Clinical Trial Protocol

TITLE PAGE

	Document Number: c11669965-01
BI Trial No.:	1160.271
BI Investigational Product:	Pradaxa® (Prazaxa® in Japan), Dabigatran etexilate, BIBR 1048 MS
Title:	Bioequivalence of tablet formulation of dabigatran etexilate compared to commercial capsule formulation following oral administration in healthy male subjects (an open-label, randomised, single-dose, replicate design in a two-treatment, four-period, two-sequence crossover study)
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Address: [redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator:	[redacted] Address: [redacted] Phone: [redacted] Fax: [redacted]
Status:	Final Protocol
Version and Date:	Version: 1.0 Date:10 Feb 2017
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Pradaxa® (Prazaxa® in Japan)			
Name of active ingredient: Dabigatran etexilate, BIBR 1048 MS			
Protocol date: 10 Feb 2017	**Trial number:** 1160.271		**Revision date:** Not applicable

Title of trial:	Bioequivalence of tablet formulation of dabigatran etexilate compared to commercial capsule formulation following oral administration in healthy male subjects (an open-label, randomised, single-dose, replicate design in a two-treatment, four-period, two-sequence crossover study)
Principal Investigator:	[redacted] Address: [redacted] Phone: [redacted] Fax: [redacted]
Trial site:	[redacted] Address: [redacted] Phone: [redacted] Fax: [redacted]
Clinical phase:	I
Objective:	To establish the bioequivalence of tablet formulation of 110 mg dabigatran etexilate compared to commercial capsule formulation
Methodology:	Randomised, single-dose ,open-label, replicate design in a two-treatments, four-period, two-sequence crossover design
No. of subjects:	
total entered:	160
each treatment:	160 (80 subjects in the each treatment sequences)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 20 to 40 years, body mass index (BMI) of 18 to 25 kg/m^2
Test product:	Dabigatran etexilate tablet formulation: (T)
dose:	110 mg
mode of admin.:	Oral with 200 mL of water after an overnight fast of at least 10 h
Comparator product:	Dabigatran etexilate capsule formulation (R)
dose:	110 mg
mode of admin.:	Oral with 200 mL of water after an overnight fast of at least 10 h
Duration of treatment:	One day (single dose) for each treatment period

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Name of finished product: Pradaxa® (Prazaxa® in Japan)			
Name of active ingredient: Dabigatran etexilate, BIBR 1048 MS			
Protocol date: 10 Feb 2017	**Trial number:** 1160.271		**Revision date:** Not applicable
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-tz} and C_{max} of free dabigatran Secondary endpoints: AUC_{0-tz} and C_{max} of total dabigatran and $AUC_{0-\infty}$ of both free dabigatran and total dabigatran Further parameters of interest: time from dosing to the maximum measured concentration of both free dabigatran and total dabigatran in plasma (t_{max}), λ_z, terminal half-life of both free dabigatran and total dabigatran in plasma ($t_{1/2}$) , AUC_{t1-t2}, $\%AUC_{tz-\infty}$, MRT_{po}, CL/F, V_z/F		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	The assessment of bioequivalence will be based upon two-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary and secondary endpoints using an acceptance range of 80.0-125.0%. This method is equivalent to the two one-sided t-tests procedure, each at the 5% significance level. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	Within 28 days before first drug administration			Screening (SCR)[1]	X		X	X	
1/2/3/4	2/3/4/5	-1	-12:00	21:00	Admission to trial site	X				X
		1	-1:00	08:00	Allocation to treatment (visit 2 only)		X[3]		X[3]	X[3]
			0:00	09:00	Drug administration					↑
			0:30	09:30			X			
			1:00	10:00			X			
			1:30	10:30			X			
			2:00	11:00	200 mL fluid intake		X		X	
			3:00	12:00			X			
			4:00	13:00	200 mL fluid intake, thereafter lunch[4]		X			
			6:00	15:00			X			
			8:00	17:00			X			
			11:00	20:00	Dinner					
			12:00	21:00			X			X
		2	24:00	09:00	Breakfast[4]	X	X		X	X
			36:00	21:00			X			
		3	48:00	09:00			X			X
			48:30	09:30	Discharge from trial site					↓
EOT	6	5 to 14 days after day 1 of Visit 5[7]			End of trial (EOT) examination[5]	X		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 height and body weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Breath alcohol test and safety laboratory. Safety laboratory to be taken and to be medically evaluated within 24 hours prior to administration of trial drug. Samples for safety laboratory will be collected after the subjects have fasted for at least 10 hours except for Visit 1. Breath alcohol test will be performed at screening and within 24 hours prior to each treatment period, and may be repeated at any time during the trial.
3. The time is approximate; the procedure can be acceptable to be performed and completed within 3 h prior to drug administration.
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
7. In case of premature discontinuation, 5-14 days after the last drug administration

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BE	Bioequivalence
BI	Boehringer Ingelheim
b.i.d.	*Bis in die*, twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CrCl	Creatinine clearance
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
DE	Dabigatran etexilate
ECG	Electrocardiogram
EOT	End of trial
GCP	Good Clinical Practice
ICSR	Individual Case Safety Reports
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result

NOS	No sample available
NVAF	Non-valvular atrial fibrillation
PCI	Percutaneous coronary intervention
P-gp	P-glycoprotein
PK	Pharmacokinetics
PKS	PK parameter analysis set
PR	Pulse rate
q.d.	Quaque die, once daily
R	Reference treatment
RE-LY	Randomised Evaluation of Long-Term Anticoagulant Therapy with Dabigatran Etexilate
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SE	Systemic embolism
SOP	Standard Operating Procedure
SPAF	Stroke prevention in patients with non-valvular atrial fibrillation
T	Test treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
ULN	Upper limit of normal
VTE	Venous thromboembolism
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Dabigatran etexilate (DE) has been developed as an orally active anticoagulant and was granted in 2011 for the indication of the stroke prevention in patients with non-valvular atrial fibrillation (SPAF) in Japan. Globally, the first marketing authorisation for SPAF was granted in the US in 2010.

In addition to SPAF, DE has also been developed for the prevention and treatment of venous thromboembolism (VTE) in patients with undergoing hip or knee surgery, for the acute treatment and secondary prevention of VTE, and for reduction in cardiovascular complications in patients with acute coronary syndrome including those following an index myocardial infarction. First marketing authorization for DE was granted in 2008 in the European Union and the European Economic Area for the indication “Primary prevention of VTE in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery”. In 2014, the two indications acute VTE treatment and secondary VTE prevention was approved in the US. Marketing authorization for DE has been granted in more than 108 countries world-wide.

DE is recommended as the first choice medicine as well as warfarin for SPAF according to the 2013 edition of the Guidelines for pharmacotherapy of atrial fibrillation Japanese Circulation Society 2013) [R15-5604] in Japan and widely used in medical practice.

The prevalence of atrial fibrillation increase with age. It occurs in about 1% of those under 60 years of age but in about 6 % of those over 80 years of age (Fuster, et al.,2001) [R03-1231]. However, currently only available formulation for DE is a capsule containing tartaric acid starter pellets coated with the active ingredient. Due to size of the capsules (i.e., No.2 capsule in size for 75 mg formulation and No.1 capsule in size for 110 mg formulation), this formulation has a limitation in administration for elderly patients who have difficulty in swallowing. Thus, more convenient formulation of DE (i.e., a tablet), which is smaller than commercial capsule, has high medical needs.

1.2 DRUG PROFILE

Pharmacokinetics
The pharmacokinetics (PK) profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with maximum measured concentration of the analyte in plasma (C_{max}) attained within 0.5 and 2.0 hours post administration, and half-life depending on renal function (see the reference [c01632884-04] for prolongation of half-life with decline in renal function). Dabigatran C_{max} and area under the curve increase in a dose proportional manner. Dabigatran is eliminated primarily by the kidneys with urinary excretion accounting for approximately up to 80% of the dose administered intravenously.
In phase I drug-drug interaction studies, there was no significant influence of DE on the PK of atorvastatin, diclofenac or digoxin (P-glycoprotein [P-gp] substrate), and the exposure of dabigatran was not significantly altered by these drugs. DE and dabigatran are not

metabolised by the cytochrome P450 system [U01-1602] and have no in vitro effects on human cytochrome P450 enzymes. There was, however, an effect on DE bioavailability after co-administration with some P-gp inhibitors or inducers. The maximum increase, approximately 2.5 fold, in dabigatran exposure was observed after single and multiple doses of co-administered ketoconazole while chronic rifampicin reduced the dabigatran exposure to 1/3 of control values. However, co-administration of P-gp inhibitors (such as amiodarone, quinidine and verapamil) in the Randomised Evaluation of Long-Term Anticoagulant Therapy with DE (RE-LY) had much smaller effects (increase of dabigatran plasma concentration of up to 16%) [U09-3249-02] than those observed in phase I studies.

In the relative bioavailability (BA) study (i.e.1160.246) of tablet formulation of DE, time from dosing to maximum measured concentration of the analyte in plasma (t_{max}) and terminal half-life ($t_{1/2}$) were 1.50 hours for t_{max} and ranged 8 to 9 hours for $t_{1/2}$. In comparison with the capsule formulation, the adjusted gMean ratio of tablet formulation was approximately 110 % for both C_{max} and $AUC_{0\text{-}tz}$ [c09145064-01].

Safety and Efficacy
In Japan, the indication to reduce the risk of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAF) was approved in 2011 based on the result of the RE-LY study, a phase III, prospective, randomised, open-label, multinational study of stroke prevention in subjects with NVAF at risk of stroke. Over 700 Japanese subjects/patients have received DE in phase I, II, and III studies. Globally including Japan, the effects of DE have been investigated in more than 27 000 subjects/patients in the clinical studies. Overall, more than 1,000 healthy volunteers have been included in phase I studies with DE.

A total of 72 Japanese healthy subjects have been included in 4 phase I studies ([U05-3052], [U06-3091], [U05-3334], and [U06-3420]) at a daily dose from 50 mg through 300 mg. The method of administration was single dose of 50, 150, 220, and 300 mg and multiple doses of 150 mg q.d, 220 mg q.d, and 150 mg b.i.d.
Gastrointestinal disorder was a relatively frequently reported adverse event (AE) and 11 events occurred in 10 subjects treated with a daily dose of more than 220 mg (flatulence, abdominal pain, nausea, periodontitis, upper abdominal pain, and gingival bleeding). For the bleeding event, gingival bleeding and haematuria were observed in 1 subject each. In the patient with haematuria, the score of blood urine test was changed from 1+ at baseline to 3+ after treatment with a single dose of 300 mg.
In addition to the phase I trials mentioned above, a total of 35 Japanese healthy subjects have been included in the relative BA study of tablet formulation of DE at a daily dose of 110 mg [c09145064-01].
2 AEs, eosinophil count increased and upper respiratory tract infection, were reported after treatment with a single dose of 110 mg in the relative BA study. Eosinophil count increased was considered to be related to DE by the investigator. The intensity of these AEs was mild or moderate and no bleeding event was observed in the trial.

In the RE-LY study, a total of 18 113 patients were randomised to one of two blinded doses of DE (110 mg b.i.d. or 150 mg b.i.d.) or to warfarin (international normalised ratio [INR]

2.0-3.0) [U09-3249-02][c03032935-01]. Details of safety and efficacy in the RE-LY study are described briefly as follows:

In the RE-LY study, DE 150 mg b.i.d. was demonstrated to be superior to warfarin for the prevention of stroke and SE and reduced the rate of intracranial haemorrhage compared to warfarin. In addition, DE 150 mg b.i.d. showed similar rate of major bleeding compared to warfarin [P09-11669]. DE 110 mg b.i.d. was demonstrated non-inferior to warfarin for the primary endpoint of stroke and SE and reduced rate of intracranial haemorrhage, major bleeding, and total bleeding.

Subjects treated with DE had a slightly higher incidence of AEs compared with warfarin (78.6%, 78.3%, and 75.9% for DE 110 mg b.i.d., 150 mg b.i.d. and warfarin, respectively). Gastrointestinal AEs were reported more frequently for DE treatment. There was no evidence of increased frequencies on DE compared to warfarin in transaminase elevations, or concomitant transaminase and bilirubin elevations. Instead, the abnormalities were more frequent on warfarin. Transaminase elevations <2x upper limit of normal (ULN) were common (27 to 31%) in this population. For transaminases >3x ULN, the overall frequency was 1.7 to 2.0%. For potential Hy's Law cases, there were 11 subjects (0.2%) on DE 110 mg b.i.d., 14 subjects (0.2%) on DE 150 mg b.i.d., and 21 subjects (0.4%) on warfarin. All but four of these cases (three subjects with DE, one subject with warfarin) had identifiable alternative causes.

Post-marketing experience
Overall including Japan, taking all granted indications into consideration, experience with marketed product of 6 478 207 patient-years has been gained since first launch (period: 18 March 2008 to 31 August 2016). In total, during the post-marketing experience period, BI received a total of 166190 individual adverse events from 90 860.

Haemorrhagic events are the most commonly reported post-marketing adverse drug reactions. In approximately 42% of all Individual Case Safety Reports (ICSRs), a haemorrhagic event(s) is reported. Approximately 52% of these cases are serious, and approximately 8% of all haemorrhage cases have a fatal outcome. Approximately 50% of all haemorrhagic events reported are from the gastrointestinal tract.

Gastrointestinal disorders are reported in approximately 40% of the ICSRs. The events are haemorrhagic in nature in approximately 38%. The non-haemorrhagic events are in over 85% non-serious. The most commonly reported non-haemorrhagic gastrointestinal events are "dyspepsia", "diarrhoea", "abdominal discomfort" and "nausea".

Ongoing studies in Japan
In Japan, the following clinical studies are ongoing for DE: RE-SPECT ESUS (Secondary stroke prevention in patients with stroke of undetermined source), RE-DUAL PCI (Efficacy and safety in patient with NVAF that undergo a percutaneous coronary intervention [PCI] with stenting), RE-CIRCUIT (Safety of uninterrupted treatment with DE in NVAF patients undergoing a first ablation procedure), and GLORIA AF (Global registry program on long-term oral anti-thrombotic treatment in patients with atrial fibrillation).

For more detailed description of DE profile, please refer to the current Investigator's Brochure [c01632884-04].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

According to the Japanese Guideline for Bioequivalence Studies of Generic Products [R07-0628, R12-3703], bioequivalence (BE) trial with health volunteers is required to be conducted to guarantee the therapeutic equivalence of generic products against original drug.BE trial is essential for the tablet formulation of DE to be approved by the regulatory as well as delivered to the patients for commercial use.

In the previous relative BA study, PK parameters were obtained preliminary. Based on the results from the study as well as manufacturability a tablet formulation was considered to be the best to confirm BE with capsule formulation in this study.

This study is conducted to meet requirements from the regulatory agency using the tablet formulation which was selected according to the results from the previous study.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to establish the bioequivalence of tablet formulation of 110 mg DE compared to commercial capsule formulation following oral administration under fasted condition.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the treatments.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Participation in this trial is without any (therapeutic) benefit for healthy subjects. Their participation in the trial, however, is of major importance to the development of tablet formulation of DE. The subjects are exposed to the risks of the trial procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to veinipuncture for blood sampling.

The total volume of blood withdrawn during the entire trial per subject will be around 285 mL. No health-related risk to healthy subjects is expected from this blood withdrawal.

Drug-related risks and safety measures

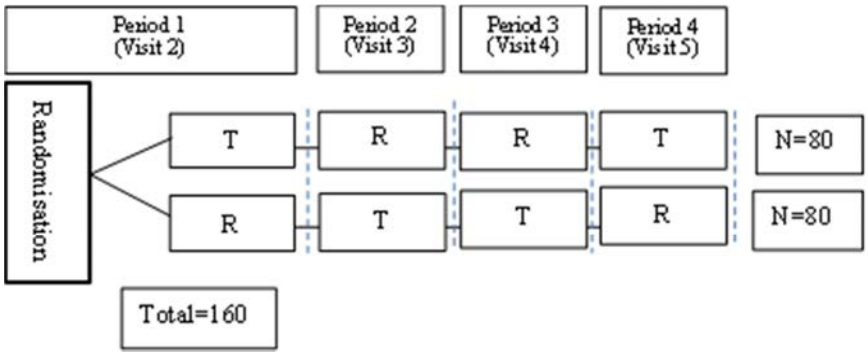
The most significant potential risk associated with DE is a minor bleeding tendency at doses 600 mg and higher per day during steady state in Caucasian healthy volunteers [U00-1856]. For Japanese healthy volunteers, bleeding event was observed after treatment with a single dose of 300 mg.For details of adverse events in Japanese subjects included in phase I trials, see the Section 1.2.

In Japan, DE has market authorisation with the dose regimen of 150 mg b.i.d. (reduction to 110 mg b.i.d. should be considered for the patients aged 70 and older, with moderate renal failure [creatinine clearance 30-50 mL/min], or with history of gastrointestinal haemorrhages, or those who are receiving P-gp inhibitors). The risks to the subjects are low after a single dose of 110 mg which is the dosage selected for the present study. Regardless of the low bleeding risk and the overall good tolerability of the available formulations of DE, subject's safety will be ensured by the monitoring of subjects for both expected and unexpected AEs clinically, verbally, and by laboratory monitoring. Based upon preclinical and clinical information, healthy subjects will not be exposed to undue risks from this trial.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will be performed as a randomised, single-dose, open-label, replicate design in, two-treatment, four-period, two-sequence crossover trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The subjects will be randomly allocated to the two treatment sequences (T-R-R-T or R-T-T-R). The treatments will be single dose of 110 mg DE / formulation tablet in the fasting state (T) and single dose of 110 mg DE / formulation capsule in the fasting state (R). For details refer to Section 4.1.



R(Reference treatment): DE commercial capsule formulation
T(test treatment): DE tablet formulation

Figure 3.1: 1 Trial Design

There will be a washout period of at least 4 days between the treatments.

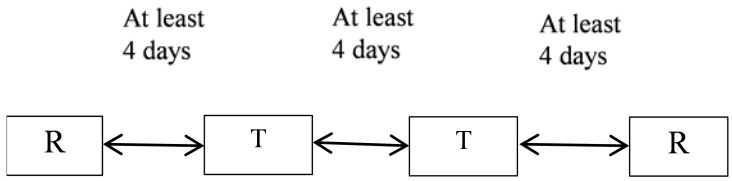


Figure 3.1: 2 Example of the timing of drug administration and washout period

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.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

NBI (Nippon Boehringer Ingelheim Co., Ltd) has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal standard Operating Procedures (SOP)s,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany and NBI.

The trial will be conducted at [redacted] under the supervision of the Principal Investigator.

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

The analyses of free, nonconjugated dabigatran and of total dabigatran concentrations in plasma will be performed at the contract research organisation [redacted]

On-site monitoring will be performed by NBI.

Data management and statistical evaluation will be done by NBI or a contract research organization appointed by NBI 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 investigator site file (ISF).

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

For bioequivalence trials, the crossover design is preferred due to its efficiency: since each subject serves as his own control, the comparison between formulations is based on a comparison within subjects rather than between subjects. This trial design therefore removes intersubject variability from the comparison between formulations [cf. R94-1529].

Blinding is not necessary. The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte provided by a bioanalytical laboratory which is blinded to treatment allocation.

Inter-individual variability of trough and post dose plasma concentrations of total dabigatran was high after oral administration (HPMC Capsule) of DE at steady state (74-82%) [c01632884-04]. Inter-individual variability in C_{max} of post dose plasma concentrations of total dabigatran was higher than 50 %[c09145064-01]. Thus, it is necessary for this BE study to be conducted with large number of subjects between the tablet formulation and the capsule formulation.

According to the Japanese Guideline for Bioequivalence Studies of Generic Products [R07-0628, R12-3703], blood sampling should be performed at least 7 times, including zero time, 1 point before C_{max}, 2 points around C_{max} and 3 points during the elimination phase, and should be continued until AUC_{0-tz} becomes over 80% of the Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$) . If the half-life of the parent substance or active metabolite of the measured active ingredient is very long, collect samples for at least 72 hours. The washout period should be more than 5 times the $t_{1/2}$. In this trial, 13 blood samplings up to 48 hours after administration are necessary to evaluate the PK profile and they cover the entire points for fulfilling the requirement of the Guideline.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 160 healthy male subjects will enter the trial . They will be recruited from the volunteers' pool of the trial site. Subjects will be randomised to one of two sequences which vary in the treatment sequence. Each treatment group consists of 80 subjects.

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

3.3.1 Main diagnosis for study entry

The trial will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the investigator’s assessment, based on a complete medical history including a physical examination, vital signs (blood pressure [BP], pulse rate [PR]), 12-lead electrocardiogram (ECG), and clinical laboratory tests
2. Age ≥20 and ≤40 years old at informed consent
3. BMI ≥18 and ≤25 kg/m^2 at screening
4. Signed and dated written informed consent prior to admission to the trial in accordance with Good Clinical Practice (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) is deviating from normal and judged as clinically relevant by the investigator
2. 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 at screening. Based on the clinical judge by the investigator, repeated measurements are allowed.

3. Any laboratory value outside the reference range before randomisation that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease considered as clinically relevant by the investigator
5. Any relevant bleeding history considered by the investigator
6. Any history or evidence of blood dyscrasia, haemorrhagic diathesis, severe thrombocytopenia, cerebrovascular haemorrhage, bleeding tendencies associated with active ulceration or overt bleeding of gastrointestinal, respiratory or genitourinary tract or any disease or condition with haemorrhagic tendencies
7. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
8. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
9. Planned surgeries within four weeks following the end-of trial examination
10. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
11. History of relevant orthostatic hypotension, fainting spells, or blackouts
12. Chronic or relevant acute infections
13. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
14. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl.Qc/QTc interval prolongation)
15. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
16. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
17. Inability to refrain from smoking in-house confinement at the trial site
18. Alcohol abuse (consumption of more than 30 g per day: e.g., 750 mL of beer, 1.5 *gous* [equivalent to 270 mL] of *Sake*)
19. Drug abuse or positive drug screening
20. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
21. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
22. Inability to comply with dietary regimen of trial site
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. An adverse event or clinically significant laboratory change or abnormality occurred that is considered by the investigator to warrant discontinuation of treatment.
5. Clinical evidence of prolongation of coagulation, i.e., prolonged bleeding at the venipuncture site (defined as >15-minute compression necessary)
6. Sustained minor bleedings which cannot be controlled by local haemostasis, or any other bleeding event considered clinically relevant by the investigator.

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at trial assessments).

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database 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 CRFs. If the discontinuation occurs before the end of the Residual effect period (REP) (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.

2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the clinical trial protocol (CTP) by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

The trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Among the investigational product, commercial capsule formulation of DE has been manufactured by BI Pharma GmbH & Co. KG and the colour (light blue opaque cap and cream-coloured opaque body) of the capsule is different from the colour (light blue opaque cap and light blue opaque body) of the capsule marketed in Japan.

The film coated tablets 110 mg have been developed for BE study. The excipients used for the tablets are fumaric acid, D-mannitol, hydroxypropylcellulose, hypromellose (2208), magnesium stearate, crospovidone (type A), partially hydrolyzed polyvinyl alcohol, sucrose esters of fatty acids, titanium oxide, and polysorbate 80. The tablet formulations have been manufactured by Qualitech Pharma.

The molecular weight of DE (free base) is 627.7 g/mol. DE is administered as methanesulfonic acid salt. Dose refers to a dose of the free base. The conversion factor is 0.867; 627.7 mg of DE free base equals 723.8 mg of DE methanesulfonic acid salt. A dose of DE was calculated as a free base.

4.1.1 Identity of BI investigational product and comparator products

The characteristics of the test product are given below:

Substance:	Dabigatran Etexilate (BIBR 1048)
Pharmaceutical formulation:	Tablet, film coated
Source:	Nippon Boehringer Ingelheim Co., Ltd
Unit strength:	110 mg
Posology:	1-0-0
Route of administration:	p.o.

The characteristics of the reference product are given below:

Substance:	Dabigatran Etexilate (BIBR 1048)
Pharmaceutical formulation:	Capsule
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	110 mg
Posology:	1-0-0
Route of administration:	p.o.

4.1.2 Method of assigning subjects to treatment groups

The randomisation list of trial subject numbers and assigned treatment sequences will be provided to the trial site in advance.

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. After providing the consent to this trial, the subjects willing to participate can choose convenient visit dates on a first come, first-served basis: as soon as approximately 20 subjects have been allocated to 1 of 8 treatment groups in 8 different periods, the following subjects will be allocated to one of the other treatment groups in 8 different periods. Therefore, the allocation of subjects to treatment groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the trial includes healthy subjects from a homogenous population, relevant imbalances between the treatment sequences are not expected.

At the beginning of the treatment phase (in the morning of Day 1 of Visit 2), subjects will be allocated to a subject number according to the randomisation list. Within the treatment sequence, subjects will be allocated in their order of providing the consent to the trial (that is, the first subject consented will be the first treated).No subject number for a screening failure subject will not be allocated. However, if the screening failure subject experiences a serious adverse event (SAE), specified subject number will be allocated to collect the safety information of the subject.

Considering the screening failure, some substitute subjects will be available.

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

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

As the standard clinical dose, 75 mg and 110 mg are available. Between 2 dosages, 110 mg is used for this study. Because in principle, BE study is conducted using higher dosage according to Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms [R07-0628].

4.1.4 Drug assignment and administration of doses for each subject

This trial is replicable design in a two-treatment, four-period, two-sequence crossover study with a. All subjects will receive 2 difference treatments in four periods in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	Dabigatran etexilate	Tablet	110 mg	1 tablet on day 1	110 mg
R (Reference)	Dabigatran etexilate	Capsule	110 mg	1 capsule on day 1	110 mg

The medication will be administered as a single oral dose together with about 200 mL of water to a subject in the sitting/standing position under supervision of the investigating

physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication. Administration will be performed following an overnight fast starting no later than 10 h before scheduled dosing.

Subjects will be kept under close medical surveillance until 48 h following drug administration. During the first 2 h after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). For restrictions with regard to diet see Section 4.2.2.2.

Treatment sequence is shown in Table 4.1.4: 2

Table 4.1.4: 2 Treatment period and allocated medication

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1	T	R	R	T
2	R	T	T	R

R: Reference products, refer to the Table 4.1.4:1
T: Test products, refer to the Table 4.1.4:1

The treatments will be separated by a wash-out period of at least 4 days.

4.1.5 Blinding and procedures for unblinding

Not applicable because this is an open-label trial.

4.1.6 Packaging, labelling, and re-supply

Tablet formulation will be provided by Nippon Boehringer Ingelheim Co., Ltd. Capsule formulation will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply of tablet formulations consists of boxes enclosing aluminium pouches in which the trial medication is packed in press through package (PTP) sheets.
The clinical trial supply of capsule formulation consists of bottles holding the trial medication.
All packages mentioned above are labelled with trial identification.
For details of packaging and the description of the label, refer to the ISF.

Examples of the labels will be available in the ISF.

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 according to the recommended (labelled) storage conditions. Where 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 immediately contacted.

4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the institutional review board (IRB) / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial site
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated CTP

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator / pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of the return to the sponsor, the investigator / pharmacist 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.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

A specific reversal agent (idarucizumab) has been approved in Japan. When clinically indicated and available, it can be given to a patient from commercial supply. If the specific reversal agent for dabigatran is given, information surrounding the clinical circumstances, treatment and clinical outcome will be collected on the CRF.

In case of adverse events in need of 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 medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

For detailed concomitant use of DE with other treatments, see the latest IB

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 10 h before and 4 h after drug intake.

From 1 hour before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 200 mL of water at 2 hours and 4 hours post-dose (mandatory for all subjects). From lunch until 24 hours post-dose, total fluid intake is restricted to 3000 mL.

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

Alcoholic beverages are not allowed 7 days prior to the admission to the trial site until discharge.

Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 h before until 24 h after each administration of trial medication.

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

In order to minimise the risk of acquiring a potential bleeding, all subjects will be instructed of the following precautions:

- be alert to early signs of bleeding such as occurring of teeth brushes, pain in the abdomen, lower back or side of the body. If any of these symptoms occur, the subject has to get in touch with the trial physician immediately.
- take care to avoid cuts or other injuries. Be careful especially when using knives, razors, nail clippers, and other sharp objects. Check with a physician for the best way to clean the teeth and mouth without injuring the gums.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations 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. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety of the investigational drugs will be assessed based on:

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

These parameters will be evaluated in a descriptive way only, and are therefore considered to be 'further parameters of interest'. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

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.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

An SAE is defined as any AE which:

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

  or
- is to be 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.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

The following events will be handled as ‘deemed serious for any other reason’. An AE which possibly leads to disability will be reported as an SAE.

AEs considered ‘Always Serious’

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 given above.

The latest list of ‘Always Serious AEs’ can be found in the RDC system, a remote 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.

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Adverse events of special interest (AESIs)

The term 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. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

No AESIs have been defined for this trial.

Intensity of AEs

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

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

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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 diminished).

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.

5.2.2.2 Adverse event collection and reporting

AEs collection

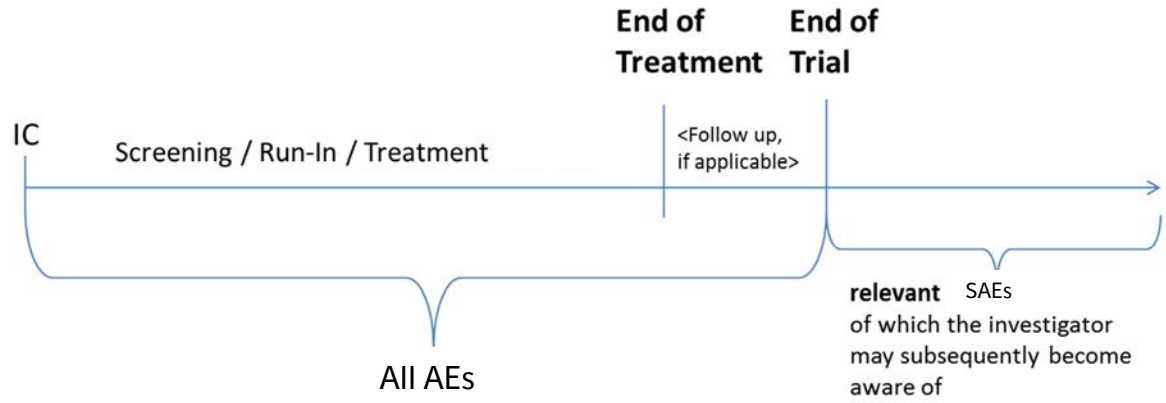
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, 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 careful 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, and intensity of the event as well as 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 through the residual effect period (REP), until an individual subject's end of trial:
    - All AEs (serious and non-serious).
    - The only exception to this rule are AEs (non-serious) 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 relevant SAEs and relevant of which [redacted] may become aware of.



The REP for DE, when measurable drug levels or pharmacodynamic effects are still likely to be present, is defined as 3 days after each administration of DE. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment and as off treatment 4 days and greater after each administration of DE; please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

The follow-up period describes the period of time from the last administration of trial medication including the REP until the end of trial examination (last per protocol contact).

AE reporting to sponsor and timelines

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

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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and on the 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 trial inclusion they will be considered as baseline conditions.

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h except for Visit 1. The subjects have fasted for at least 6 hours at Visit 1. Overnight fasting is not required at the discretion of the investigator or designee for retests.

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 should be performed if the investigator consider that further examination is necessary based on the results of automatic WBC differential regardless of the abnormality of the count.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit
	Haemoglobin
	Red blood cell count (RBC)
	White blood cell count (WBC)
	Platelet count
Automatic WBC differential (relative)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC(if the investigator considers follow up is necessary)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT)
	Prothrombin time (Quick's test and INR)
Enzymes	Aspartate transaminase (AST/GOT)
	Alanine transaminase (ALT/GPT)
	Alkaline phosphatase (AP)
	Gamma-glutamyl transferase (GGT)
Substrates	Plasma glucose
	Creatinine
	Total bilirubin
	Total protein
Electrolytes	Sodium
	Potassium

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name
Urinalysis[1] (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine sediment[1] (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

1 Urinalysis/urine sediment only at screening and end of trial (EOT).

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

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/ methylenedioxyamphetamine (MDA) Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/ methylenedioxymethamphetamine (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) Syphilis test (rapid plasma reagin [RPR] Treponema pallidum [TP] antibody method)
Alcohol test	Breath alcohol test

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at screening and within 24 hours prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial site.

Laboratory data will be transmitted electronically from the laboratory to the database of BI.

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart.

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

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible. Repeated measurements can be performed based on the investigator’s consideration.

5.2.5.2 Medical examinations

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

5.2.5.3 Local tolerability

Not applicable.

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

Pharmacogenetic measurements are not planned.

5.4 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 pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

Exact time points of plasma sampling will be documented in the CRFs by the medical personnel. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for free dabigatran:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of free dabigatran in plasma over the time interval from 0 to the time of the last quantifiable data point)
- C_{max} (maximum plasma concentration of free dabigatran)

5.5.1.2 Secondary endpoints

Additionally the following secondary endpoints will be evaluated:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of total dabigatran in plasma over the time interval from 0 to the time of the last quantifiable data point)
- C_{max} (maximum plasma concentration of total dabigatran)
- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of total dabigatran in plasma over the time interval from 0 extrapolated to infinity)

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

[redacted]

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of dabigatran plasma concentrations, 3 mL of blood will be taken from an antecubital or forearm vein into an K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be immediately placed in an ice/water bath (0-4°C) until centrifuged at 4 to 8°C and about 2500 g for 10 minutes for plasma preparation. Centrifugation is to be started within 30 minutes after blood sampling. Following the centrifugation, plasma will be transferred to two pre-labelled polypropylene storage tubes (at least 0.5 mL in the first tube, the remainder in the second tube – back-up). Storage tubes will be frozen in an upright position at about -70°C or below as soon as possible, within max. 90 minutes after blood withdrawal. During handling blood/plasma samples will be continuously kept refrigerated (ice/water bath or cooled centrifuge). Until shipment on dry ice to the analytical laboratory, the plasma samples will be stored at about -70°C or below at the clinical site and at the analytical laboratory until analysis. The back-up samples will be shipped to the analytical lab shortly after the shipment of the first aliquot samples.

Generally, PK samples will be uniquely labelled with trial number, subject number, visit number (according to Flow Chart), planned time (according to Flow Chart) and “PK-1” (first aliquot) or “PK-2” (second aliquot).

Further details to the information on sampling are provided in the ISF and/or lab manual.

5.5.2.2 Urine sampling for pharmacokinetic analysis

Not applicable.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

Concentrations of free, nonconjugated dabigatran and of total dabigatran after alkaline cleavage of glucuronic acid conjugates will be determined by a validated high performance liquid chromatography, tandem mass spectrometry (HPLC-MS/MS) assay with a lower limit of quantification of 1.0 ng/mL at the contract research organisation [redacted]

During sample analysis, the bioanalyst will be blinded to subject allocation and will have no access to the random code.

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 end of trial examination are given in the Flow Chart.

Trial 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, ECG and laboratory tests will be ±30 minutes before 24 hours from DE administration. For procedures ≥24 hour, tolerance will be ±60 minutes.

If several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters. Furthermore, the intake of meals and water will be the last action.

For planned individual plasma concentration 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 determination of pharmacokinetic parameter.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment periods

If upon completion of screening, a subject has been determined eligible to enter the trial by the investigator, the subject will be randomised to one of 2 treatment sequences in the morning of Day 1 of Visit 2 prior to the drug administration.

Each subject will be given one dose of assigned trial medication in the morning of Day 1 of each period orally by the investigating physician or his/her designee.

If a subject displays any significant changes in blood pressure and/or pulse rate that may indicate a bleeding disorder after receiving dabigatran, the subject will receive appropriate treatment and will not receive trial medication in the following treatment periods. Adequate

diagnostic measures will be taken as soon as possible to investigate whether the subject has the bleeding disorder that might be causally related to previous dabigatran treatment.

Each subject is expected to participate in four treatment periods (Days -1, 1, 2, and 3 in each period). The treatment periods will be separated by at least 4 days between drug administrations.

On Day -1 of each treatment period trial participants will be admitted to the trial site and kept under close medical surveillance for at least 48 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.5.2.

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

6.2.3 End of trial and follow-up period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should visit the trial site undergo the examination to check the subject's safety where applicable, and then undergo the EOT examination 5 to 14 days after the day of last treatment.

All abnormal values (including laboratory parameters) that are considered 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 subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to establish the bioequivalence of tablet formulation of 110 mg DE compared to commercial capsule formulation following oral administration under fasted condition. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the treatments. The secondary objective(s) will be assessed by descriptive statistics.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

Bioequivalence is to be determined on the basis of the primary endpoints (see Section 5.5.1).

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘sequence’, ‘subjects within sequences’, ‘period’ and ‘treatment’. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

y_{ijkm} = logarithm of response (endpoint, see Section 5.5.1) measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the ith sequence effect, i = 1, 2

s_{im} = the effect associated with the mth subject in the ith sequence,
m = 1, 2, ..., 80

π_j = the jth period effect, j = 1, 2, 3,4

τ_k = the kth treatment effect, k = 1, 2,

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

It is assumed that random errors were normally distributed and different formulation can have different variability, that is $e_{ijkm} \sim N(0, \sigma_k{}^2)$.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The assessment of bioequivalence will be based upon two-sided 90% confidence intervals (CIs) for the ratio of the geometric means (test/reference) for the primary and secondary endpoints using an acceptance range of 80.0-125.0%. This method is equivalent to the two one-sided t-tests procedure, each at the 5% significance level (on the log scale).

In general, the hypothesis of inequivalence is tested:

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta \quad or \quad \mu_T - \mu_R \geq \delta$

where μ_T and μ_R are the means of the log-transformed endpoint for the test and reference treatments, respectively, and δ is the bioequivalence limit that defines the acceptance range on the logarithmic scale.

Thus the null hypothesis is that the difference of the population average responses is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range.

Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

i.e. the difference of the population average responses is both greater than the lower bound and less than the upper bound of the acceptance range.

In this trial, the bioequivalence limit δ is ln(1.25). By back-transforming (exponentiating), this translates to an acceptance range of 80.00 to 125.00% for the ratio of the geometric means (test/reference) for endpoints on the original (linear) scale.

The above null hypothesis H_0 of inequivalence and its alternative H_a can be decomposed into two one-sided null hypotheses, H_{01} and H_{02}, with their accompanying alternatives:

H_{01}: $\mu_T - \mu_R \leq -\delta$ vs. H_{a1}: $\mu_T - \mu_R > -\delta$

H_{02}: $\mu_T - \mu_R \geq \delta$ vs. H_{a2}: $\mu_T - \mu_R < \delta$

Due to the nature of normal-theory confidence intervals, the test of the null hypothesis H_0 at the level of significance of $\alpha = 0.05$ is equivalent to carrying out two one-sided tests of the above null hypotheses H_{01} and H_{02} each at the level of significance of $\alpha = 0.05$. The rejection

of both null hypotheses at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range $(-\delta, \delta)$.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The pharmacokinetic endpoints listed in Section 5.5.1 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters may be:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be taken either from the median t_{max} for the reference product or from median t_{max} for the test product, depending on whether the subject had experienced emesis after taken the test or the reference product. Median t_{max} is to be determined excluding the subjects experiencing emesis.
- Time deviations
- Use of restricted medications
- A pre-dose concentration is >5% of the C_{max} value of that subject

The subject set for the evaluation of PK endpoints (PK parameter analysis set [PKS]) will include all treated subjects that provide at least one observation for at least one primary endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints. It will also be decided in the Report Planning Meeting which subjects are to be included in the PKS.

Point estimates of bioavailability, the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see 5.5.1.1, 5.5.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model (cf. Section 7.1.3). 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 (LeastSquares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Bioequivalence is considered established if the 90% confidence intervals of both ratios of the geometric means for the primary endpoints (see Section 5.5.1.1) are contained in the pre-defined acceptance range (see Section 7.2). Therefore, no adjustment of the level of significance is necessary.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will statistically be assessed using the same methods as described for the primary endpoints. $AUC_{0-\infty}$ will be calculated using the $AUC_{0-\infty}$ based on observed and predicted last concentrations, and for statistical analysis, $AUC_{0-\infty}$ based on both observed and predicted last concentrations will be used.

[redacted]

7.3.4 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of trial drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by 'treatment at onset'.

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of 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 'screening', those between first trial medication intake until end of the residual effect period (see 5.2.2.2) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end of trial examination will be summarized as 'post-treatment', those after the end of trial examination will be assigned to 'post-trial'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Relevant ECG findings will be reported as AEs.

7.3.5 Interim analyses

No interim analysis is planned.

7.3.6 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for DE will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472). Pharmacokinetic analyses will be performed using validated software programs, normally. Phoenix Winnonlin (Pharsight®) with applications validated for the respective purpose. Graphs and tables will be generated using validated customised SAS® macros or appropriate graphic software. A reference to the software used, e.g., name, will be indicated in the clinical trial report.

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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).

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ (below limit of quantification), but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

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

Drug concentration data identified with no sample available (NOS), no valid result (NOR), not analysed (NOA), BLQ, or no peak detectable (NOP) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

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

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Subjects will be randomised to one of the two treatment sequences in a 1:1 ratio.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

The sample size for the trial was determined assuming a geometric mean of 110% (tablet/capsule) and an intra-subject coefficient of variation (gCV) of 70% for AUC or C_{max} based on the following possible scenarios. The gCV for capsule formulation were observed as 49.67% for C_{max} and 49.83% for AUC in trial 1160.117*. The gCV for tablet formulation were observed as 62.9% for C_{max} and 69.3% for AUC in trial 1160.246. The Geometric mean ratio of AUC and C_{max} was observed as 1.08 (tablet/capsule) in trial 1160.246.

Since both endpoints of tablet and capsule formulations are highly variable, possible outcome scenarios are conservatively assumed to detect possible bioequivalence. It is assumed that gCV for both formulations can be variable from 50% to 70% as observed in gCV for test formulation in further analysis of the pilot BA study of 1160.246 and geometric mean ratio can be increased from 1.08 to 1.10.

Based on the scenarios and the sample size of 160, the power to reject the null hypothesis of bio-inequivalence for one parameter (for AUC or C_{max}) in favour of equivalence at the 5% level of significance is displayed in Table 7.6: 1 under various assumptions for the intra-subject ratio.

Table 7.6: 1 Power for concluding bioequivalence in a replicate design crossover trial (N=160) based on a geometric mean of 110% and a geometric coefficient of variation of 70% and an acceptance range of 80-125% for different expected ratios of means (tablet/capsule) and gCVs

Given Sample Size 160		Possible gCV		
		0.5	0.6	0.7
Possible Geometric mean ratio	1.08	98.8%	94.3%	89.2%
	1.09	98.4%	93.9%	86.9%
	1.1	94.7%	90.8%	81.7%

1) Ratio of the geometric means (tablet/capsule) for a PK endpoint defined by exp(μT)/exp(μR) (cf. Section 7.2)

From Table 7.6:1, a sample size of 152 will have at least 80% power to conclude bioequivalence if the ratio is between 108% and 110%, that is not more than 10% different from the ratio of 100% that reflects perfect equivalence and the gCV is between 50% and 70%. 160 subjects should be recruited in the trial.

If bioequivalence cannot be demonstrated because of an insufficient sample size, an extension of the trial can be performed by adding not less than half the number of subjects in the initial trial.

The calculation was performed as described by Diletti et al [R94-1445] using SAS 9.4..

*Trial 1160.117 is an open-label, randomised, single dose, replicate design in a two treatments, four periods crossover phase I study to compare two different capsule formulations of dabigatran etexilate and its sample size was 180 subjects. The true gCVs of its reference capsule formulation are assumed to be identical to those of the capsule formulation used in this study.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective 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 are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the trial master file.

8.3 RECORDS

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

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) 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 regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R03-1231 Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation). Circulation 2001;104:2118-2150.

R07-0628 National Institute of Health Sciences (NIHS). Guideline for bioequivalence studies of generic products (amendment 2, November 2006). 13F; Original in Japanese. 2006

R12-3703 Guideline for bioequivalence studies of generic products (English translation of attachment 1 of division-notification 0229 no. 10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012). Website:nihs.go.jp/drug/be-guide(e)/Generic/GL-E_120229_BE.pdf (access date: 20 August 2012); 2012.

R15-5604 Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013).Original in Japanese. Website: j-circ.or.jp/guideline/pdf/JCS2013_inoue_h.pdf (access date: 3 November 2015); Japanese Circulation Society (JCS) (2013)

9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c01632884-04 Dabigatran etexilate(BIBR 1048MS) Investigator's Brochure Current version.

c03032935-01 Randomised Evaluation of Long term anticoagulant therapy (RE-LY®) comparing the efficacy and safety of two blinded doses of DE with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® STUDY). BI Trial No. 1160.26. 20 March 2015.

c09145064-01 Relative bioavailability of dabigatran after single oral administration of five different tablet formulations of dabigatran etexilate compared to commercial capsule formulation in healthy male subjects (an open-label, randomised, single-dose, six-period, five-sequence crossover study). BI Trial No. 1160.246. 6 December 2016.

U00-1856 Safety, pharmacodynamics and pharmacokinetics after multiple oral doses of 50, 100,200 and 400 mg BIBR 1048 MS solution administered t.i.d. for 7 days to healthy volunteer subjects. An open study, placebo-controlled, randomised, double blind at each dose level. BI Trial No. 1160.2. 22

U01-1602 [redacted] Investigation of the human cytochrome P450 enzymes involved in the metabolism of [14C]BIBR 1048 MS and [14C]BIBR 953 ZW. Study no. B1765. 16 August 2001.

U05-3052 [redacted] Safety, pharmacokinetics and pharmacodynamics after single rising oral doses of 50, 150 and 350 mg BIBR 1048 MS as capsules in healthy subjects of Japanese and Caucasian origin. Double-blind at each dose level, placebo-controlled, randomised study 1160.28 19 May 2005.

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U09-3249-02 Randomised Evaluation of Long term anticoagulant therapy (RE-LY®) comparing the efficacy and safety of two blinded doses of DE with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® STUDY). BI Trial No. 1160.26.16 October 2009. Revision No. 1 dated05 January 2011.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
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		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c11669965 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Bioequivalence of tablet formulation of dabigatran etexilate compared to commercial capsule formulation following oral administration in healthy male subjects (an open-label, randomised, single-dose, replicate design in a two-treatment, four-period, two-sequence crossover study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	14 Feb 2017 06:19 CET
Author-Trial Clinical Pharmacokineticist		14 Feb 2017 07:39 CET
Approval-Team Member Medical Affairs		14 Feb 2017 08:41 CET
Approval-Therapeutic Area [redacted]		15 Feb 2017 17:45 CET
Author-Trial Statistician		16 Feb 2017 04:26 CET
Verification-Paper Signature Completion		17 Feb 2017 00:44 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed