1361608 are transferred to:

5.3.3.4 Analytical determination of plasma concentration

concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

Plasma samples dedicated to the analysis are transferred to:

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

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

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

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.4 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, and laboratory tests will be ± 60 min.

Starting from a planned time of 48 hours after drug administration (and beyond) a time window of +/- 120 minutes will be allowed for all procedures.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs 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.

The subjects may have their dinner together in all trial periods.

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

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.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.3).

6.2.2 Treatment period

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 24 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, subjects will be treated in an ambulatory fashion.

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

The safety measurements performed during the treatment period are specified in Section 5.3 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 Sections 5.2.2 to 5.2.6.
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 rosuvastatin (Part 1, Reference 1) and dabigatran (Part 2, Reference 2) given alone compared to a combined administration with BI 1358894 (Part 1 - Test 1, Part 2 - Test 2) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Sections 2.1.2 and 2.1.3. Both trial parts are designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.3.

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 1358894 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 entered and treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

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, BI 1358894 and BI 1361608 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
- 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 primary endpoints (refer to Section 2.1.2) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472).

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

'subjects' will be considered as random, whereas 'treatment' will be considered as fixed. The model is described by the following equation:

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

y_{km} = logarithm of response measured on subject m receiving treatment k,
μ = the overall mean,

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

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

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

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

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

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

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but with 'subject' considered as fixed effect.

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 assigned treatment will be discussed in the minutes of the Report Planning Meeting or Decision Log).

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

In each trial part, the subjects receive all treatments in the same order, thus no randomisation for the treatment assignment is performed (see also Section 4.1.3).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 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 and for dabigatran in previous trials [c08983809-01, c13060859-01, U09-3249-02] were ranging from 10% to 30%.

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 fixed sequence, two period crossover trial *(N=12)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
10.0	1.103	50.0	45.34	55.14
10.0	1.103	100.0	90.68	110.28
10.0	1.103	150.0	136.02	165.41
20.0	1.214	50.0	41.18	60.72
20.0	1.214	100.0	82.35	121.43
20.0	1.214	150.0	123.53	182.15
30.0	1.334	50.0	37.49	66.68
30.0	1.334	100.0	74.99	133.36
30.0	1.334	150.0	112.48	200.03

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

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 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 delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan 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 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 descrybed in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the , 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

BI 1358894 will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany. Rosuvastatin and dabigatran will be obtained from a public pharmacy in Germany.

Pharmacokinetic analysis of rosuvastatin and dabigatran is done by .

Pharmacokinetic analysis of BI 1358894 and its metabolite is done by

Pharmacokinetic analysis is done by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

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

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

Data management and statistical evaluation will be done by BI 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.

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10. DESCRIPTION OF GLOBAL AMENDMENT(S)

10.1 GLOBAL AMENDMENT 1

Date of amendment		28 August 2019
EudraCT number **EU number**		2019-002763-10
BI Trial number		1402-0009
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1358894 in healthy male subjects (open, single-dose, fixed sequence, 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. Section 3.3.4.3 2. Synopsis, section 3.3, section 3.3.5 3. section 3.3.3 4. title page, synopsis
Description of change		1. trial stopping criterion 1 has been extended 2. maximum number of replacement subjects has been defined 3. trial specific exclusion criteria have been added based on contraindications given in the SmPC 4. doses of rosuvastatin, dabigatran and BI 1358894 have been removed from study title
Rationale for change		1-3: request of Competent Authority 4: BI-internal recommendation

APPROVAL / SIGNATURE PAGE

Document Number: c27867536 **Technical Version Number:2.0**

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

Title: Relative bioavailability of rosuvastatin (Part 1) and dabigatran (Part 2) given alone and together with BI 1358894 in healthy male subjects (open, single-dose, fixed sequence, two-period crossover design in each trial part)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		28 Aug 2019 16:19 CEST
Author-Trial Statistician		28 Aug 2019 16:37 CEST
Approval-Therapeutic Area		29 Aug 2019 09:19 CEST
Verification-Paper Signature Completion		29 Aug 2019 09:22 CEST
Approval-Team Member Medicine		29 Aug 2019 10:08 CEST
Author-Clinical Trial Leader		29 Aug 2019 17:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed