Clinical Trial Protocol

Doc. No.: c02244185-04

EudraCT No.:	2013-003444-24
BI Trial No.:	1160.189
BI Investigational Product:	Pradaxa®, Dabigatran etexilate
Title:	**R**andomized, double-blind, **E**valuation in secondary **S**troke **P**revention comparing the **E**ffica**C**y and safety of the oral **T**hrombin inhibitor dabigatran etexilate (110 mg or 150 mg, oral b.i.d.) versus acetylsalicylic acid (100 mg oral q.d.) in patients with **E**mbolic **S**troke of **U**ndetermined **S**ource (RESPECT ESUS)
Clinical Phase:	III
Trial Clinical Monitor:	Phone: Fax:
Coordinating Investigator:	Phone Fax
Status:	Final Protocol (Revised Protocol (based on global Amendment 1 and 2)
Version and Date:	**3.0** **Date: 21 Apr 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Pradaxa®			
Name of active ingredient: Dabigatran			
Protocol date: 27JUN2014	**Trial number:** 1160.189		**Revision date:** 21 Apr 2016

Title of trial:	Randomized, double-blind, evaluation in secondary stroke prevention comparing the efficacy and safety of the oral thrombin inhibitor dabigatran etexilate (110 mg or 150 mg, oral b.i.d.) versus acetylsalicylic acid (100 mg oral q.d.) in patients with embolic stroke of undetermined source (RESPECT ESUS)
Co-ordinating Investigator: Phone Fax	
Trial site(s):	Multi-center trial
Clinical phase:	III
Objective(s):	To demonstrate that the efficacy of dabigatran etexilate (110 mg b.i.d. or 150 mg b.i.d., with dosing according to age and renal function), is superior to ASA (100 mg once daily) for the prevention of stroke recurrence in patients with embolic stroke of undetermined source. The trial will also characterize the safety of dabigatran etexilate in this setting.
Methodology:	This is a double-blind, randomized, active comparator, event driven phase III superiority trial. Patients with ischemic ESUS within the last 3 months will be included (if aged ≥ 60 years with additional risk factor, patients with ESUS within the last 6 months can be included). It is designed to evaluate recurrent strokes (ischemic, hemorrhagic, or unspecified) with dabigatran etexilate versus the comparator acetylsalicylic acid (aspirin) (ASA), 100 mg quaque die (once a day) (q.d.).
No. of patients:	
total entered:	Approx. 6000*
each treatment:	Approx. 3000* dabigatran etexilate Approx. 3000* acetylsalicylic acid * These are approximations, as this is an event driven trial requiring 353 primary outcome events (OEs) to be reported to be sufficiently powered. The actual number of patients entered may increase or decrease based upon actual event rate. Sites will be notified when recruitment ends.
Diagnosis :	Recent (≤ 3 months; up to 6 months in selected patients) ESUS

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Main criteria for inclusion:	Patients aged ≥18 years after ESUS within the last three months (six months, if aged ≥ 60 years with additional risk factor) prior to randomization who are eligible for treatment with antithrombotic therapy (i.e. dabigatran etexilate / ASA). ESUS, defined as follows: ▪ Non-lacunar ischemic stroke detected by Computed Tomography (CT) or Magnetic Resonance Image (MRI) ▪ Absence of extracranial/intracranial atherosclerosis causing ≥50% luminal stenosis in artery supplying the area of recent brain ischemia. ▪ No major-risk cardioembolic source of embolism ▪ No other specific cause of stroke identified (e.g. cerebral arteritis, arterial dissection, migraine with aura/vasospasm, drug abuse)
Test product(s):	Dabigatran etexilate (DE)
doses:	110 mg and 150 mg twice daily (b.i.d.)
mode of admin.:	Oral
Comparator products:	Acetylsalicylic acid (Aspirin)
dose:	100 mg once daily (q.d.)
mode of admin.:	Oral
Duration of treatment:	Expected minimum: 6 months Expected maximum: 3 years This event driven trial may conclude earlier, once adequate number of events are reported, or later; if more events are needed.

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Criteria for efficacy:

Primary efficacy endpoint (adjudicated):

• Time to first recurrent stroke (ischemic, hemorrhagic, or unspecified)

Secondary efficacy endpoints (time to event)

Key secondary efficacy endpoints

• Ischemic Stroke

• Composite endpoint of nonfatal stroke, nonfatal myocardial infarction (MI) and cardiovascular death

Other Secondary efficacy endpoint (time to event):

• Disabling stroke (modified Rankin Scale ≥4, as determined 3 months after recurrent stroke)

• All-cause death

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Criteria for safety:	**Main safety endpoint**: • Time to first major bleed **Other safety endpoints (time to event)**: • Intracranial hemorrhage • Life-threatening bleed • Fatal bleed • Any bleed		
Statistical methods:	The Cox proportional hazards regression model will be used to analyze time-to-event endpoints.		

FLOW CHART

Investigations/Tests and Procedures	**SCREENING**	**RANDOMIZATION**	**TREATMENT PERIOD[4]**											**FOLLOW UP PERIOD**	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[2]**	**8**	**9[2]**	**10**	**11[2]**	**12**	**13[2]**	**EOT[3]**	FINAL VISIT[3, 5]	PHONE CALL[6]
Months since Randomization			3	6	9	12	15	18	21	24	27	30	33			
Time Window (days)[4]	Up to -14 days	0[1]	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14		+/- 14	+/- 14
Informed Consent	X															
Check Eligibility	X	X														
Medical History	X															
Demographics	X															
Confirm Inclusion/Exclusion		X														
Randomization via IRT		X														
Physical Exam	X														X	
Vital Signs (BP, sitting heart rate)[7]	X	X	X	X	X	X		X		X		X		X	X	
ECG[8]	X	(X)		(X)		X		(X)		X		(X)		X	(X)	(X)
Documentation of Cardiac Monitoring[8]	X	(X)	(X)	(X)	(X)	(X)		(X)		(X)		(X)		(X)	(X)	
Pregnancy Test[9] for WOCBP	X		X	X	X	X		X		X		X		X	X	X
Safety Laboratory Tests[10]	X	(X)[10]		X		X		X		X		X		X	X	
Weight	X			X		X		X		X		X		X	X	
Height	X															

Investigations/Tests and Procedures	**SCREENING**	**RANDOMIZATION**	**TREATMENT PERIOD[4]**													**FOLLOW UP PERIOD**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[2]**	**8**	**9[2]**	**10**	**11[2]**	**12**	**13[2]**	**EOT[3]**	FINAL VISIT[3, 5]	PHONE CALL[6]
Months since Randomization			3	6	9	12	15	18	21	24	27	30	33			
Time Window (days)[4]	Up to -14 days	0[1]	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14		+/- 14	+/- 14
NIHSS[17]	X															
Stop Restricted Meds[18]		X														
Brain re-imaging in select patients[19]	(X)[19]		(X)[19]													
Dispense Study Meds		X	X	X	X	X		X		X		X				
Study Med Compliance Check			X	X	X	X		X		X		X		X		
Concomitant Therapy[20]	X	X	X	X	X	X		X		X		X		X	X	X
Study Med. Termination														X[3]		
Record OEs[21] SAEs, bleeds, AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transition to SOC per PI's discretion														X		
Remind patients of plan to collect Vital Status (regardless of status of study drug administration)														X		

1. It is preferred randomization to occur as soon as possible after confirming eligibility. Informed consent will be signed any time before screening procedures. Randomization must occur within 3 months of index stroke event. In patients ≥ 60 years plus additional risk factor (see inclusion criteria Section 3.3.2) the time window is 6 months after index stroke event.
2. Visits 7, 9, 11, 13 can be conducted via phone to assess OEs and AEs.
3. Patients who discontinue study treatment early should complete EOT assessments and continue to attend regularly scheduled visits. Refer to Section 3.3.4.1 for details on management of patients that wish to reduce study participation for any reason. Collection of vital status, adverse events and endpoints for all patients at the end of the trial is important and described in Section 6.2.3. For patients that continue on treatment until the end of the trial, EOT and Final Visit assessments can be done at the same visit.
4. Follow-up visits should be scheduled every three months within the specified visit window (+/- 14 days) where feasible.
5. Final Visit will take place at the conclusion of the trial. This event-driven trial is expected to take place over 3 years, however, the trial can conclude earlier, if adequate number of events are reported sooner. It can conclude later (or enroll additional patients) if more time is needed to observe the minimum number of required events. If it continues beyond 3 years, follow-up visits will occur every 3 months (with alternating phone and office visits with same assessments as for example in visits 9 and 10). At the time of trial conclusion (when adequate number of events were reported), all patients would be notified of study conclusion and have a final study visit scheduled instead of their next scheduled follow-up visit (with assessments as outlined in the Final Visit).
6. A follow-up phone call will be conducted one month after the EOT visit (for patients with premature study medication discontinuation) or one month after the Final Visit (for patients without premature study medication discontinuation).
7. Recording of vital signs will include blood pressure (BP) and sitting heart rate with palpation of the pulse for 1 minute. Also, the subject should be queried about new palpitations that would warrant additional cardiac rhythm monitoring at the discretion of the investigator. An Electrocardiogram (12-lead ECG) is required at follow-up visits per instructions in footnote 8.
8. A 12-lead ECG should be performed at Visits 1, 6, 10 and at the EOT visit and will be documented in the Electronic Case Report Form (eCRF). It will be documented, whether the patient carries an implantable cardiac monitor for continuous cardiac monitoring. A subsequent ECG should also be done, if palpation of the pulse (for one minute) in subsequent visits indicates irregular rhythm or symptoms of irregular pulse have been reported. If any ECGs are performed during the course of the trial as part of patient normal care and demonstrate a clinically relevant change from Visit 1 or a newly developed pathology, this should be documented in the Electronic Case Report Form (eCRF) and the ECG will be provided to the Sponsor`s designee. Additional cardiac monitoring (e.g. Holter-ECGs) may be performed at the discretion of the Investigator according to local standard of care. Where this is done, the results of these cardiac monitoring efforts will be documented in the eCRF.
9. Women of child-bearing potential (WOCBP) who are not sterilized should have a urine pregnancy test at screening, at each clinic visit and at least 7 days after the EOT (urine dipstick result to be reported back at final phone visit). Pregnancy testing is one indicator of pregnancy. Changes in a patients' menstrual cycle that may indicate pregnancy must also be considered and a further pregnancy test can be taken if the Investigator feels it to be appropriate.
10. Standard safety lab panel to be analyzed by central lab (hematology and chemistry, including renal function and liver function tests (LFTs) will be collected). Lab testing is specified in Section 5.2.3. Local labs (within 14 days prior to randomisation) can be used to verify eligibility (in addition to collection of central labs) where it is necessary to avoid delaying the initiation of study drug. Refer to Section 5.2.3 for calculation of Creatinine Clearance (CrCl) and Section 4.1.3 for information about dose changes based upon CrCl value. Central labs must also be collected from all patients to provide a baseline for the study. This should preferably occur at Visit 1, however, it can alternatively be collected at Visit 2 prior to first study drug intake. Follow-up safety labs do not need to be drawn on the actual day of the visit. They may be drawn earlier as long as it is within the visit time window.

17. National Institutes of Health Stroke Scale (NIHSS) is a tool used to evaluate impairment after a stroke outlined in Section 5.3.2. This neurological assessment is to be completed for qualifying stroke only. NIHSS is not required after recurrent stroke.
18. Restricted medications are listed in Section 4.2.2.
19. Recommendations on timing of starting study medication after index stroke and recurrent stroke are provided in Table 4.1.4:1. Patients with mRS of 1,2 or 3 AND initiating study medication within 10 days of index event require repeat imaging of the brain to rule out bleeding into the brain (per Exclusion #6). For index strokes, this repeat imaging must occur prior to randomization. This repeat imaging done specifically to initiate study drug is required per protocol in select patients. Conversely, brain imaging for initial evaluation of index and recurrent strokes should occur according to local clinical practice (i.e. not done specifically for this trial).
20. Concomitant medication will include medications of interest taken during the 30 days prior to randomization plus those given as treatment for index stroke.
21. For endpoint events which require adjudication as per Section 3.1.1.4., copies of relevant source documentation (e.g. imaging reports) should be collected and submitted.

TABLE OF CONTENTS

ABBREVIATIONS

ACCP	American College of Chest Physicians
ACT	Activated Clotting Time
APCC	Activated prothrombin complex concentrates
ACS	Acute Coronary Syndrome
AE	Adverse Event
AF	Atrial fibrillation
AHA	American Heart Association
ALT (SGPT)	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
ASA	Acetylsalicylic acid (Aspirin)
ASS	Acetylsalicylsäure (German brand name for ASA)
AST (SGOT)	Aspartate transaminase
AUC	Area under the Curve
b.i.d.	Twice daily
BI	Boehringer Ingelheim
BMI	Body Mass Index
BP	Blood Pressure
BRPM	Blinded Report Planning Meeting
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CI	Confidence Interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	Creatine kinase myoglobin
CML	Local Clinical Monitor
CoI	Coordinating Investigator
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRNMBE	Clinically Relevant Non Major Bleeding Event
CT	Computed Tomography
cTn	Cardiac Troponin
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CUS	Compression Ultrasound
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DE	Dabigatran etexilate
DMC	Data Monitoring Committee
dTT	Diluted thrombin time
DVT	Deep vein thrombosis
eCRF	Electronic Case Report Form

EC	Ethics Committee
ECG	Electrocardiogram
ECT	Ecarin clotting time
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End of Treatment
ESUS	Embolic stroke of undetermined source
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GFR	Glomerular Filtration Rate
gMean	Geometric mean
HPMC	Hydroxyl, propyl-methyl cellulose
HPLC-MS/MS	High-Performance Liquid Chromatography tandem mass spectrometry
HR	Hazard Ratio
hscTnI	High-sensitivity cardiac troponin I
hsCRP	High-sensitivity C-reactive protein
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IL-6	Interleukin 6
IRB	Institutional Review Board
ISF	Investigator Site File
ISTH	International Society of Thrombosis and Hemostasis
i.v.	Intravenous
IRT	Interactive Response Technology
IUDs/IUSs	Intra Uterine Devices/Systems
LBBB	Left Bundle Branch Block
LFTs	Liver Function Tests
LMWH	Low-molecular Weight Heparin
LPO	Last Patient Out
LTFU	Lost to Follow-Up
LVH	Left Ventricular Hypertrophy
MBE	Major Bleeding Event
MCP-1	Monocyte chemotactic protein-1
MDRD	Modification of Diet in Renal Disease
mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Image

mRS	Modified Rankin Scale
N	Number
NCB	Net Clinical Benefit
NIHSS	National Institutes of Health Stroke Scale
NOAC	Novel oral anticoagulant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OE	Outcome Event
OPU	Operative Unit
P-gp	P-glycoprotein
p.o.	per os (oral)
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PE	Pulmonary embolism
PFO	Patent foramen ovale
PK	Pharmacokinetic
PR	Pulse Rate
PT	Prothrombin time
q.d.	quaque die (once a day)
REP	Residual Effect Period
RS	Randomized set
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SC	Steering Committee
SD	Standard deviation
SE	Systemic Embolism
SPAF	Stroke prevention in atrial fibrillation
SPC	Summary of Product Characteristics
SUSARs	Suspected Unexpected Serious Adverse Reactions
TCD	Transcranial Doppler
TE	Thromboembolism
TEE	Transesophageal echocardiogram
TGF-β1	Transforming growth factor beta 1
TIA	Transient Ischemic Attack
TMA	Transcription-mediated amplification
TMF	Trial Master File
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TT	Thrombin time
TTE	Transthoracic echocardiogram
UFH	Unfractionated Heparin

ULN	Upper Limit of Normal
URL	Upper Reference Limit
VKA	Vitamin K antagonist
VPLS	Ventilation/perfusion lung scan
vs.	Versus
VTE	Venous thromboembolism (i.e. DVT and/or PE)
vWF	von Willebrand Factor
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

About 20-25% of ischemic strokes are not lacunar (i.e. due to small artery disease), are not associated with occlusive atherosclerotic stenosis, and do not have a major cardioembolic source, such as in atrial fibrillation (AF) (P14-04527). Recent monitoring and imaging studies have characterized a substantial number of potential sources of embolism in these patients, supporting that most strokes that were formerly called *"cryptogenic"* can be more usefully characterized as Embolic Stroke of Undetermined Source (ESUS) (P14-04527).

Improvements in imaging technologies and a better understanding of the underlying pathophysiology of ESUS have resulted in a pragmatic clinical definition. An International "ESUS Working Group" has been established consisting of lead neurologists and cardiologists in the field. The ESUS working group has defined "ESUS" as a new stroke entity (P14-04527). These patients can be reliably and consistently identified using widely-available diagnostic techniques. The ESUS definition is pragmatic and offers the potential for randomized trials of secondary prevention. The ESUS definition has been derived from the former definition of "cryptogenic" stroke. However, cryptogenic stroke is a diagnosis by exclusion, including cases, where certain diagnostic examinations have not been performed. Thus, cryptogenic stroke is rather defined by what it is not, whereas the ESUS concept postulates an embolic pathophysiological mechanism for the ischemic stroke, and is thus positively defined. Embolic Stroke of Undetermined Source is not considered a diagnosis of exclusion, but rather a diagnosis based on a visualized non-lacunar infarct in the absence of proximal occlusive atherosclerosis or major-risk cardioembolic source such as AF or intracardiac thrombus.

The sources of embolism underlying ESUS include the heart (the left heart valves or chambers, or via paradoxical embolism from a venous source), aortic arch, or the large cervical and cerebral arteries. Confident identification of the embolic source in individual patients is not feasible. Multiple potential embolic sources occur in the same patient with sufficient frequency that a causal relationship is unclear; sophisticated diagnostic testing is of limited availability and often not illuminating. However, the embolic mechanism implies a common potential treatment strategy (i.e. anticoagulation), making precise characterization of the embolic source of uncertain clinical value.

Underlying Causes of ESUS

There seems to be no single, dominant cause of ESUS. In studies in which patients with cryptogenic ischemic stroke undergo prolonged cardiac rhythm monitoring for silent AF, paroxysmal AF is detected in 10% - 20% (R11-4017, R13-4009, R13-4062). Cardiac rhythm abnormalities other than AF, which can lead to formation of atrial thrombi and embolic stroke, include for example atrial asystole and paroxysmal atrial tachycardia. Additional other cardioembolic sources such as moderate left ventricular systolic dysfunction/heart failure, left ventricular diastolic dysfunction promoting atrial stasis, remote MI with left ventricular regional wall motion abnormalities, myxomatous mitral valves with prolapse, mitral annular calcification, and calcific aortic stenosis are likely to contribute to ESUS in some patients

(P92-68903). Patent foramen ovale (PFO) can cause ESUS via paradoxical embolism of thrombi originating in the venous system entering the arterial system through an inter-atrial defect; case-control studies consistently show a higher frequency of PFO in patients with cryptogenic stroke (R13-4063). Another important cause of ESUS is atherosclerosis of the aortic arch serving as a source of arteriogenic embolism (R13-4059, R13-4058). There is a persuasive relationship between nonstenotic ulcerated plaques of the carotid artery and distal brain ischemia mediated through embolism (R13-4064).

Characterization and Description ESUS

Investigations to establish the diagnosis of ESUS must be sufficient to exclude major-risk cardioembolic sources, proximal occlusive atherosclerosis of intra and extra-cranial great arteries, and cerebral small artery disease causing lacunar strokes (for diagnostic criteria see Table 1.1: 1).

Evaluation must also be sufficient to exclude recognized major-risk cardioembolic sources such as AF and left ventricular thrombus that would warrant anticoagulation (P14-04527).

Table 1.1: 1 Criteria for diagnosis of ESUS (all must be fulfilled)[1]

1. Stroke detected by CT or MRI that is not lacunar[2]
2. Absence of extracranial or intracranial atherosclerosis causing ≥ 50% luminal stenosis in artery supplying the area of recent brain ischemia.
3. No major-risk cardioembolic source of embolism.[3]
4. No other specific cause of stroke identified (e.g. autoimmune arteritis, arterial dissection, migraine with aura, vasospasm, drug abuse).

[1] Requires completion of minimum diagnostic evaluation (see Table 3.3.1: 1)
[2] Lacunar is defined in Section 3.3.3 exclusion criterion No. 21
[3] Paroxysmal, persistent or permanent AF (please see inclusion criterion 4 for guidance on the detection of AF), atrial flutter, intracardiac thrombus, prosthetic cardiac valve (mitral or aortic, bioprosthetic or mechanical), atrial myxoma or other cardiac tumors, moderate or severe mitral stenosis, recent (<4weeks) MI, valvular vegetations, or infective endocarditis.

Prevalence

An estimated 300,000 patients have an incident of ESUS annually in North America and Europe (P12-14353, R06-2203). Among them, the stroke recurrence rate is substantial. Approximately 3-4% per year occur despite antiplatelet treatment which is the standard guideline-recommended therapy for secondary stroke prevention for patients with cryptogenic stroke (P14-04527, P11-00444).

Current guideline recommendations on antithrombotic treatment for secondary stroke prevention.

The routine use of anticoagulants (such as warfarin) in clinical practice is not established for cryptogenic stroke nor in patients with ESUS. The 2008 American College of Chest Physicians (ACCP) guideline and 2008 American Heart Association (AHA) guideline specifically recommend antiplatelet therapy for patients with cryptogenic ischemic stroke (P08-06684, P08-09258). The European Stroke Organization guideline, the 2011 and 2014 AHA/American Stroke Association revised guidelines, the 2012 ACCP guideline and the 2010 Canadian Best Practice Recommendations for Stroke Care do not comment specifically on cryptogenic stroke, but recommend antiplatelet therapy for secondary stroke prevention in patients with non-cardioembolic ischemic stroke (P13-11327, P08-08481, P11-00444, P14-07233). As acetylsalicylic acid (ASA) monotherapy is currently recommended by international guidelines for acute treatment of ischemic stroke and TIA and secondary prevention of recurrent stroke, most ESUS patients will have been treated with ASA during the interval between qualifying stroke and randomization. A once daily dosage of 100 mg of ASA is included in all guidelines and is acceptable to most clinicians around the world.

There is clear evidence of the superiority of warfarin anticoagulation over acetylsalicylic acid for stroke prevention in AF (P07-07953). The novel oral anticoagulant (NOAC) dabigatran etexilate (DE) has been demonstrated to be effective against cardioembolic stroke related to AF with significantly reduced risk of intracranial hemorrhage compared to warfarin. Thus, it is hypothesized that DE may be a safe and effective therapy for secondary prevention of stroke in patients with ESUS (see Section 2.3 for Benefit-Risk Assessment).

Patients are at highest risk of recurrent stroke in the first days after index stroke as demonstrated by the CHANCE trial (R15-2975). The RE-SPECT ESUS study will assess the effectiveness and safety of DE versus ASA with study medication started early during this high risk period. Providing cerebral hemorrhage is ruled out, study drug can be started as early as one day after index stroke. For details on recommended earliest study drug start according to stroke severity, refer to Table 4.1.4:1.

1.2 DRUG PROFILE

Dabigatran etexilate is the orally bioavailable prodrug of dabigatran, a novel, synthetic, direct thrombin inhibitor. Following oral administration DE is rapidly converted to the active moiety dabigatran, which is a potent, competitive, and reversible inhibitor of thrombin.

In vivo and ex vivo animal studies have demonstrated antiaggregatory efficacy and anticoagulant activity of dabigatran after both intravenous (i.v.) administration and oral administration in various animal models of arterial and venous thrombosis.

Dabigatran etexilate was well tolerated in more than 40 Phase I studies to date at all doses evaluated (up to 400 mg three times a day) with no evidence of major bleeding. These studies have established the PK, pharmacodynamics (PD) and tolerability of dabigatran, including selected populations (Japanese, elderly, those with renal and hepatic impairment) and its potential for food-drug and drug-drug interactions and QT prolongation.

The PK profile is characterized by peak plasma concentrations of dabigatran that occur approximately two hours after oral administration of the prodrug and half-life depending on renal function (see Table 4.2.1: 1 and U98-3208 for prolongation of half-life with decline in renal function). Dabigatran maximum plasma concentrations and area under curve increase in a dose proportional manner. Pharmacokinetic steady state is reached by three days with twice daily (b.i.d.) dosing, PD (anticoagulant) activity is closely correlated with dabigatran plasma concentrations. Dabigatran is eliminated primarily by the kidneys with urinary excretion accounting for approximately 80% of the dose administered intravenously. The absolute bioavailability of the current capsule formulation of DE is approximately 6.5%.

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. Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system 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 ketoconazole single and multiple dose co-administration 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 long-term Phase III study, Randomized Evaluation of Long-Term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY) (1160.26) had much smaller effects (increase of dabigatran plasma concentration of up to 16%) (U09-3249-02) than those observed in Phase I studies.

The PK and PD of dabigatran in subjects with normal renal function in comparison to patients with varying degrees of renal impairment (mild, moderate, severe and dialysis dependent end stage renal disease) have been studied in an open, group-comparison design trial of 36 subjects. In otherwise healthy volunteers with mild (CrCl ≥50 and <80mL/min), moderate (CrCl ≥30 and <50mL/min), and severe (CrCl <30mL/min) renal impairment, the area under the curves (AUCs) of dabigatran were increased 1.8, 2.7 and 6.8 fold respectively, compared to healthy volunteers with normal renal function (CrCl >80mL/min) (U06-1704). This is in accordance with the fact that dabigatran is mainly renally excreted.

The RE-LY trial was a Phase III, prospective, randomized, open-label, multinational trial of stroke prevention in patients with non-valvular AF at risk of stroke. A total of 18,113 patients were randomized to one of two blinded doses of DE (110 mg b.i.d. or 150 mg b.i.d.) or to warfarin (target INR 2.0-3.0) (U09-3249-02).

RE-LY demonstrated that DE, 150 mg b.i.d., was superior to warfarin for the prevention of stroke and SE in patients with non-valvular AF and at least one risk factor for stroke with comparable rates of major bleeding. Dabigatran etexilate 150 mg b.i.d. resulted in reductions of intracranial hemorrhage, total bleeding and vascular mortality. Dabigatran etexilate 110 mg b.i.d. was non-inferior to warfarin for the primary endpoint of stroke and SE and reduced intracranial hemorrhage, major bleeding and total bleeding. In RE-LY, ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations: Lower plasma concentrations were associated with a higher risk of ischemic stroke, whereas the risk of major bleeding increased with higher plasma concentrations (P13-12662). However, the plasma concentration in an individual patient must be interpreted in the context of the patient profile taking all potential covariates, such as age and renal function, into account. Renal function and age are equally important in determining a patient`s overall risk of bleeding.

By considering the characteristics of the targeted population for this trial (specifically renal function and age) PK dose modeling shows that the median trough plasma level of dabigatran is predicted to be 89 ng/mL in patients with ESUS receiving DE 110 mg b.i.d., which is only slightly higher compared to patients receiving DE 150 mg b.i.d. in this trial (median of 74 ng/mL). The overall exposure target in this trial (77 ng/mL) is thus higher than the level achieved with 110 mg b.i.d. in RE-LY (median 65 ng/ml) but below the level obtained with 150 mg b.i.d. (median 93 ng/ml). This target is chosen based on the fact that that treatment start will be early after the index stroke event in patients with an ischemic brain lesion and due to the fact this is a different patient population compared to RE-LY, i.e. patients with AF are excluded from this trial.

Antiplatelet agents (ASA or clopidogrel) are known to increase bleeding. In RE-LY (U09-3249-02), the yearly major bleeding events (MBEs) were about twice as high in patients receiving additional ASA or clopidogrel, but this effect was similar to that observed when ASA or clopidogrel was administered with warfarin (P13-00071). The use of concomitant antiplatelet medication in this trial will increase the risk of bleeding and is thus prohibited in this trial with the exception of selected patients who may receive masked ASA or ASA-placebo via Interactive Response Technology (IRT) (see Section 4.1.1).

Given the common thromboembolic mechanism in both AF and ESUS, it is likely that DE would reduce recurrent brain ischemia in patients with ESUS more effectively than antiplatelet therapy. The overall benefit of dabigatran to treat this indication, specifically to reduce the risk of recurrent stroke, is hypothesized to outweigh known bleeding risks.

The current version of the Investigator's Brochure (IB) (U98-3208) contains additional information on drug-drug interaction studies, completed Phase II/III trials and studies in special patient populations.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

There is uncertainty over the optimal stroke prevention treatment for patients with ESUS. The current treatment recommendations of ASA alone, sometimes given with clopidogrel or ticlopidine (P08-06684, P08-08481) are based on limited data.

There is some evidence from subanalyses of secondary stroke prevention trials that the use of anticoagulants (such as warfarin) may provide benefits over antiplatelets after strokes with a clear embolic pattern, although a prospective randomized trial in this specific patient population has not yet been conducted. The only randomized evaluation of anticoagulation in cryptogenic stroke is the subgroup analysis of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) (R03-0581, R13-4061). Patients with recent (<30 days) ischemic stroke were randomized to ASA 325 mg/d or adjusted-dose warfarin (target INR 1.4-2.8, median achieved INR = 1.9). Of the 2206 patients, 26% (n=576) were deemed cryptogenic/of undetermined etiology based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, although the extent of diagnostic evaluation was not reported (R97-1235). In cryptogenic stroke patients, the primary outcome of ischemic stroke or death occurred in 15.0% assigned to warfarin vs. 16.5% assigned to acetylsalicylic acid over two years (Hazard Ratio (HR) 0.92, 95% Confidence Interval (CI) 0.6-1.4) (R03-0581). For 338 participants of the WARSS trial with cryptogenic stroke whose CT showed an "embolic topography" (i.e. eliminating lacunar strokes), the two-year rate of recurrent ischemic stroke or death was 12% with warfarin vs. 18% with acetylsalicylic acid (HR=0.66, 95% CI 0.4-1.2) (R13-4061). In another substudy of WARSS (PFO in Cryptogenic Stroke Study), 260 of the 576 patients with cryptogenic stroke underwent transesophageal echocardiography (R13-3472). In this subset of patients, the primary outcome (two-year rate of recurrent ischemic stroke or death) was halved in those assigned to warfarin (9% warfarin vs. 17% acetylsalicylic acid) despite the low achieved intensity of warfarin anticoagulation. The WARSS subgroup data support the hypothesis that anticoagulation may be more efficacious than acetylsalicylic acid for patients with cryptogenic ischemic stroke when those with lacunar stroke topography are excluded.

In the ESPRIT trial involving 1068 patients with presumed arteriogenic ischemic stroke (i.e. not restricted to cryptogenic stroke) randomized to an oral vitamin K antagonist (mean achieved INR 2.6) vs. ASA, recurrent ischemic stroke was reduced by 24% (HR: 0.76; 95% CI 0.51-1.15) by anticoagulation (P07-00680). Of note, the relationship between achieved INRs and stroke rates in each of the three modern randomized trials comparing vitamin K antagonists with ASA for secondary prevention of non-cardioembolic stroke (P07-00680, P05-03338, R03-0581) paralleled those from trials testing warfarin in AF patients (R13-4120, R13-4060).

For major-risk cardiogenic sources of embolism (i.e. AF), randomized trials have demonstrated that anticoagulants markedly reduce embolic strokes relative to antiplatelet

agents (P07-07953, P06-06455, R11-0578, R12-2020). The novel factor Xa inhibitors apixaban, endoxaban and rivaroxaban and the direct thrombin inhibitor DE have demonstrated to be at least as effective as warfarin for prevention of stroke in AF patients with significantly lower rates of intracranial bleeding (P09-11669, R11-4223, R11-4190, R13-5082).

A randomized trial comparing an oral anticoagulant with antiplatelet therapy for secondary prevention among ESUS patients is warranted and justified by the effectiveness of warfarin for stroke prevention in patients with major-risk cardioembolic sources such as AF, subgroup analyses from prior warfarin trials, and the introduction of safer and more effective novel anticoagulants. The NOAC DE is highly effective against embolic stroke in AF and has an excellent safety profile with a low risk of intracranial hemorrhage (U09-3249-02). Dabigatran etexilate is likely to reduce stroke recurrence in ESUS compared with ASA and to be associated with an acceptably low rate of major hemorrhage. The current trial intends to deliver evidence of the effectiveness and safety of DE in ESUS patients with the goal of expanding the market authorization of dabigatran etexilate and improving patient care.

2.2 TRIAL OBJECTIVES

The objective of this study is to demonstrate that the efficacy of DE (110 mg b.i.d. or 150 mg b.i.d., with dosing according to age and renal function), is superior to ASA (100 mg once daily) for the prevention of stroke recurrence in patients with stroke of undetermined source. The trial will also characterize the safety of DE in this setting. See Section 4.1.3 for more details on DE dose assignments.

Refer to Section 5 for list of primary, secondary and other endpoints.

2.3 BENEFIT - RISK ASSESSMENT

At the time this protocol was prepared, the safety and efficacy of DE had been evaluated in more than 27,000 patients in over 40 Phase I studies, nine completed Phase II studies, and 10 completed Phase III studies within multiple populations including:

- Venous thromboembolism (i.e. DVT and/or PE) prevention in patients who have undergone major orthopedic surgery
- prevention of stroke and SE in patients with nonvalvular AF
- acute treatment and secondary prevention of VTE (deep venous thrombosis and pulmonary embolism (PE))

The most commonly reported adverse reactions of DE are bleedings events. Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes. Standard management for bleeding (such as transfusion of blood products, etc.) needs to be applied as described in Section 4.2.1 and in Figure 4.2.1: 1. A specific reversal agent (idarucizumab) has been developed and is currently being reviewed for registration in various countries. When clinically indicated and available, it can be given to a patient in the context of a clinical trial

(e.g. BI trial 1321.3) or from commercial supply when it becomes approved. See Section 4.2.1 Overdose, for more information regarding the specific reversal agent for dabigatran.

The risk of major bleeding correlates with dabigatran plasma concentrations (P13-12662), but also depends on individual patient characteristics, such as age and renal function. Bleeding risk may also be higher in patients concomitantly treated with an antiplatelet agent, such as ASA or clopidogrel. Factors, such as decreased renal function (CrCl 30-50 mL/min), age ≥ 75 years, low body weight (< 50 kg), or mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels, thereby contributing to the overall risk of bleeding in an individual patient.

Therefore, the doses of DE which will be used in this clinical trial have been carefully chosen taking individual patient characteristics into account (i.e. age and moderate renal impairment) to offer the best likelihood of preventing recurrent strokes with the least chance of causing bleeding side effects.

Additional safeguards will be implemented to protect patient safety:

- The use of concomitant antiplatelet medication in this trial may increase the risk of bleeding and is thus prohibited in this trial with the exception of selected patients with coronary artery disease (CAD) who may receive masked ASA or ASA-placebo via IRT (see Section 4.1.1).

- Patients will undergo CrCl measurements at screening and patients with CrCl <30mL/min (at screening) will be excluded from participation to reduce the risk of bleeding, see Section 3.3.3 exclusion criteria.

- If a patient experiences severe renal impairment (CrCl <30mL/min) during the study, study drug will be withheld or stopped (see Section 3.3.4.1 and Section 5.2.3).

- If a patient experiences worsening of renal function (CrCl < 50 mL/min but greater than or equal 30 mL/min), experiences a gastrointestinal (GI) bleed (see Section 4.1.3 and Section 5.2.3), or reaches the age of 75 years during the course of the trial, DE dose assignment will be changed to 110 mg b.i.d. (see Section 3.3.4.1 and Section 5.2.3).

- Due to the high rate of stroke recurrence early after the index event, patients included in this trial will be randomized preferably early after ESUS (see Table 4.1.4: 1) to prevent stroke recurrence.

- Severely disabled patients with a mRS of 4 or higher will be excluded from this trial, because their size of ischemic brain lesion may predispose them to secondary bleeding into the brain when receiving an anticoagulant.

- Re-imaging of the brain is required in patients with mRS of 1, 2 or 3 if starting study medication within 10 days after index stroke to reduce the possibility of initiating study drug in patients with bleeding into the brain that was not detected at onset of

index stroke event. Randomization should only occur after re-imaging of the brain has been performed and eligibility has been confirmed (see Table 4.1.4: 1).

- Based on the findings on the nonclinical studies with DE conducted to date and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.

- Female patients are required to immediately contact the investigator if they experience signs and/or symptoms suggesting a potential pregnancy, or know that they are pregnant.

- A Data Monitoring Committee (DMC) will be established to monitor safety data of the study throughout the trial, and will recommend to the Sponsor whether to continue, modify or terminate the study (refer to Section 3.1.1.3 for details).

Given the common thromboembolic mechanism in both AF and ESUS, it is likely that DE would reduce recurrent brain ischemia in patients with ESUS more effectively than antiplatelet therapy. The overall benefit of DE to treat this indication, specifically to reduce the risk of recurrent stroke, is expected to outweigh known bleeding risks of DE. Thus, the risk benefit assessment is considered favorable for the initiation and conduct of this trial.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a phase III, event-driven, double blind, randomized controlled trial of DE versus (vs.) ASA. Patients with qualifying ESUS must be randomized within 3 months of the index stroke or within 6 months in selected patients as described in Section 3.3.2, Inclusion 2.b.

Eligible patients will be randomized (1:1 ratio) to double-blind treatment of one of the following two arms:

- Dabigatran etexilate plus placebo (matching ASA)

or

- Acetylsalicylic acid plus placebo (matching DE)

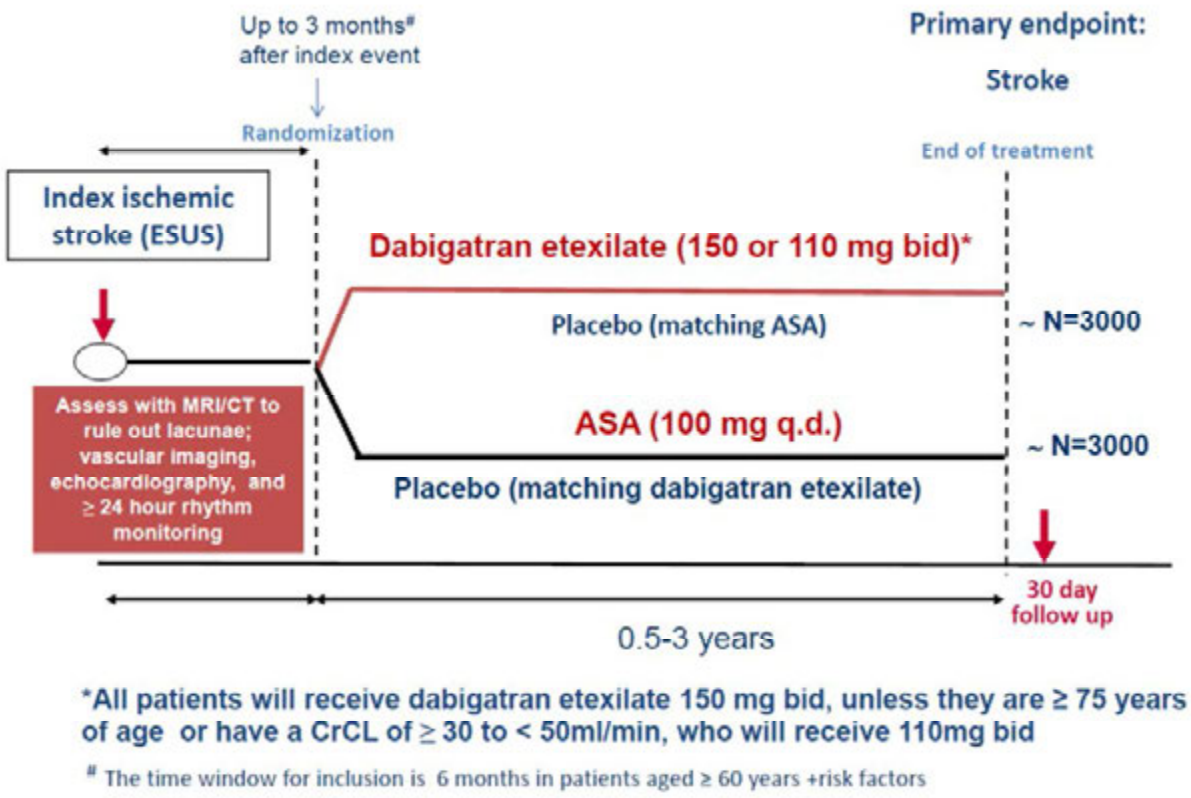


Figure 3.1: 1 Study Design

All patients will be followed until the end of the trial (regardless of study drug discontinuation status). To conclude the trial, at least 353 stroke events must be reported. The definition of stroke will be in accordance to the 2013 published recommendations of the AHA/American Stroke Association (R13-4110). Symptom resolution within 24 hours with

pathological imaging evidence of infarction (formerly classified as TIA) will be considered a stroke and the patient is eligible for this trial.

It is estimated that 6,000 patients and a total observation period of approximately 3 years will be necessary to achieve this number of events. The actual duration of the trial and number of patients enrolled may be increased or decreased as appropriate in order to achieve the necessary number of events. The Sponsor will monitor the observed cumulative blinded event rate and based upon this, the forecasted time to end of study will be calculated.

With recruitment estimated to take place during the first 2.5 years of the trial, average individual patient participation will be 21 months.

3.1.1 Administrative structure of the trial

The Sponsor of this trial is Boehringer Ingelheim (BI).

Investigators selected for participation will be neurologists or other physicians that are preferably affiliated with stroke centers or other healthcare institutions that routinely conduct work-up on stroke patients.

A central laboratory will perform all protocol specified blood analyses. To allow for early randomization, it is permitted, in exceptional cases, to randomize patients based on local laboratory results; for details see Section 6.2.1. Randomization based on central laboratory results is strongly encouraged and preferred.

Urine pregnancy testing will also be done (see Section 5.2.3).

An IRT will perform the randomization of patients and ensure appropriate distribution of trial medication to trial sites during the course of the trial.

All trial-related documents will be stored in the Trial Master File (TMF) at each individual BI Operative Unit (OPU) in accordance with standard operating procedures.

3.1.1.1 Executive Committee

Overall organization will be overseen by an Executive Committee, consisting of one Coordinating Investigator (CoI), two Co-chairs (one of which is the CoI), several Sponsor representatives and other experts in Neurology and Cardiology. The Executive Committee will provide the scientific leadership for the trial. They will oversee the conduct and execution of the trial, provide input on study design, provide advice on implementation of the trial and interactions with National Coordinators of the Steering Committee (SC) and/or Investigators to facilitate enrolment, patient retention and provide advice on issues that may arise during the conduct of the study. The activities of the Executive Committee will be described in a separate charter.

The CoI is selected based on expertise in this therapeutic area and reputation for being a leader in field. The CoI will review and sign the Clinical Trial Protocol (CTP) and Clinical Trial Report (CTR).

3.1.1.2 Steering Committee

A SC will be composed of the Executive Committee plus Country National Coordinators, other experts and representatives of the Sponsor. Country National Coordinators will provide scientific leadership for the conduct of the study within their country. This committee will be led by a member (non-Sponsor) of the Executive Committee. They will review the final protocol and other trial documents, and provide support for the organization of national logistics in the initiation and conduct of the study. Further details regarding the activities of the SC will be described in the SC charter filed in the Trial Master File (TMF).

3.1.1.3 Data Monitoring Committee

An independent DMC will review patient data to monitor patient safety and trial conduct. A DMC charter will be written to govern the activities of this committee and be filed in the TMF. The DMC analyses and operations will be formally separated from the Sponsor, the Investigators, the Executive Committee and the Steering Committees. The use of electronic data capture (EDC) and a central laboratory will support quick turnaround times and up to date data for the independent DMC to provide an unbiased review of data.

The DMC Charter will be used to document their objectives and working practices. The DMC will hold regular meetings with a view to protecting the safety of the trial participants, in particular with respect to the incidence of all-cause mortality, stroke, and bleeding. If the data at hand would precipitate a substantial safety concern about treatment with dabigatran etexilate, the DMC will carefully balance the observed risk profile against possible signs of improved efficacy.

The DMC will seriously consider recommending early termination of the trial when dabigatran treatment would show a statistically significant (two-sided $p < 0.05$) increased rate of the incidence of stroke or of all-cause mortality that is not potentially attributable to any confounding baseline imbalance, would not be mitigated by other observed benefits and could not be controlled by modification of the protocol. Similar action will be considered when an excess in clinically relevant bleeding events is observed in the patients treated with dabigatran etexilate that exceeds the expected bleeding rates and leads to either excess deaths or life-threatening events (two-sided $p<0.05$).

While monitoring guidelines have been provided, the DMC will use all available evidence and its collective judgment to base its recommendation to continue, stop or modify the study. In any scenario, the DMC will consider the net clinical benefit of the tested interventions in its recommendations to the steering committee.

There will be no formal interim analysis with efficacy stopping rules. In order to change the future clinical practice of a majority of clinicians who would know the results of this and other trials in the field, any benefit from dabigatran etexilate observed would need to be sustained, statistically overwhelming and consistent across a range of subgroups and secondary endpoints, for which the full sample size and follow-up period are likely to be necessary. The DMC should only under exceptional circumstances consider early termination

of the trial for overwhelming evidence of efficacy of dabigatran etexilate relative to ASA, because this would compromise the scientific validity of the final analysis.

3.1.1.4 Independent Event Adjudication Committee

An Independent Event Adjudication Committee will be established for the blinded adjudication of these selected OEs: death (including cause of death), stroke, SE, TIA, MI, VTE and major bleeding including intracranial hemorrhage, life threatening and fatal bleeds. An Adjudication Committee Charter will govern their activities. The charter will describe the processes by which adjudication will occur, including how blinding will be preserved.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A double-blind design was selected to reduce Investigator and patient bias in reporting outcome and adverse events. As an event driven, superiority trial, the actual recruitment and trial duration will be flexible in order to ensure an adequate number of events are collected and subsequently produce meaningful trial results (see Section 7.6).

As noted in Section 1.1, ASA once daily dose of 100mg was selected as the comparator based upon its inclusion in treatment guidelines and acceptability to most clinicians around the world. Dose and dose-interval selection is described in Section 4.1.3 and Section 4.1.4.

3.3 SELECTION OF TRIAL POPULATION

An estimated 6,000 patients will be randomized at approximately 550 sites in approximately 40 countries. It is anticipated that each of the sites will enter an average of 11 patients during the 30-month recruitment period (i.e. 0.5 patients per month per site).

Predefined site selection criteria will be applied to identify appropriate sites for participation. A special focus will be on stroke units to allow for an early inclusion of patients after the index stroke where recurrence risk is highest. Qualification of stroke units is available in many countries. It is preferred that sites have received qualification/certification, either on a national or local level. Among sites without certification, participation will be restricted to those sites that routinely perform or have access to the diagnostic pathway specified in Table 3.3.1: 1 and who fulfill site selection criteria. If other healthcare providers perform some of the diagnostic pathway, this is also acceptable providing investigator can obtain documentation.

Reasonable attempts should be made to include diverse populations during recruitment and to ensure retention in the trial. Greater diversity in clinical trial enrolment allows for broader generalization of study results, improved standards of care, decreased disparities in disease treatment and outcomes, and improved external validity supported by a more representative sample.

Investigators should consider regional disease prevalence demographics (e.g. race, gender, age) when screening potential study participants.

Enrollment will be competitive and the trial will be terminated when the total number of events has been observed, regardless of enrolment at individual centers. If enrolment is delayed, additional study centers may be recruited.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

If a patient is deemed ineligible for a reason which later resolves and all eligibility criteria can be met (e.g. time since an exclusionary event), patients can be rescreened up to one time provided it is still within 3 months since index stroke (within 6 months for select patients). Patients cannot be re-screened if any of the following exclusions were met: # 4, 7e, 8, 9, 19, 20, or 21; during the initial screening.

3.3.1 Main diagnosis for study entry

Patients with ESUS within 3 months before randomization (6 months in patients ≥ 60 years + additional risk factor) who are eligible for treatment with antithrombotic therapy (i.e. DE / ASA) may be screened for participation in this trial.

There are several steps required to identify patients with ESUS. The minimum required diagnostic tests are listed in Table 3.3.1: 1. The order in which tests are completed can be done according to local standard of care and at the investigator's discretion:

- Visualization of the acute ischemia on neuroimaging to confirm the diagnosis (stroke mimics are not uncommon) and to exclude lacunar infarcts.
- Exclude occlusive atherosclerosis in the arteries supplying the ischemic brain by means of arterial imaging.
- Assess for major-risk cardioembolic sources (primarily to detect AF through ECG-monitoring or to detect intra-cardiac thrombus by transthoracic or transesophageal echocardiography[1]).
- Consider other uncommon causes of brain ischemia (migraine-related, arteritis, arterial dissection). A focused review of the medical history should be performed to exclude rare causes of stroke, e.g. migraine with aura.

[1] Transesophageal echocardiogram (TEE) is not mandatory.

Table 3.3.1: 1 Minimum required diagnostic evaluations for embolic stroke of undetermined source[1] (all of the following procedures 1 through 5 are required prior to screening potential study patients):

1. Brain CT or MRI
2. 12-lead ECG
3. Precordial or transesophageal echocardiography
4. Cardiac monitoring for ≥20 hours with automated rhythm detection[2]
5. Imaging of both extracranial and intracranial arteries supplying the area of brain ischemia (by one or more of the following: catheter angiography, MRI angiography, computed tomographic angiography, cervical ultrasonography plus transcranial Doppler (TCD) ultrasonography).

3.3.2 Inclusion criteria

The patient must meet all the inclusion criteria:

1) Age ≥ 60 years

or:

Age 18-59 years plus at least one of the following additional risk factors for stroke:

a) Mild to moderate heart failure, i.e. NYHA Class ≤ 3 with left ventricular ejection fraction ≤ 40% as documented by e.g. echocardiogram, radionuclide or contrast angiogram in the last 6 months

b) Diabetes mellitus (either type 1 or type 2)

c) Hypertension requiring medical treatment with antihypertensive medication

d) Patent foramen ovale[3] with no interventional occlusion planned

e) Prior stroke or TIA (before index stroke)

[1] Imaging of the aortic arch is not required; special blood tests for prothrombotic states may be performed at the discretion of the Investigator only if there is a personal or family history of unusual thrombosis or associated systematic signs or disorder. Rare causes of stroke, such as migraine (with aura) should be excluded by focused review of medical history.
[2] Cardiac telemetry is not sufficient unless the data of telemetry had been recorded and summarized results are available. Monitoring duration can be extended at the discretion of the Investigator, if the patient is suspected for higher likelihood of paroxysmal AF. Eligible patients can be enrolled with a minimum of 20 hours of cardiac monitoring completed and results demonstrate < 6 min AF. Cardiac monitoring with interruption is acceptable, if the total recording time of at least 20 hours is completed within the same hospital stay or within consecutive 10 days.
3 Open foramen ovale with confirmed right-to left shunting at normal breathing (not only after Valsalva) in precordial echocardiogram. Transesophageal echocardiogram is not mandatory to establish diagnosis of PFO.

f) CHA_2DS_2-VASc score ≥ 3 (see Appendix 10.1)

2) 2a) Ischemic stroke with a brain lesion visualized by neuroimaging (either brain CT[1] or MRI). The visualized stroke is a non-lacunar infarct , e.g.. involving the cortex or >1.5 cm (>2.0 cm if measured on MRI diffusion-weighted images) in largest diameter if exclusively subcortical. Visualization by CT usually requires delayed imaging >24-48 hours after stroke onset. See Exclusion 21 for definition of lacunar stroke.

   2b) The index stroke must have occurred either:

   a. up to 3 months before randomization (mRS ≤3 at randomization)

      OR

   b. up to 6 months before randomization (mRS ≤3 at randomization) in selected patients that are ≥ 60 years plus at least one additional risk factor for recurrent stroke (see stroke risk factors a - f as outlined in Inclusion 1).

3) Arterial imaging or cervical plus TCD ultrasonography[2] does not show extra-cranial or intracranial atherosclerosis with ≥ 50% luminal stenosis in artery supplying the area of acute ischemia[3].

4) As evidenced by cardiac monitoring for ≥ 20 hours[4] with automated rhythm detection, there is absence of AF > 6 minutes in duration[5] (within a 20 hour period, either as single episode or cumulative time of multiple episodes).

5) The patient must give informed consent in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and local legislation and/or regulations.

3.3.3 Exclusion criteria

The patient must not meet any exclusion criteria:

1. Modified Rankin Scale of ≥4 at time of randomization or inability to swallow medications.

[1] ~~Visualization by CT usually requires delayed imaging >24-48 hours after stroke onset~~.
[2] Arterial imaging may be done with catheter arteriography, MRI angiography, computed tomographic angiography, or cervical plus TCD ultrasonography. The recommended cut-off point to exclude a moderate (i.e. ≥ 50%) stenosis of intracranial arteries by TCD ultrasonography is a Peak systolic velocity (PSV) ≥ 200 cm/s (R14-0781).
[3] Plaque characteristics (e.g. ruptured/ calcified/irregular) do not affect eligibility. Aortic arch atheroma is not an exclusion to enrolment. Cases with acute full artery occlusion deemed by Investigator to be of embolic origin are allowed.
[4] Cardiac telemetry is not sufficient, unless the data of telemetry had been recorded and summarized results are available. Cardiac monitoring efforts (beyond minimum required per Inclusion 4) may continue after randomization at the Investigator or a treating physician's discretion. All cardiac monitoring data and findings collected during the trial will be recorded in the eCRF.
[5] If < 6 minutes of AF is detected, the patient will be eligible depending on local Investigator judgment.

2. Major risk cardioembolic source of embolism such as:
    a. intracardiac thrombus as evidenced by transthoracic or transesophageal echocardiography,
    b. paroxysmal[1], persistent or permanent AF,
    c. atrial flutter,
    d. prosthetic cardiac valve (mitral or aortic, bioprosthetic or mechanical),
    e. atrial myxoma
    f. other cardiac tumors,
    g. moderate or severe mitral stenosis,
    h. recent (< 4weeks) MI,
    i. valvular vegetations, or
    j. infective endocarditis.

3. Any indication that requires treatment with an anticoagulant as per Investigator`s judgment.

4. History of AF (unless it was due to reversible causes such as hyperthyroidism or binge drinking, and has been permanently resolved).

5. Other specific stroke etiology (i.e. cerebral arteritis or arterial dissection, migraine with aura/vasospasm, drug abuse).

6. Primary intracerebral hemorrhage on qualifying neuroimaging[2]

7. Conditions associated with increased risk of bleeding[3] such as:

    a) Major[3] surgery in the previous month (in which case the patient may be eligible when one month has passed)

    b) Planned major surgery or intervention in the next 3 months

    c) History of intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired per Investigator judgment (e.g. by surgery)

    d) Gastrointestinal hemorrhage within the past six months unless the cause has been permanently eliminated or repaired per Investigator judgment (e.g. by surgery), or endoscopically documented gastroduodenal ulcer disease in the previous 30 days

    e) Hemorrhagic disorder or bleeding diathesis, e.g. history of thrombocytopenia or platelet count <100 x10^3/ µL at screening, von Willebrand disease,

[1] Please see inclusion 4 for guidance on the detection of AF.
[2] A hemorrhagic transformation of a primarily ischemic stroke may be included as per Investigator`s judgment. Sporadic microbleeds may be included as per Investigator`s judgment. As a general recommendation, a cerebral microbleed is considered to be ≤ 5mm, but sometimes up to 10mm, in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences. Any blood visualized on a CT will be classified as a macrobleed. A macrobleed is an exclusion criterion for the trial.
[3] Definition of "increased bleeding risk" and "major" is per Investigator judgment

hemophilia A or B or other hereditary bleeding disorder, history of prolonged bleeding after surgery/intervention.

f) Fibrinolytic agents within 48 hours of study entry

g) Uncontrolled hypertension Systolic Blood Pressure (SBP) >180mmHg and/or Diastolic Blood Pressure (DBP) >100 mmHg)

h) Any history of intracranial aneurysm (unless it was permanently resolved with either clipping or coiling at least one year prior to the study entry)

8. History of symptomatic nontraumatic intracranial hemorrhage with risk of recurrence according to Investigator judgment.

9. Renal impairment with estimated CrCl (as calculated by Cockcroft-Gault equation) <30mL/min at screening, or where Investigator expects CrCl is likely to drop below 30mL/min during the course of the study.

10. History of hypersensitivity or known contraindication to DE or ASA.

11. Known requirement for treatment of a concomitant disease (i.e. other than the index ESUS stroke) with ASA (with the exception of optional concomitant medication as provided by the Sponsor for patients with coronary artery disease, see section 4.1.1), clopidogrel, dipyridamole, dipyridamole+ASA, prasugrel, ticagrelor or ticlopidine at Visit 1, known need for continuous dual antiplatelet therapy after randomization.

12. Known requirement for treatment with methotrexate ≥15mg/week systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, St. John's Wort or any cytotoxic/myelosuppressive therapy. See Section 4.2.2.

13. Concomitant disease that increases the risk of an adverse reaction to study interventions or with life expectancy < 6 months (for any reason) per Investigator judgment.

14. Any recent malignancy or radiation therapy (≤ 6 months) unless the malignancy was a basal cell carcinoma that was completely removed.

15. Pre-menopausal women (last menstruation ≤ 1 year prior to informed consent) who:

- are nursing or pregnant,
  or
- are of child bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the study and/or do not agree to adhere to pregnancy testing required by this protocol.
  Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) (R15-5904) that result in a low failure rate of less than 1% per year when used consistently and

correctly. A list of contraception methods meeting these criteria is provided in the patient information.

16. Patients who participated in another trial within 14 days prior to screening. Patients with residual effect from another investigational product remaining at time of screening. Patients participating in a purely observational study will not be excluded.

17. Patients considered unreliable by the Investigator concerning the requirements for follow-up during the study or at the end of the study (e.g. not able to comply with regular medication intake)

18. Any condition the Investigator believes would not allow safe participation in the study, e.g. other neurological condition that would complicate assessment of outcomes (e.g. severe dementia, high propensity for falls where Investigator deems a patient's potential risk for bleeding exceeds the potential benefits of study drug).

19. Active liver disease, as indicated by at least one of the following:

    a) Prior and persistent Alanine aminotransferase (ALT (SGPT)) **or** Aspartate transaminase (AST (SGOT)) **or** Alkaline Phosphatase (AP) >3 × upper limit of normal (ULN)

    and/or

    b) Known Active hepatitis C (as evidenced by positive hepatitis C virus ribonucleic acid assay by sensitive polymerase chain reaction (PCR) based assay, such as Roche Monitor or Bayer TMA assay)

    c) Known Active hepatitis B (HBs antigen + or anti HBc IgM+[1])

    and/or

    d) Known Active hepatitis A.

20. Severe[2] glucose-6-phosphate dehydrogenase deficiency

21. Lacunar stroke. Lacunar infarcts of restricted size in the deep parts of the brain in the territories of small penetrating arteries. They are absent from the cerebral and cerebellar cortex. On brain CT and MR images they are <1.5 cm in largest diameter or <2.0 cm if measured on MRI diffusion sequences. In several pathological studies, sites of predilection included the lenticular nucleus, thalamus, central white matter, internal capsule, centrum ovale, corpus callosum, basis pontis, and, rarely, the cerebellum, midbrain and medulla. Infarcts <1.5 cm in largest diameter, or <2.0 cm if measured on MRI diffusion sequences, in the dorsal or lateral areas of the brainstem,

1 Patients having received recent hepatitis B vaccination and thus tests positive for these antibodies will not be excluded.
2 Definition of "severe" is per Investigator Judgement.

in the territory of circumferential, rather than deep penetrating, arteries are not lacunar infarcts (note: history of lacunar stroke is not exclusionary).

3.3.4 Removal of patients from therapy or assessment

3.3.4.1 Removal of individual patients

It is important to distinguish between premature study drug discontinuation and premature study discontinuation.

Patients can stop study drug for various reasons as described below however they should be encouraged to re-start study medication at the Investigator's discretion and when he/she considers it safe to do so.

Regardless of whether or not study drug continues to be taken, patients will continue to participate in regularly scheduled follow-up visits and assessments until the end of the trial. Patients not actively taking study drug are permitted to reduce their level of participation but are strongly encouraged to continue trial participation, contribute to end of study vital status collection and report OEs at minimum.

Data collected for all randomized patients will be used in the analysis. This includes randomized patients who never take study medications and patients that prematurely discontinue study drug. Procedures to be followed for patients prematurely terminating the trial are detailed in Section 6.2.3. Patients that withdraw from trial participation or study drug will not be replaced.

Removal from study drug

If study drug is permanently stopped, patients should continue to attend scheduled study visits until the trial ends. Refer to Section 6.2.2 for further details.

An individual patient is to be discontinued from study drug if the following occurs:

- Development of an indication for antithrombotic therapy including:
    - dual anti-platelet therapy (study drug can be restarted once dual antiplatelet therapy is no longer needed)
    - non-AF indication for anticoagulation (e.g. treatment of VTE)
    - Atrial fibrillation (with duration exceeding 6 minutes, either as single episode or cumulative time of several episodes recorded within 20 hours, or as per Investigator discretion), or atrial flutter

- Patients who are found to have a CrCl <30mL/min during the course of the trial should have study drug temporarily discontinued (see Section 5.2.3 for calculation of CrCl and risks of taking DE with reduced renal function). Labs can be repeated before stopping study drug if Investigator wishes to confirm initial lab result. The patient will be permanently discontinued from study drug, unless CrCl recovers to ≥30mL/min within seven days. A patient should also be permanently discontinued from study drug if CrCl drops <30mL/min on two different occasions during the trial. During period of interruption, a patient can be treated per standard of care according Investigator's discretion. Guidelines for transitioning to non-study antithrombotic medications are provided in Section 10.2.2.

- Patient noncompliance with study drug administration (per Section 4.3)

- If a patient becomes pregnant or a pregnancy is suspected during the trial the investigational drug will be stopped, the patient will be discontinued from treatment and the patient will be followed up through the end of the trial and until birth or otherwise termination of the pregnancy. For further information, including the process for follow-up on the outcome of the pregnancy please see Section 5.2.2.3.

- Withdrawal of consent

At the discretion of the Investigator/patient, an individual patient may be discontinued from study drug if:

- The patient is no longer able to continue study drug for other medical reasons (e.g., surgery, AEs, other diseases or concomitant therapies)

- In the opinion of the Investigator, continuation on the study drug is not in the patient's best interest, if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at trial assessments, and reason to be recorded in the electronic Case Report Form (eCRF)) or if the patient develops a high propensity for falls where Investigator deems a patient's potential risk for bleeding exceeds the potential benefits of study drug.

- The patients elects to stop taking study drug

The date of last dose of study drug and reason for study drug discontinuation will be recorded on the eCRF.

3.3.4.2 Discontinuation of the trial by the Sponsor

Boehringer Ingelheim reserves the right to discontinue the entire trial or at any individual site at any time.

The following reasons are examples that may lead to discontinuation of some or all of the trial sites:

1. Failure to meet expected enrollment goals overall or at a particular trial site

2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk assessment
3. Violation of GCP, the CTP, or the contract by a trial site or Investigator, disturbing the appropriate conduct of the trial.
4. Advice of the independent DMC, decision by an independent ethics committee (IEC)/institutional review board (IRB) or Competent Authority (CA)

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and comparator product(s)

The investigational product DE, the comparator ASA and respective matching placebos will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. The composition of these drugs capsules are as follows:

Table 4.1.1: 1 Dabigatran etexilate (Investigational drug)

Substance:	Dabigatran etexilate
Brand name:	Pradaxa®
Pharmaceutical formulation:	Capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	110 mg, 150 mg
Total Daily dose:	220 mg or 300 mg
Route of administration:	per os (oral) (p.o.)
Posology:	1 capsule, b.i.d. (Section 4.1.4)

The main excipients of the dabigatran capsule include tartaric acid, acacia, hypromellose, dimeticone, talc, and hydroxylpropyl cellulose, HPMC (hydoxylpropylmethylcellulose) capsule shell consisting of titanium dioxide (E171) FD&C Yellow 6/Sunset Yellow (E110), FD&C Blue 2 /Indigo Carmine (E132) hypromellose, carrageenan and potassium chloride.

Table 4.1.1: 2 Placebo matching dabigatran

Substance:	placebo matching dabigatran 150 mg placebo matching dabigatran 110 mg
Brand name:	not applicable
Pharmaceutical formulation:	Capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	0 mg
Total Daily dose:	not applicable
Route of administration:	p.o.
Posology:	1 capsule, b.i.d. (Section 4.1.4)

Table 4.1.1: 3 Acetylsalicylic acid

Substance:	Acetylsalicylic acid (immediate-release tablet)
Brand name:	Acetylsalicylsäure (ASS) 100mg HEXAL
Pharmaceutical formulation:	Tablet
Source:	Hexal AG, Germany
Unit strength:	100 mg
Total Daily dose:	100 mg
Route of administration:	p.o.
Posology:	1 tablet, once daily (q.d)

Table 4.1.1: 4 Placebo matching ASA

Substance:	placebo matching ASA (ASA-placebo)
Brand name:	not applicable
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	0 mg
Total Daily dose:	not applicable
Route of administration:	p.o.
Posology:	1 tablet, once daily (q.d)

In general, the concomitant use of non-study ASA is prohibited with the exception of patients with CAD. For patients with CAD, Investigators may (but are not required to) assign a blinded optional concomitant ASA kit (containing either ASA or placebo) via IRT. If the patient has been randomized to active DE, IRT will assign as optional concomitant ASA (100 mg q.d.). If the patient had been randomized to active ASA, IRT will assign the optional concomitant ASA-placebo (see Figure 4.1.1:1).

Table 4.1.1: 5 OPTIONAL ASA as co-medication

Substance:	Acetylsalicylic acid (immediate-release tablet)
Brand name:	Acetylsalicylsäure 100 mg HEXAL
Pharmaceutical formulation:	Tablet
Source:	Hexal AG, Germany
Unit strength:	100 mg
Total Daily dose:	100 mg
Route of administration:	p.o.
Posology:	1 tablet, once daily (q.d)

Table 4.1.1: 6 Placebo matching OPTIONAL ASA as comedication

Substance:	placebo matching ASA (ASA-placebo)
Brand name:	not applicable
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	0 mg
Total Daily dose:	not applicable
Route of administration:	p.o.
Posology:	1 tablet, once daily (q.d)

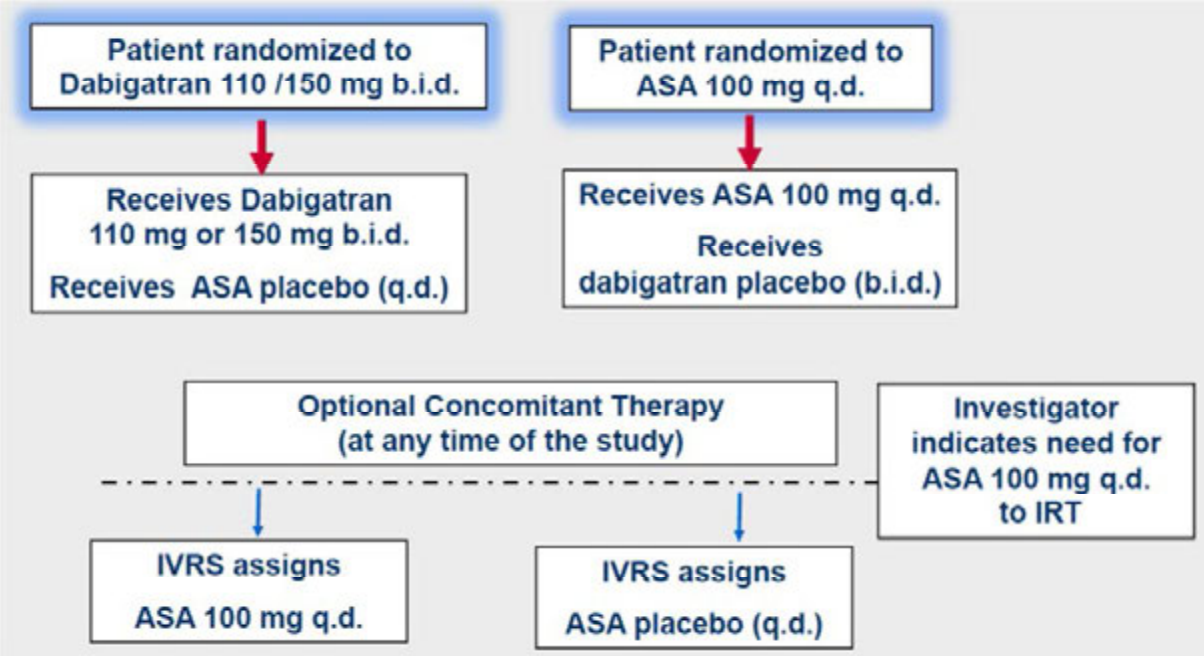


Figure 4.1.1: 1 Interactive Response Technology assignment of concomitant (optional) ASA or corresponding ASA placebo for patients with CAD

4.1.2 Method of assigning patients to treatment groups

Patient assignment to the treatment groups will be determined by IRT. Access to the randomisation code will be controlled and documented. All necessary instructions for using the IRT system will be described in a user guide/manual, a copy of which will be available in the ISF.

Patients have an equal chance of being randomized to DE or ASA with an allocation ratio of 1:1.

At Visit 2, patients will be randomized and receive study medication for the first time. If the patient is not randomized, a screen fail call will be made in the IRT System. When patients return for the next scheduled visit (see Flow Chart), unused medication will be returned by the subject. Trial drug will be supplied on a per visit basis. Supply will be managed by IRT.

All study drug dispensed and returned to patients should be recorded by Investigator/designee on the Investigational Medicinal Product Accountability Forms. These original forms will be retained and the site and a copy filed in TMF.

4.1.3 Selection of doses in the trial

The doses of DE selected for this trial are the same as those used in RE-LY, the Phase III trial for SPAF. In RE-LY, a dose of DE 110 mg b.i.d. was shown to be comparable to warfarin (INR level 2.0–3.0) for preventing strokes and SE, and superior when considering major bleeding risk with a relative risk reduction of 20% (U09-3249-02). Moreover, there was an approximately 60% reduction in intracranial hemorrhage with both dosages of DE.

The overarching goal related to this exposure level is to achieve superiority in efficacy over ASA with no clinically meaningful excess in bleeding with DE. To achieve this, the dosing instructions applied in this trial are intended to provide homogeneous exposure distribution among patients included into this trial. This means that patients at higher risk of bleeding (i.e. patients aged 75 years or older, or with moderate renal impairment) will receive the lower dose of 110 mg b.i.d. and will achieve an exposure comparable to those patients without these risk factors.

The average exposure across all patients (dabigatran trough levels) will range between the trough levels achieved with 110 mg b.i.d. (median of 66 ng/ml) in the RE-LY trial and the level obtained with 150 mg b.i.d. in RE-LY (median of 93 ng/ml): By utilizing the PK experience from RE-LY (U09-3249-02) and by considering patients characteristics such as age and renal function from a secondary stroke population included in the PRoFESS study (U08-3667-01), PK modeling has shown that the dosing algorithm in this study will result in a median of plasma trough levels of approximately 77 ng/mL. This exposure is expected to provide superior efficacy over the antiplatelet agent ASA with a comparable low rate of intracranial hemorrhage and the overall ability to deliver an optimal balance of efficacy and safety across the population in the trial.

To obtain the targeted exposure, dabigatran dosing will be adjusted for age and renal function, as follows: Patients will be assigned to DE dose of 150 mg b.i.d., unless they are 75 years or older, or have a CrCl of ≥30 to < 50ml/min, in which case they will receive DE 110 mg b.i.d.

Patients assigned to DE, who initially qualify to receive 150 mg b.i.d., will be down-titrated to 110 mg b.i.d. if their CrCl deteriorates to ≥ 30 - < 50 mL/min, if they experience a GI bleed, or the patient becomes 75 years old during the course of the trial. The patient will be

asked to return their 150 mg medication and receive 110 mg at an unscheduled visit as soon as possible if their titration is due to drop in CrCl or GI bleed. Patients who turn 75 years old during the trial will receive the 110 mg dose at their next scheduled visit. Patients will only have the option to change the dose once, i.e. there will be no up-titration from 110 to 150 mg b.i.d. if renal function recovers.

Using the characteristics of higher risk populations, modeling shows comparable exposure (median trough concentration of 89 ng/ml) in patients receiving DE 110 mg b.i.d. compared to patients without these risk factors receiving DE 150 mg b.i.d. (median trough concentration of 74 ng /ml) in this trial. Therefore it is concluded that dose adjustment to DE 110 mg b.i.d. may optimize the risk-benefit profile in patients at higher risk of bleeding.

The 100 mg dose of ASA was selected based upon recommendations in current guidelines and because this dosage is widely available and acceptable to most clinicians around the world. Patients assigned to ASA will not change their ASA dose during the course of the trial.

Because assignment of ASA vs. DE is blinded, all patients will have their DE down-titrated via IRT under the age, GI bleed or renal function conditions mentioned above. It will be unknown if the DE kits are active or placebo.

4.1.4 Drug assignment and administration of doses for each patient

Drug is dispensed by the Investigator, study coordinator, or pharmacist, depending on the study organization. IRT will be used to assign an appropriate active study drug and placebo to the patient. The site staff will be prompted to notify the IRT of all relevant information to identify patient as well as assign appropriate DE dose according to the algorithm (i.e. according to age, renal function and GI bleed that occurs during the course of the trial).

Study drug is dispensed every three months over the first year and every 6 months thereafter at regularly scheduled study visits (except the EOT and Final Visit). Study drug kits will contain enough supply to last until the next visit plus some overage.

Patients randomized to active treatment with DE will also receive an ASA placebo kit. Patients randomized to active treatment with ASA will also receive a DE placebo kit.

Patients will be instructed on the importance of taking both the active and placebo treatment because they will not know which one is active versus placebo.

Adjustments of DE dose can occur once per patient and will be managed within the IRT system.

Dabigatran etexilate capsules should be taken in the morning and in the evening, at the same time every day. The interval between doses should be as close to 12 hours as possible. If a dose of DE is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped, if it cannot be taken at least 6 hours before the next scheduled dose. The next dose of DE should not be doubled to make up for a missed dose. If a dose of ASA or matching placebo is not taken at the scheduled time, the dose

should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at the same day. For visits with pharmacokinetic trough sampling (Visit 1, Visit 3 and Visit 6 as outlined in the Flow Chart) patients should take that morning dose of trial medication at the study site (after the blood sample has been taken) to ensure the pharmacokinetic sample is taken at trough, 10:00-16:00 hours after the last drug intake and prior to the next drug intake.

Patients should be advised to take study medication with a full glass of water. Breaking or chewing of the tablets or capsules, or emptying the contents of the capsules is not permitted. The capsules and tablets should be swallowed as a whole and should not be dissolved in liquid. It is possible to take study medication with or without food. By taking study medication with food, dyspepsia-like side effects associated with DE may be reduced (U13-3509-01). If dyspeptic symptoms remain, the Investigator should consider adding a proton pump-inhibitor or H2-blocker to the concomitant therapy of the patient.

Start of study treatment following the qualifying event of ESUS:

The decision about starting study medication after qualifying stroke is at the discretion of the Investigator. In general, study medication should be started as early as possible under consideration of the severity of the stroke and after ensuring that intracranial hemorrhage has been excluded. Recommendations on the earliest possible time point to start study medication are provided in Table 4.1.4: 1 (P12-02400).

Table 4.1.4: 1 Recommendations on starting study medication after index event of stroke (mRS ≤ 3 at time of randomization) and for reintroduction of study treatment after recurrent stroke (mRS ≤ 3 at time of study medication restart)

Stroke Severity (at time of randomization / at time of study medication restart after recurrent stroke)	**Earliest start of Study Medication after Stroke**
Symptom resolution within 24 hours with evidence of brain damage by imaging	As soon as imaging has excluded a cerebral hemorrhage
Modified Rankin Scale = 1 or 2	3-5 days after most recent stroke onset[1] Brain re-imaging is not required if starting study medication more than 10 days after index stroke.
Modified Rankin Scale = 3 *Please take note:* *This category includes patients with an initial Modified Rankin Scale of 4 at time of stroke, who have improved to a Modified Rankin Scale of 3.* *Patients with Modified Rankin Scale of 4 at time of randomization are excluded.* *Patients with Modified Rankin Scale of 4 cannot restart study medication unless their Modified Rankin Scale improves to 3.*	5-7 days after most recent stroke onset[1] Brain re-imaging is not required if starting study medication more than 10 days after index stroke.

[1] If starting study medication within 10 days of most recent stroke in patients with mRS of 1, 2, or 3, re-imaging of the brain is required to rule out bleeding into the brain. Randomization in these patients should only occur after reimaging of the brain has been performed and eligibility has been confirmed. Hemorrhagic transformation of a primarily ischemic stroke may be included as per Investigator`s judgment. Sporadic microbleeds may be included as per Investigator`s judgment. As a general recommendation, a cerebral microbleed is considered to be in general ≤ 5mm, but sometimes up to 10 mm, in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences. Microbleeds are incidental findings that do not constitute an exclusion criterion. In patients with hemorrhagic transformation or microbleeds, the Investigator may choose to delay the start of study medication. Any blood visualized on a CT will be classified as a macrobleed. In patients with macrobleeds, study medication should not be started.

Treatment will continue until the end of the study if there is no reason to stop treatment earlier. The date of last dose of study drug will be recorded on the eCRF.

Secondary stroke prevention treatment for patients after the completion of this trial is at the discretion of the Investigator or other treating physician.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Trial medication will be identified by a medication code number. Packaging and labelling will be otherwise identical. Interactive Response Technology will be used to assign patients to treatment groups at the start of treatment (see Section 4.1.2) and for appropriate re-supply of medication to patients throughout the duration of the trial. The IRT will also handle any required dose adjustments.

Colour, size and shape of the tablets and capsules (whether active or placebo) are identical (see Section 4.1.1 for actual sizes of each unit strength dose). These measures will ensure that the medication blind will be maintained for both patient and Investigator throughout the trial.

The randomisation schedule will be generated using validated software and will be verified by a statistician who is not involved in the trial. Individuals involved in the conduct and assessments of the trial will remain blinded to the randomisation schedule until the entire database is locked.

Randomisation codes will be accessible for any authorised person at the study site via IRT. The codes should be broken only if knowledge of the patient's treatment group is needed in order to provide appropriate medical care to that patient. Refer to Section 4.1.5.2 for rules of breaking the code for an individual or for all patients. The DMC will also be given access to unblinded patient information if required.

Refer to the DMC charter (available separately) for information about management of blinded information for the purposes of DMC review.

The randomization codes may be provided to bioanalytics (or designee) prior to last patient out (LPO) to allow them to exclude PK samples and assay validation samples taken from patients assigned to ASA from the these analyses. Bioanalytics (or designee) will not disclose the randomization code or the results of their measurements until the study is officially unblinded.

Due to the requirement to include unblinded information in suspected unexpected serious adverse reaction (SUSAR) reports, SUSAR reports will be blinded prior to distribution to sites and trial team to ensure that the BI personnel other than the drug safety representative remains blind to treatment allocation until after database lock.

4.1.5.2 Procedures for emergency unblinding

The Investigator is instructed not to measure activated partial thromboplastin time (aPTT), thrombin time (TT), diluted thrombin time (dTT) and ecarin clotting time (ECT) unless there is an emergency or urgent intervention (see Section 4.2.1).

If a patient experiences a clinical scenario resulting in a potentially unblinding coagulation test, it is preferable for another treating physician (not involved in the trial) to review lab results and manage the clinical scenario.

An emergency code will be available via the IRT. This code may only be broken in emergency situations when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or if required to assure safety of patients. If the code for a patient is revealed, the Sponsor must be informed immediately and the patient must be permanently discontinued from study drug. The reason for accessing the code must be documented on the appropriate eCRF page along with the date and the name of the person who broke the code.

4.1.6 Packaging, labeling, and re-supply

Investigational supplies will be available as trial medication kits. Each kit includes trial medication sufficient for at least 90 days, packed as follows:

- Four bottles, each containing 60 capsules DE 150 mg, 110 mg or matching placebo.
- One blister package containing 120 tablets ASA 100 mg or matching placebo.

To enable adequate supply for 3 month visit intervals as scheduled during the first year, patients will receive one kit of DE (or placebo) and one blister package of ASA (or placebo) at Visits 2, 3, 4 and 5. Beginning at Visit 6 (Month 12), patients will receive two kits of DE (or placebo) and two blister packages of ASA (or placebo) at each scheduled visit to ensure adequate supply for 6 month clinic visit intervals.

The need for a patient to receive optional concomitant ASA will be determined by the Investigator and recorded in IRT. For patients with CAD who do require this, the optional ASA (or ASA placebo as appropriate) will also be assigned by the IRT according to the patient's randomized treatment arm. Optional concomitant ASA and ASA placebo will be packaged identically to each other but different from comparator ASA by label color to allow easy differentiation of supply while maintaining the blind. They will be supplied as:

- One blister package containing 120 tablets ASA 100 mg or matching placebo. (See Figure 4.1.1: 1).

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Patients should be instructed to keep medication containers tightly closed and not to remove tablets/capsules from original package material until immediately prior to time of intake. It is not allowed to use medication from more than one DE kit at the same time.

Trial medication must be stored under the recommended storage conditions indicated on the label. A temperature log must be maintained by the site 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 (CML) for the study should be contacted immediately.

Trial medication must be stored securely at the study sites, out of reach of children and be protected from moisture and direct sunlight, e.g. in a locked cupboard or at a pharmacy. It may only be dispensed to trial patients fulfilling the inclusion and exclusion criteria by authorized study personnel as documented in the ISF. Receipt, usage, and return of the study medication must also be documented on the respective forms in the ISF.

All unused medication including bottles and outer boxes (empty or filled) must be either returned to the Sponsor, or, following written authorization from the Sponsor, may be destroyed at site. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

Drug supplies, which will be provided by the Sponsor, must be kept in a secure, limited access storage area under the appropriate storage conditions defined by the Sponsor. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

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 study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the Sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. CA, as required according to local regulations,
- availability of the curriculum vitae of the principal Investigator,
- availability of a signed and dated CTP including local signature page signed by PI,
- availability of the proof of a medical license for the principal Investigator (if applicable),
- signed financial disclosure of PI,
- for USA, availability of the Form 1572.

The Investigator/Pharmacist/Investigational Drug Storage Manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposition of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational products and trial patients. The Investigator/pharmacist/investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor.

At the time of return to the Sponsor or appointed CRO; the Investigator/Pharmacist/ Investigational Drug Storage Manager must verify that all unused or partially used drug supplies have been returned by the patient and that no remaining supplies are in the Investigator's possession.

For Japan:

The Investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the Sponsor after IRB / ethics committee approval of the study and completion of a clinical trial contract between the Sponsor and the Head of Trial Centre.

The Investigator / pharmacist / investigational drug storage manager should return the unused and collected investigational drugs (including the empty boxes) to the Sponsor after unblinding the trial.

In case investigational drugs are returned before unblinding of the trial, the Investigator / pharmacist / investigational drug storage manager should seal the opened box (excluding empty boxes) for the patient, before returning the unused and collected investigational drugs (including the empty boxes) to the Sponsor.

When returning the investigational drugs, the Investigator / pharmacist / investigational drug storage manager should exercise utmost caution to assure that the Sponsor and other relevant trial staff members remain blinded to the patient's name on the package (box or label) of the investigational drugs.

Upon completion of the trial, the Investigator / pharmacist / investigational storage manager submits to the Sponsor a copy of the investigational drug dispensing and return log. When submitting the copy, the Investigator / pharmacist / investigational drug storage manager should exercise caution to assure that the Sponsor and other relevant trial staff members remain blind to the patient's name.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Any additional concomitant therapy considered necessary for the patient's welfare may be given at the discretion of the Investigator, with the exception of those listed in Section 4.2.2.

Concomitant medications of interest (e.g. antithrombotic medications, medications to treat cardiovascular conditions, medications with potential interaction with dabigatran or ASA, treatments to manage bleeding) taken at randomization and throughout the conduct of the trial (including within 30 days of randomization) will be documented on the eCRF. Additionally, any treatments received for the index (qualifying) event of stroke will be recorded, including fibrinolytic, antiplatelet and anticoagulant medications.

The concomitant use of ASA up to 100 mg per day is discouraged, but not prohibited for patients with CAD. Patients requiring treatment with ASA for CAD can be included in the trial and can receive optional concomitant ASA 100 mg (or ASA 100 mg placebo) q.d. as concomitant medication. See Section 4.1.1 and Section 4.1.6 for details.

Certain concomitant therapies (e.g. fibrinolytics, anticoagulants) or surgery/intervention may require the temporary discontinuation of blinded DE and ASA. Study medication should be restarted as soon as safely possible, at the discretion of the Investigator. Following study drug discontinuation due to AEs (e.g. bleeds) the patient should be treated according to local clinical practice. After resolution of an AE, consideration should be given to resuming study medication at the assigned treatment and dose. In case of a temporary interruption, a restart of study medication is possible at the Investigator's discretion. All study drug stop and restart dates will be recorded on the eCRF.

4.2.1 Rescue medication, emergency procedures, and additional treatment

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies that may occur during the study. In situations where there is an increased hemorrhagic risk (e.g. recent biopsy or major trauma, bacterial endocarditis), close observation (looking for signs of bleeding or anemia) is generally required.

Recommendations on the management of study medication for invasive procedures or at the time of OEs are listed below. As study medication is blinded, the Investigator is asked to consider the individual bleeding risk of the patient and type of intervention and to weigh the risk of bleeding against the risk of thromboembolism associated with treatment interruption of either ASA or DE.

Coagulation tests should not be performed in this trial to avoid unblinding. Investigators are discouraged to perform TT, dTT, aPTT or the ECT in this trial. Under certain exceptional circumstances, such as emergency procedures, stroke or life-threatening bleeding as described below, it may become necessary for patient management to perform a coagulation test. Preferably, another treating physician (not involved in the trial) should review lab results and manage the clinical emergency scenario.

In the event that the identity of the trial drug must be known, see Section 4.1.5.2 for emergency unblinding.

For the latest information on DE, refer to the current version of the IB (U98-3208).

For specific guidance relating to ASA consult also the relevant Summary of Product Characteristics (SPC) of the HEXAL ASS 100 mg tablet (SPC - see Section 04 of the ISF).

Detailed information regarding the management of patients receiving study medication is provided below.

Elective Procedures

Preoperative Phase:

Some interventions in individual patients may be affected by the characteristics of ASA, others by DE. As study medication is blinded, the Investigator is asked to consider the type of intervention and individual bleeding risk of the patient and to weigh the risk of bleeding against the risk of thromboembolism associated with treatment interruption of assigned study drug. The impact of IRT-assigned optional ASA-co-medication should also be considered. Serum creatinine should normally be checked 1-2 weeks before surgery and the CrCl should be calculated using the Cockroft-Gault formula (Section 5.2.3) and the impact on cessation of dabigatran must be considered in patients with reduced renal function.

Where the Investigator becomes aware of a planned procedure/surgery, it is recommended that the study Investigator contact the treating surgeon. Refer to Appendix 10.2 on transitioning to non-study medication in case bridging therapy is chosen.

Study drug assignment should not routinely be unblinded in preparation for an elective procedure. Guidelines for stopping DE in advance of surgery are provided in Table 4.2.1: 1. These guidelines should in general be followed for all patients irrespective of their assigned study medication, unless the situation requires that the antiplatelet effect of ASA be completely resolved. In that case, study drug should be stopped for approximately 7 days or longer depending on the type of intervention planned.

The following is a guide to the discontinuation of study medication before surgery taking renal function and additional risk factors into account. With elective procedures, timing of study medication stop and restart may depend on patient characteristics, type of intervention and type of study medication. Unless explicitly mentioned, the recommendations given for DE can also be applied to patients receiving ASA in the trial.

Table 4.2.1: 1 Recommendations on cessation of blinded study drug in relation to the timing of surgery – under special consideration of the pharmacokinetics of dabigatran

Renal function (CrCl, mL/min)[1]	Estimated half-life in hours (for dabigatran)	Stop study drug before surgery[3]	
		High risk of bleeding[2]	Standard risk
>80	~13	2 days before	24 h before (2 doses)
≥50-80	~15 (12-18)	2-3 days before	1-2 days before
≥30 to <50	~18 (18-24)	4 days	at least 2 days (> 48 hours)
<30	~27 (>24)	> 5 days	2-5 days

[1] CrCl can be estimated using serum creatinine by the Cockroft-Gault formula (see Section 5.2.3). Patients who develop CrCl <30mL/min during the course of the trial should have study medication temporarily stopped (see Section 3.3.4.1). For rules and prerequisites to restart DE treatment see Section 4.2.1.
[2] In addition to renal function, high risk determinants of bleeding risk include type of surgery, advancing age, comorbidities (e.g. major cardiac, respiratory or liver disease), and concomitant use of antiplatelet therapy. The type of surgery associated with a high risk of bleeding includes but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function.
[3] If the clinical situation requires that the antiplatelet effect of ASA should be completely resolved, study drug should be stopped for approximately 7 days or longer depending on the type of intervention planned.

During a temporary interruption, thrombosis prophylaxis therapy with commercial antiplatelet(s) or a parenteral anticoagulant e.g. Low-molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) (according to local practice) is at the discretion of the Investigator depending on duration of interruption, type of intervention and individual thromboembolic risk of the patient. See Appendix 10.2 for additional information related to initiation of thrombosis prophylaxis and switching back to study medication.

Emergency Procedures

In the case of emergency surgery, study medication should be discontinued (including IRT-assigned optional ASA-co-medication). If possible, surgery should be postponed until 12 hours after the last oral intake of study drug.

In an emergency event, a measure of anticoagulation may become necessary to manage the situation. A physician may consider using the TT, dTT, aPTT or the ECT. Coagulation times should be interpreted in relation to the timing of last drug intake of DE. In RE-LY, patients receiving chronic therapy with dabigatran 150 mg bid, the median peak aPTT was approximately two-fold that of control. Twelve hours after the last dose (trough level), the median aPTT is approximately 1.5-fold that of control, with less than 10% of patients exhibiting two-fold increases in aPTT (P10-03790).

An elevated TT or dTT should lead the clinician to consider delaying surgery. If the TT/dTT test is not available, an aPTT, though less precise than the TT, can be used. A persistently prolonged TT or dTT in the absence of heparin, fibrin/fibrinogen degradation products (e.g. with disseminated coagulation activation, sepsis, severe inflammation, and other conditions)

or high concentrations of serum proteins (e.g. myeloma) suggests persistently elevated levels of dabigatran in the blood.

If the condition is considered life threatening, consider reversal of anticoagulation as described under major bleeds. See Section 4.2.1- Overdose, for more information regarding the specific reversal agent for dabigatran.

Refer also to Section 4.1.5.2 for Emergency Unblinding Procedures.

ASA characteristics relevant in the context of surgery/intervention

The antiplatelet effect of ASA is present up to 7-10 days after medication cessation. Nonetheless, most interventions can be performed without an interruption of ASA therapy. The type of surgery associated with a high risk of bleeding and which may preferably be performed after the antiplatelet effect of ASA has elapsed, includes but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. It is at the discretion of the Investigator whether a complete resolution of the antiplatelet effect of ASA for a certain procedure is required. In this case, study medication (including IRT-assigned optional ASA-co-medication) may have to be stopped for 7-10 days before the intervention and the risk of thromboembolism during this period must be weighed against the risk of bleeding. ASA does not lead to a prolongation of coagulation times such as aPTT, dTT, TT or ECT.

Dabigatran etexilate characteristics relevant in the context of surgery/intervention

Physicians may consider the following information regarding DE when patients need to undergo surgery or elective procedures. Providing the patient has normal renal function, the onset of effect of dabigatran is within 1 hour of dosing and dabigatran has peak concentrations 2-3 hours after an oral dose. Steady state is reached within 2-3 days.

Plasma levels of dabigatran in steady state will vary across the population and are particularly affected by renal function. Patients with renal dysfunction may have elevated concentrations of dabigatran due to longer half-lives of active drug (see Table 4.2.1: 1). Serum creatinine should normally be checked 1-2 weeks before an elective surgery and the CrCl should be calculated using the Cockroft-Gault formula (Section 5.2.3). Patients with a CrCl <30mL/min during the course of this study should not be receiving study medication (Section 3.3.4.1). In patients where renal function is impaired or procedures undertaken which may temporarily compromise renal function, the impact on plasma levels of dabigatran must be considered.

The current version of the IB should be referenced for further information about DE (U98-3208).

Post Procedural Period

Study medication will be initiated as soon as the patient is hemodynamically stable and hemostasis is achieved. If bridging medication has been used, please see Appendix 10.2.1 on how to switch back to study mediation after temporary interruption.

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture

Procedures such as spinal anesthesia may require complete hemostatic function. See Table 4.2.1: 1 for recommendations on when to stop DE before spinal/epidural anesthesia.

It is at the discretion of the Investigator whether a complete resolution of the antiplatelet effect of ASA is required for these types of procedures. Complete resolution of ASA antiplatelet effect would require a stop of study medication approximately 7-10 days.

The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, resume treatment with study medication after complete hemostasis is achieved, but at minimum an interval of at least 1 hour should elapse for all patients. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

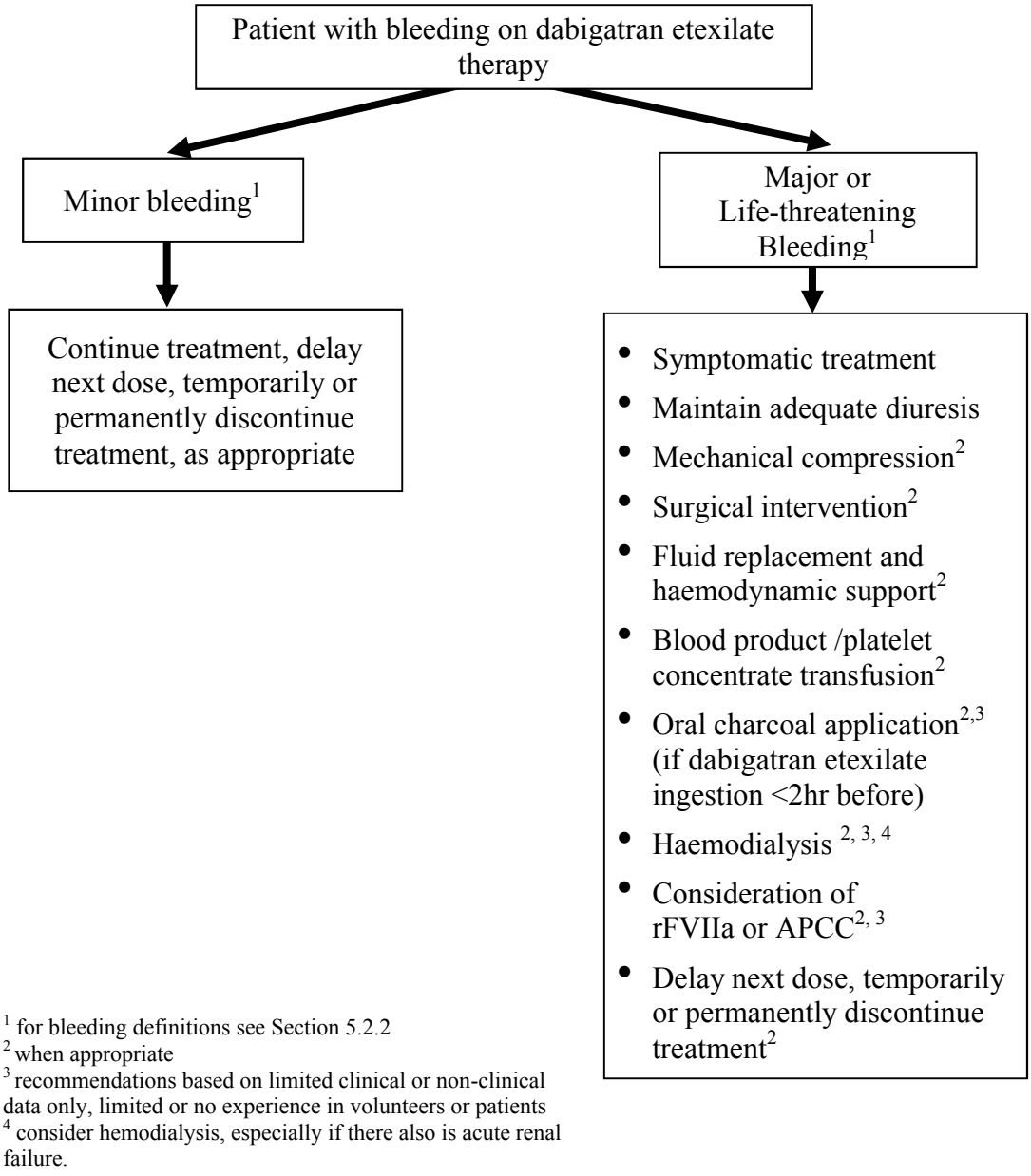
Major Bleeds

If a patient experiences a major bleed, the study medication should be stopped and the source of bleeding investigated and treated. In an emergency bleeding situation, this may involve coagulation testing (aPTT, TT, dTT, ECT, platelet count as described above in Emergency Procedures), and possibly transfusion, diagnostic procedures and/or surgical hemostasis.

The recommendations given below are derived from guidelines to manage bleeding with DE, however, with the exception of recommendations on the specific reversal agent for dabigatran, they can be applied to all patients in this trial irrespective of assigned study medication (i.e. DE or ASA).

See section 4.2.1 Overdose, for more information regarding the specific reversal agent for dabigatran. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate standard treatment, e.g. surgical hemostasis as indicated and volume replacement should be undertaken as appropriate. In addition, consideration may be given to the use of fresh frozen plasma (P10-03790). As protein binding is low, dabigatran is dialyzable, however there is limited clinical experience in using dialysis in this setting. Clearance of dabigatran by hemodialysis was investigated in patients with end-stage renal disease. Dialysis was conducted with 700mL/min dialysate flow rate, four hour duration, a blood flow rate of either 200mL/min or 350 - 390mL/min. This resulted in a removal of 50% or 60% of free or total dabigatran concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate (U11-1642-01). There is some experimental evidence to support the role of agents such as activated prothrombin complex concentrates (APCC) (e.g. Factor Eight Inhibitor Bypassing Activity (FEIBA)), recombinant Factor VIIa and three or four factor concentrates (factors II, IX and X with or without Factor VII) in reversing the anticoagulant activity of dabigatran. The usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or where ASA (100 mg daily) has been assigned as co-medication. All symptomatic treatment has to be given according to the physician's judgment.

A summary how to manage bleeding on DE is presented in Figure 4.2.1: 1. Unless explicitly mentioned, the recommendations given for DE can also be applied to patients receiving ASA in the trial.



[1] for bleeding definitions see Section 5.2.2
[2] when appropriate
[3] recommendations based on limited clinical or non-clinical data only, limited or no experience in volunteers or patients
[4] consider hemodialysis, especially if there also is acute renal failure.

Figure 4.2.1: 1 Management of bleeding

As study medication is blinded, the following characteristics of ASA should also be taken into consideration for the management of bleeding (adapted from P10-03790):

There is no specific reversal agent to counteract the antithrombotic activity of ASA. Since ASA is renally excreted adequate diuresis must be maintained. Alkalinization of the urine is a

key concept in the management of salicylate overdose (see "Overdose" later within this section).

Re-administration of study medication after a major bleed

Re-administration of study medication (at the assigned dose) after the bleeding has resolved and hemostasis has been achieved, is at the discretion of the local Investigator.

Minor Bleeds

If a patient experiences a minor bleed, study medication may be continued, interrupted temporarily or permanently discontinued, at the discretion of the Investigator. It is not a requirement however, that study drug is stopped in these cases.

Stroke

Patients with documented or suspected stroke should be managed according to usual clinical practice, which may include the use of fibrinolytic agents and mechanical clot removal. It is anticipated that in most cases study drug will be withheld until a CT or MRI scan has been obtained.

Ischemic stroke

For ischemic stroke, ASA and/or clopidogrel, or ASA/dipyridamole (the latter in lieu of clopidogrel) may be administered as indicated according to usual clinical practice. Treatment with study drug can be continued at the discretion of the local Investigator, in the absence of evidence of bleeding. For recommendations on timing of restart of study medication see below in section "*reintroduction of study treatment following a stroke",* see Table 4.1.4: 1.

Use of fibrinolytic agents for the treatment of acute ischemic stroke:

The use of fibrinolytic agents for the treatment of acute ischemic stroke may be considered if the patient presents with a TT, dTT, ECT, or (if TT, dTT or ECT are not available) an aPTT lab result not exceeding the ULN according to the local reference range. Either TT or dTT, ECT (one of these parameters is preferred), or aPTT will be sufficient and the choice of the parameter will depend on local availability) (U11-1642-01).

Refer to Section 4.1.5.2 for Emergency Unblinding Procedures.

Hemorrhagic Stroke

For hemorrhagic stroke or other intracranial bleeding, consultation with a coagulation expert and a neurosurgeon is recommended. See "Major Bleeds" earlier in this section for details relating to how to manage bleeding.

In case of recurrent stroke during the trial, it is at the Investigator`s discretion whether study medication will be restarted or whether the patients will be switched to appropriate standard of care antithrombotic treatment.

Reintroduction of study treatment following a stroke (i.e. after recurrent stroke)

The decision about when to restart study medication following a recurrent stroke is at the discretion of the Investigator (with the exception of strokes with mRS of 4 or higher, where restart is not allowed, unless the patient improves to a mRS of 3). Table 4.1.4: 1 shows recommendations (P12-02400) on the earliest possible time point to start study medication. These recommendations in Table 4.1.4: 1 also apply to restarting study medication after recurrent stroke. Cerebral hemorrhage must be excluded before study drug is restarted. If restarting study medication within 10 days of stroke in patients with mRS of 1, 2 or 3, re-imaging is required to rule out bleeding into the brain (for details see footnote of Table 4.1.4: 1).

Acute Coronary Syndrome (ACS)

In patients with documented or suspected ACS, study drug should be temporarily discontinued.

Medication Management of ACS

ASA, clopidogrel and glycoprotein IIb/IIIa inhibitors may be administered according to usual clinical practice. However, the concomitant use of these treatments with study medication may increase the risk of bleeding.

For the use of heparins (UFH or LMWH) or other anticoagulants to manage ACS, the following guidance is provided for consideration:
Unfractionated or low-molecular-weight heparin should be withheld until the aPTT is less than 1.5 x ULN (upper limit of normal):

- If the aPTT is between 1.2 and 1.5 x ULN, UF heparin may be commenced preferably without an intravenous loading dose and LMWH may be commenced at the usual therapeutic dose
- If the aPTT is above 1.5 times the ULN, it should be repeated every four hours until it falls below this level, after which heparin or other anticoagulation can be commenced.

Blinded study medication (either DE or ASA) can be restarted when clinically appropriate (generally ≥ 6 hours after a bolus administration of UFH or ≥ 12 hours after LMWH administration). See Appendix 10.2.1 for recommendations when to start study medication after treatment with parenteral anticoagulants.

Interventional / Surgical Management of ACS or stable CAD

Reperfusion with primary Percutaneous Coronary Intervention (PCI) is preferable over treatment with thrombolysis for patients who are anticoagulated with DE due to the increased

risk for bleeding with concurrent use of thrombolytics and DE. During percutaneous coronary intervention, the activated clotting time (ACT) should be measured and heparin administered as needed according to usual practice.

If primary PCI is not available, the Investigator or treating physician may consider thrombolytic treatment. Thrombolytics should only be administered when the potential gains of reperfusion outweigh the potential risks of severe bleeding. Particular consideration should be given to factors which further increase a patient's risk for bleeding (i.e., elderly, reduced renal function). If the physician elects to treat with thrombolytics, adjunctive treatment with UFH, or LMWH should be withheld until aPTT is ≤1.5 times control.

When coronary stent implantation is necessary, bare metal stents (BMS) should be preferred over drug-eluting stents to reduce the time of dual antiplatelet therapy due to stent implantation. Dual antiplatelet therapy will prompt withdrawal of trial-assigned treatment for the duration of dual antiplatelet therapy. The patient may return to study medication at any time once dual antiplatelets are no longer needed. Patients who permanently stop study medication will be followed-up until termination of the trial.

When Coronary Artery Bypass Grafting (CABG) Surgery is clinically indicated, it should be delayed if possible until at least 12 hours after the last dose of study medication. Elective CABG surgery should be delayed if possible until at least two to three days after the last dose of DE, depending on the renal function of the patient (see Table 4.2.1: 1). Patients with renal dysfunction may have elevated concentrations of dabigatran due to longer half-lives of active drug (see Table 4.2.1: 1). If bypass surgery is to start during elevated plasma concentrations of DE there is an increased risk of bleeding. When preparing the patient for cardiopulmonary bypass, this should be taken into account. The procedure may be performed as usual, including the control of the anticoagulation levels using e.g. aPTT, ACT or TT measurements. For further advice on when to stop study medication before surgery see Table 4.2.1: 1.

Overdose

Overdose may require discontinuation of study medication.

As study medication is blinded, the following characteristics of both DE and ASA should also be taken into consideration for the management of overdose:

Overdose with DE

Overdose following administration of DE may lead to hemorrhagic complications due to its PD properties. Suspected overdose with no clinical symptoms requires frequent observation for signs and symptoms of hematoma or overt bleeding. Symptomatic treatment includes the administration of fresh frozen plasma or fresh whole blood. In case of excessive bleeding, special measures to terminate bleeding (concentrates of coagulation factors II, VII, IX or X, or recombinant factor VII) may be indicated, although there is limited clinical data available to support the application of coagulation factors. Consideration should also be given to

administration of platelet concentrates in cases where thrombocytopenia is present. All symptomatic treatment has to be given according to the Investigator's judgment.

For a summary how to manage bleeding on DE see Figure 4.2.1: 1.

In cases of suspected overdose it may be required to assess the anticoagulation status of a patient. To maintain the blind, the determination of anticoagulation status should only be performed in an emergency. In general, the risk of bleeding increases with increasing plasma level of dabigatran: An aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT of greater than 2.0 – 3.0-fold of normal range at trough, i.e., when the next dose is due, is associated with a higher risk of bleeding (U11-1855-01). In such cases, the Investigator should consider delay in the next intake of study medication until the aPTT is < 1.5 fold of the ULN range.

Specific reversal agent to dabigatran

A specific reversal agent (idarucizumab) has been developed and is currently being reviewed for registration in various countries. When clinically indicated and available, it can be given to a patient in the context of a clinical trial (e.g. BI trial 1321.3) or from commercial supply when it becomes approved. If the specific reversal agent for dabigatran is given, information surrounding the clinical circumstances, treatment and clinical outcome will be collected on the CRF of the appropriate trials.

Overdose with ASA

Overdose (i.e. an intake of a dose of ≥ 3000 mg per day) following administration of ASA may lead to hemorrhagic complications due to its pharmacodynamic properties. Suspected overdose with no clinical symptoms requires frequent observation for signs and symptoms of hematoma or overt bleeding. For further information on the management of overdose with ASA, refer to the SPC for Hexal ASS provided in the ISF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or anti-rheumatic agents in general should only be used if clinically indicated and benefits are expected to outweigh risks. These medications may increase the risk of gastrointestinal ulcers and gastrointestinal bleeding.

The patients should be advised not to use over-the-counter medications containing additional ASA. In case of the need for pain relief, the use of acetaminophen, diclofenac or ibuprofen instead of ASA should be considered where appropriate. The use of these medications should be limited to the absolute minimum possible time period.

Patients with known need for long-term dual antiplatelet therapy at Visit 1 are excluded from the trial (see Section 3.3.3, exclusion criteria).

The following medications should not be taken concomitantly with study drug:

- ASA (commercial drug /over the counter medications) is not allowed except in the case of CAD where it can be taken if dispensed through IRT as outlined in Section 4.1.6. The use of IRT-assigned ASA should be limited to the absolute minimum possible time period and only if clinically indicated.

- Clopidogrel, ticlopidine, ticagrelor, dipyridamole, dipyridamole+ASA, or prasugrel, and any type of dual antiplatelet therapy

- Vitamin K antagonists (e.g. warfarin, phenprocoumon, acenocoumarol), direct thrombin inhibitors, Factor Xa inhibitors (e.g. rivaroxaban, apixaban, and edoxaban), or other oral anticoagulants

- Fondaparinux, bivalirudin

- Treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, or dronedarone.

- Concomitant administration of the P-gp inducers rifampicin, St. John`s wort (Hypericum perforatum), carbamazepine, or phenytoin, which result in decreased dabigatran plasma concentrations.

- Treatment with parenteral anticoagulants including but not limited to any heparins (UFH or LMWH), and heparinoids (e.g. danaparoid), with the following exceptions:

    - Heparins or other alternate approved parenteral therapy for initial treatment of suspected VTE or ACS if maximum duration is not exceeding 72 hours (see Section 4.2.1).

- Methotrexate ≥15 mg/week

The following medications should not be taken concomitantly with study drug except in clinical scenarios described within Section 4.2.1:

- Fibrinolytic agents (see Section 4.2.1. for exception)

- GPIIb/IIIa antagonists (e.g. abciximab, tirofiban) (see Section 4.2.1 for exception).

The following medications may potentiate or attenuate the effect of the study medication and may only be used, if expressly instructed by a physician to treat an underlying concomitant disease:

- antidiabetics (e.g. sulphonylurea agents)
- digoxin
- methotrexate <15 mg/week
- valproic acid

- aldosterone antagonists (spironolactone and canrenoate)
- loop diuretics (e.g. furosemide)
- ACE inhibitors
- uricosuric agents (e.g. probenecid, sulphinpyrazone)
- selective serotonin re-uptake inhibitors (SSRI) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)

Please see Appendix 10.2.2 for guidance on thrombosis prophylaxis or temporary requirement for a parenteral anticoagulant, which requires a temporary stop of study medication.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRI) (U11-1642-01) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) (U12-1072-01).

Co-administration of oral anti-platelet (including ASA) and NSAID therapies increase the risk of bleeding (U09-3249-02). Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases.

In patients ≥75 years, or with previous gastritis, history of peptic ulcer disease or previous gastrointestinal bleeding, the Investigator should consider prescribing a proton-pump-inhibitor (PPI) based on the local prescribing information while receiving NSAIDs/ASA.

A list of common P-gp inhibitors and P-gp inducers, which may affect plasma concentrations of dabigatran, will be provided in the ISF.

If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in hemoglobin is suggested (U12-1072-01). Investigators should assess the benefit-risk of the concomitant use of drugs that can promote bleeding, e.g., NSAIDs, or corticosteroids and use them only when the benefits are thought to outweigh the risks.

Development of an Indication for Anticoagulant Therapy During Follow-Up

If a non-AF indication for anticoagulation is identified during the course of the trial (e.g. venous thromboembolism), trial-assigned therapy will be discontinued, and the patients will be switched to an appropriate anticoagulant, which will be determined and followed by the patient's local physician. See Appendix 10.2.3 on how to transition from study drug to a non-study antithrombotic treatment. These patients should continue to attend regularly scheduled visits.

If AF is identified during follow-up and the duration of AF exceeds 6 minutes (either as single episode or cumulative time of several episodes within 20 hours), trial treatment must be discontinued (but the treatment assignment blind should not be broken), and the patient should be switched to standard of care treatment for stroke prevention in atrial fibrillation

(SPAF) (e.g. DE or other) according to local label recommendations. Shorter durations of AF may result in discontinuation of assigned treatment at the Investigator`s discretion. These patients should continue to attend regularly scheduled visits.

4.2.2.2 Restrictions on diet and life style

There are no specific dietary restrictions with DE or with ASA.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them to all visits.

Treatment compliance for capsules (DE or matching placebo) and tablets (ASA and matching placebo) will be checked by the study staff at Visit 3 and all future visits, and will be recorded in the eCRF. The compliance check will be based on the number of capsules/tablets missing (i.e. actually taken) accountability log.

Medication compliance should be ≥ 80% but ≤ 120%. If compliance does not meet this range, an explanation for this deviation should be given and recorded in the eCRF. Non-compliant patients should be advised about the importance of taking study medication strictly as directed. If the investigator or staff detect compliance is out of range on two occasions, the Investigator should notify the Sponsor. Withdrawal from treatment may then be considered after discussion and agreement between Investigator and Sponsor.

Decisions about evaluability of patients will be made at the Blinded Report Planning Meeting (BRPM) and at the latest prior to database lock.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints of efficacy

The primary endpoint in this trial is time to first recurrent stroke (ischemic, hemorrhagic and unspecified).

The key secondary efficacy endpoints are (both time to event endpoints):

- Ischemic stroke
- Composite endpoint of nonfatal stroke, nonfatal MI and cardiovascular death

For statistical error probability considerations for key secondary endpoints, refer to Section 7.3.2.

Other Secondary efficacy endpoints (all time to event endpoints):

- Disabling stroke (modified Rankin Scale ≥ 4, as determined 3 months after recurrent stroke)
- All-cause death

5.1.2 Assessment of efficacy

5.1.2.1 Recurrent stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction (!"# $ %&'(!") $**"*).

Retinal arterial occlusion will be considered as a stroke if the ophthalmological examination has been performed and the opinion of the examining ophthalmologist agrees with such a diagnosis. Other retinal vascular events (e.g. retinal venous occlusion, non-confirmed retinal arterial occlusion), will not be considered strokes.

Ischemic Stroke

+,-./01- ,2345/ 1, 6/718/6 9, 98 9-:2/ /;1,46/ 47 74-9< -/3/=39<(,;189<(43 3/2189<>,7:8-2148 -9:,/6 => 18793-2148 7-/8239<8/3?4:, ,>,2/0 21,,:/ @!"# $%&'(!") $**"* AB
Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage (!"# $ %&'(!") $**"*). It does not include the hemorrhagic transformation of an ischemic stroke.

Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic stroke.

Fatal stroke

Fatal stroke is defined as death from any cause within 30 days of stroke.

Severity of recurrent stroke

Severity of recurrent stroke will be assessed by mRS at the onset of stroke and at 3 months after recurrent stroke, if this time frame falls anytime within the study participation (See Section 5.3.2 for definition of mRS). Disabling stroke is defined as a stroke with mRS ≥4 at 3 months.

Stroke etiology

Investigators are asked to further classify the type of stroke according to the five etiologic subtypes according to modified TOAST criteria, where possible: large-artery atherosclerosis, cardioembolism, small-artery occlusion (lacunar), acute stroke of other determined etiology, cryptogenic stroke (R97-1235). The category "ESUS" will also be collected.

5.1.2.2 Systemic embolism

Systemic embolism is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, or grafts) and must be documented by angiography, surgery, scintigraphy or autopsy.

5.1.2.3 Death

Death from any cause includes cardiovascular death, non-cardiovascular-death, and undetermined cause of death, as classified by adjudication:

Cardiovascular death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Non-cardiovascular death

Non-cardiovascular death is defined as any death with a specific cause that is not thought to be cardiovascular in nature, as listed above. These are possible examples of non-CV causes of death:

- C:<04893>
- !/89<
- D9,234182/,2189<
- E/;924=1<193>
- C98-3/921-
- +87/-2148@18-<:6/,/;,1,A
- +87<9009243>@/BF0B<,2/01- +87<9009243>/,; 48,/ G>86340/ @G+!GA+00:8/ @18-<:618F 9:24100:8/A
- E/0433.9F/ 2.921, 8/12./3 -93614?9,-:<93=</618F439 ,2345/
- I48 $JK ;34-/6:3/ 43,:3F/3>
- L39:09
- G:1-16/
- I48 $;3/,-31;2148 63:F 3/9-2148 43 4?/364,/
- C3/,-31;2148 63:F 3/9-2148 43 4?/364,/

- I/:34<4F1-9<@848$-93614?9,-:<93A
- M9<1F898->
- N2./3 848$JK @24/ ,;/-171/6A

Undetermined Cause of Death

Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and therefore the use of this category of undetermined cause of death should apply to few patients only.

5.1.2.6 Venous Thromboembolism

All VTEs should have objective verification by definitive diagnostic evaluation (e.g. Doppler/compression ultrasound (CUS), venography).

In case of death, autopsy is an additional way to confirm VTE.

Deep Vein Thrombosis

Deep Vein Thrombosis (DVT) is generally documented by one of the following:

- Abnormal CUS
- An intraluminal filling defect on venography
- At autopsy

Pulmonary embolism

Pulmonary embolism is generally documented by one of the following:

- An intraluminal filling defect in segmental or more proximal branches on spiral CT scan
- An intraluminal filling defect or an extension of an existing defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram
- Perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan (VPLS)
- Inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by CUS or venography
- At autopsy

5.1.2.8 Cardiovascular hospitalization

Hospital admission with an overnight stay in hospital, covering at least 2 consecutive dates which occur after randomization and was not scheduled prior to randomization, categorized as cardiovascular if the primary reason for hospitalization is:

- Ischemic stroke
- Hemorrhagic stroke
- Unspecified stroke
- Transient cerebral Ischemic Attack
- Venous Thromboembolism
- Myocardial infarction or Unstable angina
- Stable angina pectoris or atypical chest pain
- Other atherosclerosis related (if not otherwise specified)
- Cardiac and vascular surgery, including transcutaneous coronary, cerebrovascular or peripheral procedures
- Cardiac rhythm abnormalities (supraventricular or ventricular)
- Worsening congestive heart failure
- Major bleeding (excluding hemorrhagic stroke)
- Clinically relevant non-major bleeding
- Blood pressure related (hypertension or hypotension)
- Syncope

5.2 SAFETY

5.2.1 Endpoint(s) of safety

The primary safety endpoint is time to first major bleed according to ISTH criteria (R05-0344).

Secondary safety endpoints include:

- Time to first intracranial hemorrhage
- Time to life-threatening bleed
- Fatal bleed
- Time to any bleed (all severities)

5.2.2 Assessment of safety

5.2.2.1 Assessment of bleeding events

Patients should be carefully assessed for signs and symptoms of bleeding. Bleeding definitions are provided below and will be classified as major or minor. Major bleeds will be further sub-classified as fatal, life-threatening and other major bleeds. Minor bleeds will be further sub-classified CRNMBEs and non-CRNMBEs. The location of the bleeding including the specific critical area or organ into which the bleeding occurred and whether or not it prolongs hospitalization will be recorded.

Definition of Intracranial Hemorrhage

Intracranial hemorrhage comprises the subtypes of intracerebral bleeds, subdural bleeds, epidural bleeds and subarachnoid bleed and will be recorded in eCRF. Microbleeds (for definition see below) do not qualify as ICH, except when they are symptomatic.

- Definition of a microbleed:

A cerebral microbleed is in general ≤ 5mm, but sometimes up to 10 mm, in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences (R15-2999). Any blood visualized on a CT will be classified as a macrobleed. Asymptomatic microbleeds are incidental findings that do not constitute an exclusion criterion. Irrespective of size, any cerebral bleed that causes focal neurologic symptoms and/or signs does not constitute a microbleed, but will be reported as a stroke endpoint (hemorrhagic stroke) and bleeding event (intracerebral hemorrhage).

Definition of a Major Bleed

Major bleeds will be defined according to the ISTH definition of a major bleed, as follows (R05-0344).

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,

and/or

- Bleeding associated with a reduction in hemoglobin of at least 2g/dL (1.24mmol/L), or leading to transfusion of two or more units of blood or packed cells[1]

and/or

[1] Bleeding should be overt and the hemoglobin drop should be considered to be due to and temporally related to the bleeding event.

- Fatal bleed

Definition of a life-threatening bleed

Major bleeds are to be classified as life-threatening if they meet one or more of the following criteria:

- Fatal, or symptomatic intracranial bleed; reduction in hemoglobin of at least 5g/dL; transfusion of at least four units of packed red blood cells, associated with hypotension requiring the use of i.v. inotropic agents; necessitated surgical intervention.

Definition of a fatal bleed

Fatal bleeding is defined as a bleeding event that the Independent Adjudication Committee (IAC) determines is the primary cause of death or contributes directly to death.

Definition of a minor bleed

Minor bleeds are clinical bleeds that do not fulfill the criteria for major bleeds. Minor bleeds will be further divided to those that are CRNMBEs, and those that are not.

Definition of a CRNMBE

A CRNMBE is a clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission,

or

- A physician guided medical or surgical treatment for bleeding,

or

- A physician guided change, interruption[1] or discontinuation of study drug.

Definition of a non-CRNMBE

Clinical bleeds that do not meet the criteria for a CRNMBE will be classified as a non-CRNBE.

Any bleed

This is the sum of all major and minor bleeds.

[1] Interruption of study drug (more than omitting one dose) due to the bleeding event.

5.2.2.2 Definition of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, 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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

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

Mild:	Awareness of sign(s) or symptom(s) which 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 adverse event

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. Assessment of causal relationship should be recorded in the case report forms.

For Japan: The reason for the decision on causal relationship needs to be provided in the eCRF.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

If a SAE is reported from a still blinded trial, the causal relationship must be provided by the Investigator for all potential trial drugs, i.e. dabigatran etexilate and ASA.

Outcome Events

Since efficacy and safety endpoints are considered to be disease-related or are well-known side effects of anticoagulation. These events are considered OEs (OEs) and will not be reported as SAEs on the SAE form and consequently will not be reported in an expedited manner to the Competent Authorities. For handling of OEs, please see Appendix 10.4.
A key objective of the independent DMC is to protect patient safety by monitoring the incidence and clinical relevance of safety data including outcome events, collected throughout the conduct of this study.

In addition, for the safety parameters of primary interest, namely any major bleeding event (see Section 5.2.2.1) and for the major mortality/morbidity clinical endpoints of interest (see Section 5.1.2), a blinded IAC will be in place with the responsibility to confirm and classify events as listed in Section 3.1.1.4.

Any Outcome Event (OE) that occurs prior to randomisation and fulfils the criteria of an SAE will be reported as SAE in the corresponding format and timelines; however, if the patient has been randomized, the events will not be reported as SAEs, but only entered in the eCRF as OEs.

Outcome Events are therefore defined as follows:

- Any bleeding including intracranial haemorrhage
- All deaths
- All MIs
- All strokes
- All SE
- All TIAs
- All DVTs
- All PEs

The Investigator (or designee) will enter these OEs (even if they meet the criteria of an SAE) in the corresponding OE and AE pages in the eCRF in an expedited manner. A standard narrative[1] and any required supporting documentation (including e.g. TEE, TTE, MRI, CT, ECG examinations, or other) must also be provided to the DMC and IAC, as defined in their respective process documents.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the Investigator.

[1] A narrative will only be requested if needed

Residual effect period (REP)

The residual effect period (REP) is the time period after the last dose administration of trial medication when measurable drug levels or PD effects are still likely to be present.
Events occurring in the REP are handled as occurring on treatment. The residual effect Period in this trial is defined as six days after last intake of administration of trial medication.

5.2.2.3 Adverse event and SAE reporting

Except where noted otherwise in Section 5.2.2.2, all SAEs occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the end of the follow-up period) will be collected, documented and reported to the Sponsor by the Investigator on the appropriate eCRF pages and SAE reporting forms. Non-serious AEs medically related to the reported SAE must also be reported on the SAE form.

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

For each adverse event, the Investigator will provide at least the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The Investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.2. All events, irrespective of their seriousness, must include an assessment of its causal relationship to study medication made by the Investigator.

The Investigator does not need to actively monitor patients for new adverse events once the clinical trial has ended. However, if the Investigator becomes aware of an SAE that occurred after the end of the follow-up period, the Investigator should report it to the Sponsor if he considers it related to BI investigational product.

The Investigator must report the following events by completing the SAE form and faxing it immediately (within 24 hours or the next business day, whichever is shorter) to the Sponsor:

- Serious Adverse Events
- Non-serious AEs medically related to the SAE

Always serious Adverse Events (AEs)

BI has set up a list of AEs which are defined to be always serious. The investigator can find the list of these "always serious" AEs via the RDC system. In order to support the Investigator with the identification of these "always serious" AEs, if the investigator reports a non-serious AE which is identified to be serious per BI definition, a query will be raised. The Investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and a completed SAE form has to be reported in expedited fashion following the same procedure as above. In Japan, this information must be also reported immediately to the head of the trial site.

The list of these AEs can be found via the remote data capture (RDC) system.

With receipt of further information to any of these events, a follow-up SAE report must be provided. All AEs, including those persisting after trial completion, must be followed up until resolution or the site confirms that no further information can be obtained.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File) or by using the electronic submission process. This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified significant events becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the Investigator must report immediately any drug exposure during pregnancy to the Sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the ISF).

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

An abbreviated hematology panel and chemistry panel including liver and renal function testing will be analyzed for safety at specific time-points throughout the trial by a certified central laboratory. With the exception of early randomization after index event of stroke (see below), all pre specified laboratory tests will be performed by a central laboratory.

Exception: It is permitted to randomize patients based on local lab results in exceptional cases, specifically when the regular turnaround of central lab results would result in a delay of start of study medication early after index stroke event. If local lab results are used, central laboratory samples must also be collected from all patients to provide a baseline for the study. This should preferably occur at Visit 1, however, it can alternatively be collected at Visit 2 prior to first study drug intake. Randomization based on central lab results is strongly encouraged and preferred. The central laboratory will provide the required materials for processing the samples, and will also provide instructions regarding centrifugation, processing, storage and shipment of samples (as outlined in a Laboratory Manual). Results of the central laboratory analyses will be uploaded directly into the trial database. In addition, the Investigator will receive a laboratory report for information on a per visit basis. Clinical significance including any related comments will be entered directly in the eCRF.

If any of the results are judged as being clinically significant by the Investigator, the Investigator should consider whether the result should be recorded as an AE. If deemed necessary, laboratory parameters may be retested or followed as unscheduled tests.

Unscheduled tests should be performed by the Central Laboratory unless immediate results are required for the patient's safety.

Blood samples will be collected for the following tests in accordance with the visit Flow Chart:

Chemistry	Hematology	Other
ALT (SGPT)	Hemoglobin	PK
AST (SGOT)	Hematocrit	Biomarkers
Alkaline Phosphatase	Platelet Count	Assay Validation
LDH	Erythrocytes	
GGT	White Blood Cells	
Bilirubin, Total		
Indirect Bilirubin*		
Creatinine		
Creatinine Clearance**		
Sodium		
Potassium		
Urea		
Total Protein		
Albumin		

* Indirect Bilirubin only reported if total bilirubin is elevated
** According to Cockcroft-Gault formula

In addition to the determination of creatinine clearance according to the Cockcroft-Gault formula, which represents the primary measure for renal function estimation, the glomerular filtration rate (GFR) will be assessed by Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (R12-1392). GFR according to MDRD and CKD-EPI will not be used for dosing decisions in this trial.

Pregnancy testing

Women of child bearing potential must have a urine pregnancy test at screening, at each study visit in the clinic and at least 7 days after the EOT visit. A urine dipstick test will be given to the patient at the EOT visit for use by the patient at least 7 days after the EOT. The patient will be asked to report the result to the site at the post treatment follow-up phone call.

Renal Function Measurements

Creatinine clearance (in mL/min) will be calculated based upon a single blood sample generally using the Cockcroft-Gault formula, as follows:

For creatinine in micromol/L:

Males: $\frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine [micromol/L]}}$

Females: $\frac{0.85 \times (140\text{-age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine [micromol/L]}}$

For creatinine in mg/100 mL:

Males: $\frac{(140\text{-age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$

Females: $\frac{0.85 \times (140\text{-age (years)}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$

Creatinine Clearance value at Visit 1 and during the trial will determine the dose of DE (or placebo) assigned to the patient. Assignment of dabigatran dose (110 mg or 150 mg b.i.d.) is based upon renal function as measured by the CrCl (see Section 4.1.3 for details). See Section 3.3.4.1 regarding rules for stopping study drug when CrCl falls below 30 mL/min.

Investigators should be aware that patients with decreased renal function may experience a prolonged elimination of study drug (specifically dabigatran) and steady state levels could increase compared to a patient with normal renal function. Such patients are therefore at increased risk for bleeding.

For patients on study drug with borderline creatinine clearance, physicians should consider conducting (per standard of care) more frequent monitoring of creatinine clearance than required by this protocol to ensure that CrCl does not drop below 30 mL/min.

5.2.4 Electrocardiogram

A 12-lead ECG is collected at Visits 1, 6, 10 and at the EOT Visit. At all other Visits, a 12-lead ECG should be performed if palpation of the pulse indicates irregular rhythm or symptoms of irregular pulse have been reported. If any ECGs are performed during the course of the trial as part of patient normal care and demonstrate a clinically relevant change from the previously recorded ECG or a newly developed pathology, this should be documented in the eCRF.

Copies of all ECGs and reports form cardiac monitoring will be provided to the Sponsor's designee.

5.2.5 Assessment of other safety parameters

5.2.5.1 Full Physical Examination

A full physical examination will be completed on all patients at screening (Visit 1) and this will be repeated at the end of the study. The physical examination will include auscultation of cardiac sounds, which will be performed with the patient seated after having rested for at least five minutes. All clinically relevant abnormal findings at the screening visit will be recorded on the Medical History/Baseline Conditions eCRF page. New abnormal findings or worsening of baseline conditions detected at follow-up physical examinations will be recorded as AEs on the appropriate eCRF page. All AEs, including those persisting after trial completion must be followed up until they have resolved or have been sufficiently characterized.

5.2.5.2 Vital Signs

Vital Signs will include seated SBP and DBP after 5 minutes in the sitting position and pulse rate (PR) in beats per minute. For patients who cannot sit, supine BP is acceptable.

Recording of vital signs also includes sitting heart rate with palpation of the pulse for one minute. A subsequent 12-lead ECG should be done if an irregular rhythm is detected or if the patient informs the Investigator about irregular heartbeats (see Section 5.2.4 above).

5.4 APPROPRIATENESS OF MEASUREMENTS

Efficacy endpoints

This study is powered for all strokes as the primary endpoint. Although the trial is not powered for other morbidity/mortality endpoints, it is appropriate to collect data on death, stroke, TIA, SE, VTE and MI.

Safety endpoints

The key safety endpoint in this trial is major bleeding, as categorized using the ISTH definition (which is very similar to that used in CURE (R02-1059), ESTEEM (R03-2266) and the Sponsor's large phase III trial in the AF population, RE-LY (U09-3249-02). Classifications of bleeding events will be confirmed by the IAC and provided on an on-going basis to the DMC.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Informed consent of all study patients will be obtained in compliance with ICH and GCP guidelines and the principles stipulated in the Declaration of Helsinki prior to any study related procedure.

The study will consist of three sequential periods, a Screening period of up to 14 days, a Treatment Period of approximately 6-36 months and a Follow up Period of one month. The maximum treatment duration is expected to be 36 months, however, the trial can conclude earlier, if adequate number of events are reported sooner. It can conclude later (or enroll additional patients) if more time is needed to observe the minimum number of required events.

The schedule for trial visits is summarised in the study Flow Chart including time windows for study visits. All visit dates are calculated from the date of randomisation. In the event that visits are missed or out of sequence, subsequent visits will be planned according to the date of randomisation.

No protocol waivers will be given (e.g. Sponsor will not grant permission to include a known ineligible patient). In the case of medical emergencies, prior approval from the Sponsor for protocol deviations (e.g. visit schedule) will not be required, but BI should be notified as soon as possible. The relevance of any such protocol deviation will be assessed prior to analysing the data.

The procedures to be conducted at each visit are provided in the Flow Chart and further described below.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in periods

The investigations outlined in Table 3.3.1: 1 are to be completed and documented per standard of care as a prerequisite to consideration for study participation. (Note: a minimum of 20 hours cardiac monitoring is required for enrollment).

Once ESUS is confirmed, a patient can be considered for eligibility and approached to assess their interest in volunteering as a participant in this trial. Written informed consent must be obtained prior to any study specific procedures.

The screening visit (see Flow Chart) will include review of medical history, demographics, inclusion/exclusion criteria, physical exam, vital signs (including BP and heart rate), ECG, urine pregnancy test for women of child-bearing potential who are not sterilized, safety laboratory tests collected according to central laboratory instructions, weight, and concomitant medications reviewed. The MoCA test will also be performed. Modified Rankin

Scale/NIHSS will be determined and recorded. If the patient has a mRS >3 at time of qualifying stroke but the value improves to ≤ 3 within 3 months (6 months for patients aged ≥ 60 years plus additional risk factor), the patient can be considered for enrollment. A PK sample (and optional samples for biomarker assessment and assay validation for participating patients) will additionally be taken (this must occur prior to first intake of study drug).

All patients will have baseline blood samples sent to the central laboratory (preferably at Visit 1). Randomization based on central lab results is strongly encouraged and preferred. However, local laboratory test results that have been collected within 14 days prior to randomization can also be used to verify eligibility (blood must additionally be collected and sent to central lab for analysis). In these exceptional cases it is permitted to randomize patients based on local lab results. Local lab results must include at a minimum: hemoglobin, platelet count, creatinine, creatinine clearance, and LFTs (ALT (SGPT), AST (SGOT), AP, total bilirubin).

Detailed results of the required diagnostic imaging for the index stroke (from diagnostic evaluations specified in Table 3.3.1: 1) must be available in the source notes for all patients and in the case of recurrent stroke or death must also be provided to the Sponsor or Sponsor`s designee as part of the adjudication package. All of the required diagnostic examinations related to the index stroke must be completed prior to randomization.

Patients with mRS of 1, 2 or 3 at time of randomization who are scheduled for initiation of study medication within 10 days of index event require repeat imaging of the brain to rule out bleeding into the brain (per Exclusion #6). This repeat imaging must occur prior to randomization.

For sites participating in the Imaging substudy, brain images (i.e. CT, CT-angiography, MRI, MRI angiography, or other) related to the index stroke event and any imaging performed during the trial (plus corresponding reports) must be provided to Sponsor's designee where possible (see also Appendix 10.6).

6.2.2 Treatment periods

All tests for the visits in the treatment phase are detailed in the Flow Chart.

After eligibility has been confirmed and all Visit 1 procedures completed, Visit 2 can be conducted including randomization via IRT. IRT should not be called in advance of Visit 2, as randomization of a patient cannot be reversed.

At the start of Visit 2, it should be ensured that all Visit 1 procedures have been successfully completed within the past 14 days.

Randomization can occur as soon as patient eligibility is confirmed, and up to a maximum of 3 months after the qualifying stroke (or 6 months in patients ≥ 60 years of age with one additional risk factor as noted in Inclusion Criterion 2b). Visit 2 procedures are outlined in

the Flow Chart and include randomization, collection of vital signs and recording of concomitant therapies of interest.

Restricted medications as outlined in Section 4.2.2 will be stopped. Study medication will be dispensed and should be initiated as outlined in Section 4.1.4 and Table 4.1.4: 1[1]. AEs, SAEs and OEs (after randomization) will be collected as described in Section 5.1 and Section 5.2.

Treatment visits will take place every three months during the first year of the trial and every six months thereafter (with interim telephone contacts between visits).

Unscheduled visits will be possible at any time, specifically in the first 3 months after treatment initiation, in order to check the safety of the patient including a potential worsening of renal function (CrCl). It is at the discretion of the investigator to perform an unscheduled visit including safety laboratory assessments, if deemed necessary.

Labs do not need to be drawn on the actual day of the visit. They may be drawn earlier as long as it is within the visit window.

Heart rate must be checked at all follow-up visits by palpation of the pulse. If palpation of the pulse indicates irregular rhythm or symptoms of irregular pulse have been reported, a 12-lead ECG must be done and additional cardiac monitoring may be performed at the Investigator`s discretion. If the pulse is normal and no symptoms are reported, a follow-up ECG is not necessary.

A 12-lead ECG should be performed at Visits 6 and 10. ECGs done per standard of care that demonstrate a change compared to the previously recorded ECG or a newly developed pathology, should be recorded in the eCRF.

Copies of all ECGs documented on the eCRF should be provided to the Sponsor's designee.

Additional cardiac monitoring (e.g. Holter-ECGs) may be performed at the discretion of the Investigator according to local standard of care. The results of these cardiac monitoring efforts will be documented in the CRF. Results obtained from implantable cardiac monitors will also be captured.

Permanent study drug discontinuation is only justified when clear, persistent contraindications arise or when the patient requests to be withdrawn from study drug, see Section 3.3.4.1.

All randomized patients must be followed up until the end of the study. Patients who discontinue treatment must continue to be followed up according to the visit schedule until the end of the study. At these visits collection of AEs, OEs (including bleeding) and use of concomitant medication of interest will be made.

[1] As a reminder, if a patient has mRS of 1, 2 or 3 at time of randomization and study medication is to be started within 10 days of index event, repeat imaging is mandatory to rule out bleeding into the brain. Randomization should only occur after reimaging of the brain has been performed and eligibility has been confirmed. Refer to Table 4.1.4: 1 for details.

Patients that are not actively taking study drug may be less motivated to adhere to the study visit schedule. Investigator and site staff should work to detect early signs of losing interest and readily present such patients (not actively taking study drug) with the following opportunities to encourage continued participation:

- continue to attend regularly scheduled study visits until the trial ends
- conduct only the final visit in person. All other visits would be done over the phone.
- conduct all remaining study visits over the phone
- discontinue participation in remaining trial activities but collect vital status and OEs at the end of the trial.
- discontinue participation in remaining trial activities but permit collection of vital status at the end of the trial.

According to regulatory agencies' recommendations, the Investigator should inform subjects that withdrawal of consent for follow-up will jeopardize the validity of the study. Therefore the patient will be asked to choose the most rigorous follow-up they are willing to comply with.

The site must make periodic documented attempts (at least every three months) to locate patients who are potentially lost to follow-up (LTFU).

6.2.2.1 Interim Telephone Calls

After year one, interim telephone calls will be made to patients (at Visits 7, 9, 11 and 13). Phone calls will be scheduled 3 months after each regular office visit. During the phone calls, AEs, SAEs, and OEs will be collected and recorded in the eCRF.

6.2.3 End of trial and follow-up period

6.2.3.1 End of Treatment Visit

At the time that study drug is permanently stopped (whether this is done prematurely or due to the end of the trial), the EOT visit should be completed. Study drug should be stopped and all unused study drug collected. A 12-lead ECG should be performed.

The need to transition to non-study antithrombotic treatment should be determined by the clinical Investigator or treating physician taking current guidelines into consideration (see Appendix 10.2.3 for guidance on transition to a non-study antithrombotic medication). If the patient will be switched to ASA, the first dose of non-study ASA can be taken on the day the last dose of study drug was taken. Patients who continue study medication until the Final Visit must have EOT and Final Visit assessments done at the same visit. In these cases, it is expected that EOT and Final Visit eCRFs will be completed at the Final Visit. Refer to Flow Chart for required assessments.

6.2.3.2 Final Visit

Refer to Flow Chart for list of required assessments at the final visit. For patients that are on treatment at the end of the trial, the EOT and Final Visit assessments can be done at the same visit. The MoCA test will also be performed.

It will be documented whether the patient had received an implantable cardiac monitor for continuous cardiac monitoring during the course of this trial, including the results from this long-term cardiac monitoring.

6.2.3.3 Post Treatment Phone Call

For all patients that stopped study drug at the Final Visit, a follow-up phone call will be conducted one month later. During this call, concomitant medications of interest, AEs, SAEs and OEs during the 30 day period after last dose of study drug will be recorded in the eCRF.

Patients that permanently discontinued study drug within a month preceeding another scheduled visit do not need to have this additional phone call. Their follow-up information, (inclusive of information about the month after their last dose of study drug) will be collected at their next scheduled visit. A urine dipstick pregnancy test performed by select patients (i.e. only in WOCBP) after the EOT with urine dipstick result to be reported back at Post Treatment phone visit.

6.2.3.4 Vital Status and Event Collection

It is important to record the vital status and adverse events -including Outcome Events- of all randomized patients at the end of the trial. It is critical that every randomized patient is followed until the end of the trial, even if study medication is never taken. If a patient does not attend the final visit for any reason, the site will contact them to assess their vital status, adverse events and OEs.

If a site has difficulty contacting a patient at the end of the trial (or at any time during the trial), site staff should make reasonable attempts to contact the patient using different methods (e.g. phone, email, certified letter and/or other methods) until the patient is successfully contacted or the study ends. In the absence of reaching the patient directly, alternative approaches which are allowable via local regulations and IRB/IEC should be used to establish vital status (at minimum) and incidence of recurrent stroke (where possible). It is good practice to specify in the informed consent form what processes are permitted by local regulations to establish vital status for patients that cannot be reached via phone for this visit (e.g. review of public databases, contacting primary care physician, contacting family member, etc).

6.2.3.5 Withdrawal of consent

Patients that discontinue medication and express desire to reduce degree of participation should be presented with alternative follow-up options as described in Section 6.2.2.

If a patient is not willing to continue in the trial and withdraws consent for any reason (without the need to justify the decision) prior to the end of the trial, an EOT Visit and Final Visit should be scheduled as soon as possible. A 30 day follow-up phone call should also be conducted if the patient is agreeable.

In rare cases where patients withdraw consent from any further follow-up, no more data on their medical information will be requested directly from the patient. Where permitted by local law, regulatory authorities and Ethics Committees, vital status information may be obtained via other means (e.g. medical records, public databases).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a prospective, multi-center, international, randomized, double blind, parallel-group study aiming to show superiority of DE over ASA as an active control in the prevention of recurrent stroke in patients with recent history of ESUS. Eligible patients will be randomized to DE (110 or 150 mg b.i.d. dose – actual dose will be determined by algorithm which accounts for age and renal function) or ASA 100 mg once daily.

The primary outcome is time to any recurrent stroke (ischemic, hemorrhagic, or unspecified). Key secondary endpoints are time to first ischemic stroke, and time to the first occurrence in the composite endpoint of "nonfatal stroke, nonfatal MI, and cardiovascular death". Multiplicity will be addressed using a list of hierarchical tests.

Time to event endpoints will be analyzed using the Cox model with covariates age, renal impairment, and stroke or TIA prior to index stroke (refer to Section 7.3.1 for details).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The hypotheses for the primary and key secondary endpoints are:

$$H_o: HR_{Dabigatran/ASA} = 1 \quad \text{vs.} \quad H_a: HR_{Dabigatran/ASA} \neq 1$$

Tests will be performed at the two-sided $\alpha = 0.05$ level.

7.3 PLANNED ANALYSES

Two patient populations are defined:

- The randomized set (RS) consists of all patients who were randomized, regardless of whether they took study medication. The start date of the observation period for this population is the date of randomization.

- The treated set (TS) consists of all patients who were treated with at least one dose of study medication. The start date of the observation period for this population is the date of first intake of trial medication.

Two follow-up periods are defined:

- Full follow-up: until the end of the trial, including all observed time on and off trial medication until the last known alive date (or date of death)

- On-treatment: until the date of discontinuation of trial medication + 6 days

When composite endpoints are evaluated as survival endpoints, the time to first onset date of any of the events listed in the composite endpoint will be used as the date of the event. For

combined endpoints of nonfatal and fatal events the time to the first event is taken. If the fatality is the first event, then the time to death (not the time to the event leading to death) is taken.

7.3.1 Primary analyses

The primary endpoint is time to first recurrent stroke (ischemic, hemorrhagic, or unspecified) as determined by the adjudication committee. It will be analyzed using the Cox proportional hazards regression model. Covariates included in the model will be age (binary, < or ≥ 75 years), renal impairment (binary; creatinine clearance < or ≥ 50 mL/min), and stroke or TIA prior to index stroke (binary, "yes" or "no").

The primary analysis will be performed on the RS for the full follow-up period. Patients who discontinue study medication will be followed until the end of the trial for OEs including vital status. Patients who are lost to follow-up for vital status will be censored for the primary endpoint of recurrent stroke at the time of their last known alive date.

7.3.2 Secondary analyses

The key secondary efficacy endpoints are:

- Time to first ischemic stroke
- Time to first occurrence of nonfatal stroke, nonfatal MI, or cardiovascular death

Key secondary endpoints will be analyzed in a hierarchical manner to preserve the Type I error. If the test for the primary endpoint is successful, then testing will continue for the first key secondary endpoint of time to ischemic stroke with two-sided α=0.05. If this test is successful, then the second key secondary endpoint of time to nonfatal stroke, nonfatal MI, and cardiovascular death will be tested with two-sided α=0.05. If at any point, the null hypotheses for the primary or key secondary endpoints cannot be rejected, formal testing will stop.

Other Secondary efficacy endpoints are listed in Section 5.1.1. Key secondary and other secondary endpoints will be analyzed using the same Cox proportional hazards regression model (with covariates) as the primary endpoint. All secondary analyses will be performed on the RS population for the full follow-up period.

No multiplicity adjustments are planned for other secondary endpoints. Nominal p-values will be reported for descriptive purposes.

7.3.3 Safety analyses

Analysis of all bleeding endpoints (as listed in Section 5.2.1) will be performed on the TS population for the on-treatment period. The pre-specified bleeding endpoints will also be analyzed using the RS set as a sensitivity analysis and for publication purposes.

Time to event endpoints will be analyzed using the same Cox proportional hazards regression model as the primary endpoint. No multiplicity adjustments are planned for safety endpoints. Minor bleeds and CRNMBE will be presented using descriptive statistics.

Adverse events will be analyzed from the TS population. AEs recorded prior to first intake of trial medication will be assigned to 'screening'. The REP is 6 days (refer to Section 5.2.2.2). All adverse events with an onset after the first dose of study medication up to a period of 6 days after the last dose of study medication will be assigned to the on-treatment period for evaluation. Those after the REP, but prior to the last per protocol contact will be assigned to 'post treatment", and those after the last per protocol contact will be assigned to ‘post-study’. The same applies for planned measurements (e.g. vital signs or laboratory parameters) with the exception that measurements between start and last per protocol contact will be assignment to the corresponding treatment. 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 (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced to compare the incidence of adverse events.

Laboratory data will be analyzed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the

listings. Treatment groups will be compared descriptively. Even if randomization occurred based on local lab, Visit 1 results of the central laboratory analyses will be used for the analyses.

7.3.4 Interim analyses

No formal interim analyses are planned. Refer to Section 3.1.1.3 for details about interim monitoring by the DMC.

A blinded sample size reassessment with the option to adjust the sample size will be performed by the Sponsor's Trial Statistician based on continuous assessment of the enrollment rate and the OE rate. Using data from a previous recurrent stroke trial (PRoFESS), a projection of recurrent strokes will be created using a Kaplan-Meier plot. As blinded data from the present trial comes in, this projection will be refined to predict when the projected number of OEs will occur. If the prediction is lower than expected, a decision will be made by the Executive Committee and Sponsor whether to increase the sample size, number of sites or extend the duration of the trial. Final determination will occur no later than three months prior to discontinuation of enrollment.

7.4 HANDLING OF MISSING DATA

A major goal of the trial is to obtain virtually complete follow-up of vital status and all other OEs. As mentioned in Section 7.3.1, all patients lost to follow-up will be treated as censored at the time of last known vital status.

No missing data will be imputed for the primary and secondary time to event endpoints. Regarding covariates for the Cox model, age and creatinine clearance are mandatory for trial entry, so these variables will not be missing. If prior stroke or TIA data are missing, the patient will be assumed to have no stroke or TIA prior to index stroke (for the purpose of inclusion into the analysis only), thus no covariate data will be missing for purposes of analyzing the Cox model.

7.5 RANDOMISATION

Patients will be randomized to a double-blind treatment arm in a 1:1 ratio. BI will arrange for the packaging and labeling of study medication. The randomization list will be generated using a validated system using a pseudo random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.6 DETERMINATION OF SAMPLE SIZE

The expected yearly event rate for stroke in the ASA group of ~4.1% was informed by:

- In the subset of patients with prior stroke/TIA in AVERROES the yearly event rates on ASA and apixaban were 8.3% and 2.5% respectively (R11-0578).
- In the subset of patients with prior stroke/TIA in RE-LY the yearly event rates on warfarin, DE110 and DE150 were 2.8%, 2.1% and 2.3% respectively (P10-12861).
- In PRoFESS the yearly event rates on Aggrenox® and clopidogrel in patients with stroke of undetermined source were 4.06% (U08-3667-01, and data on file).
- Recurrence rates are in general higher early after the index event of stroke (i.e. over the first 3-6 months) and decline thereafter (U08-3667-01, and data on file).

To estimate the expected yearly event rate for stroke in this trial, data from a subset of PRoFESS patients with stroke of undetermined etiology (15.5% of patients in PRoFESS, mean age 66.7 y) was reviewed. While the hazard of recurrent stroke was 4.1 on average, it was higher early after randomization (note that most patients had entered PRoFESS within 3 months after the index stroke event, as it is planned for the majority of patients in this trial) and decreased over time. The table below displays, for 6-month time intervals, the calculated yearly event rates observed in PRoFESS, the expected percentages of patients who enter the respective intervals (according to the planned recruitment schedule and the prospected length of this trial), and the expected number of events per interval assuming a 30% risk reduction favoring DE:

Table: 7.6: 1 Estimated events per interval throughout the trial

	Time since randomization						
	1 - 6 months	7 – 12 months	13-18 months	19 – 24 months	25 – 30 months	31 – 36 months	Total trial period
Yearly event rate	**7.4%**	**3.2%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**4.1%**
Patients per interval	100%	90%	70%	50%	30%	10%	100%
Events per interval*	193	71	42	29	16	3	353

* both treatment groups

Considering the decline of event rates over time, various patient population sizes were considered as shown in the table below.

This review informed the estimation that 2.5 years recruitment, 3 years total observation of approximately 6000 patients with 353 events will give ~92% power if the risk reduction is 30%.

Table: 7.6: 2 Number of events and power required for varying hazard ratios and sample sizes

	Hazard Ratio			
Total sample size	0.80	0.75	0.70	0.65
5000 patients	311 / 50%	303 / 71%	294 / 86%	286 / 95%
6000 patients*	373 / 58%	363 / 78%	353 / 92%	343 / 98%
7000 patients	435 / 64%	424 / 84%	412 / 95%	400 / 99%
8000 patients	497 / 70%	484 / 89%	471 / 97%	457 / 99%

* These are approximations, as this is an event driven trial requiring 353 primary OEs to be reported to be sufficiently powered. The actual number of patients entered may increase or decrease based upon actual event rate. As this is an event driven trial, the trial can conclude earlier, if adequate number of events reported sooner or later, if more events are needed. Sites will be notified when recruitment ends.

To protect against deviations from the assumption, the study will be event-driven and will be terminated when 353 OEs have been reported.

Regarding the impact of patients who develop AF during the study, the following additional information is given:

- A rate of ~ 10% of AF detection is expected during the course of the trial (2.5 years recruitment, 3 years total observation).
- Patients in whom AF is detected during the study need to be switched to standard of care antithrombotic treatment as considered appropriate by their Investigator), but will be observed until the end of the trial.
- Treatment with an anticoagulant may reduce the event rate in the ASA arm and dilute the extent of risk reduction with DE.
- Assuming *a* = the rate of new AF patients (switchers), and further assuming that detection of AF is uniformly distributed across study length, then the observed hazard rate is: HR_obs = HR / (1- *a*/2·(1-HR)). With a 10% overall detection rate of AF, the HR increases from 0.70 to 0.711. See Table 7.6: 3.

Table 7.6: 3 Hazard ratio required taking undetected AF into account

		Hazard Ratio			
		0.80	0.75	0.70	0.65
Rate of AF detection	10%	0.808	0.759	0.711	0.662
	20%	0.816	0.769	0.722	0.674
	30%	0.825	0.779	0.733	0.686

The slightly higher HR of 0.711 will have a limited impact on the power of the trial. For a risk reduction of 30% (in a total of 6000 patients) a power of 92% is achieved; the power will be 90% if the risk reduction is 29%.

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 Harmonized Tripartite Guideline for GCP and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator should inform the Sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP. The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a general rule, no trial results should be published prior to finalization of the CTR.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

Insurance Cover: The terms and conditions of the insurance cover are made available to the Investigator and the patients via documentation in the ISF (where applicable).

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient'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 patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

For Japan: The Investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

The following items need to be included:

1. That the clinical trial is aimed at testing.
2. Objectives of the trial.
3. The name, title, and address of the investigator to contact.
4. Trial procedures.
5. Anticipated benefits of the investigational products and anticipated disadvantages to the patient.
6. Matters concerning other therapeutic measures.
7. Duration of participation in the clinical trial.
8. That the patient may withdraw from the trial at any time.
9. That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantage to him or her.
10. That the monitors, the auditors, and the institutional review board are given access to the relevant source documents on condition that confidentiality of the patient is fully secured.
11. That privacy of the patient is kept.
12. The office of the medical institution to contact in the event of trial-related injury.
13. That necessary treatment is available to the patient in the event of trial-related injury.
14. Matters concerning compensation in the event of any trial-related injury.
15. The type of the IRB which is used for the reviews and deliberations on the matters such as appropriateness of conducting the clinical trial, the matters to be reviewed and deliberated by each IRB, and other matters concerning the IRBs involved in the clinical trial.
16. Other necessary matters concerning the clinical trial.

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

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/Clinical Research Associate (CRA)) or Clinical Quality Assurance auditors appointed by BI, 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 or 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.

In order to ensure accurate, consistent, complete and reliable data the following measures will be taken:

- Representatives from each site will have the opportunity to attend or review material from an Investigator Meeting at which trial processes will be discussed.

- Central laboratory measurements are used for all blood samples (for exception see Section 5.2.3)

- Centralized adjudication and assessment ensures a consist allocation of clinical endpoints

- Regular onsite monitoring

- Coding of concomitant medications is according to the WHO Drug Dictionary and coding of adverse events is according to the MedDRA dictionary.

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- *Steps to maintain the blind (refer to Section 4.1.5.1)*

8.3 RECORDS

Electronic Case Report Forms for individual patients will be provided by the Sponsor, via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must be available. Medical records must demonstrate eligibility.

For eCRFs all data must be derived from source documents.

In addition the following copies will need to be provided to the Sponsor:

- Screening ECGs (including reports of cardiac monitoring) and ECGs with clinically relevant changes detected during the course of the study should be provided to the Sponsor`s designee.

- For sites participating in the Imaging Substudy: Magnetic Resonance Image/CT reports and images for the index event of stroke, possible re-imaging done before randomization and any imaging related to recurrent stroke will be analyzed by the Sponsor`s designee. In addition MRIs (or CTs, if MRIs are not available) performed

during clinical routine (and corresponding reports) will be collected. (see Appendix 10.6).

- For events requiring adjudication (as noted in Section 3.1.1.4), supporting documentation and imaging (as needed and available) must be provided.

- In the case of recurrent stroke or death detailed results of the required diagnostic imaging for the index stroke must also be provided as part of the adjudication package.

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. Electronic Case Report Forms and all source documents, including progress notes 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. Food and Drug Administration (FDA)). The CRA / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the submitted data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

This section is only relevant to sites located in Japan only.

Storage period of records

Trial sites:

The trial sites must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and the Sponsor's SOP.

Sponsor:

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

When it is no longer necessary for the trial site to retain the source documents and essential documents, the Sponsor must notify the head of trial site.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfill the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided.

For DE this is the current version of the IB. For ASA this is the SPC of the HEXAL ASA 100 mg tablet. The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo and study design.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of SAEs, e.g. SUSARs, to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient'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.

8.6 COMPLETION OF TRIAL

When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

The ethics committee (EC)/CA in each participating European Union (EU) member state, and where applicable, the respective authority as defined per local regulations for each other country, needs to be notified about the end of the trial (LPO, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

8.7 PROTOCOL VIOLATIONS

For Japan: The Investigator or sub-Investigator should record all CTP violations. The Investigator should provide and submit the Sponsor and the head of the trial site the records of violations infringing the Japanese GCP or violations to eliminate an immediate hazard to trial patients and for other medically inevitable reasons.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan: In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

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10. APPENDICES

10.1 CHA_2DS_2-VASC SCORE

The CHA_2DS_2-VASc score (P11-03557) is a refinement of $CHADS_2$ score (Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/TIA), which is a stroke risk score originally validated for and applicable to patients with atrial fibrillation. The CHA_2DS_2-VASc score extends the $CHADS_2$ score by assigning additional weight to the risk factor age and by including additional stroke risk factors, specifically vascular disease and gender, as displayed below in Table 10.1.1. The maximum $CHADS_2$ score is 6, whilst the maximum CHA_2DS_2-VASc score is 9. The higher the CHA_2DS_2-VASc score, the higher is the expected risk of thromboembolism (including stroke and SE, see Table 10.1.2)

Table 10.1.1 Components of the scoring system with the acronym CHA_2DS_2-VASc

CHA_2DS_2-VASc Acronym	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65-74 years	1
Sex category (i.e. female sex*)	1
Maximum score	9

LV = left ventricular; MI = myocardial infarction; PAD = peripheral artery disease;
TE = thromboembolism; TIA = transient ischemic attack. Based on R10-5332.
*Note that female gender only scores one point if the patient has at least one other risk factor, and does not score any points in isolation.

Table 10.1.2 Stroke risk stratification with the CHA_2DS_2-VASc score (according to R10-5332)

CHA_2DS_2-VASc Score	Thromboembolic Event Rate during one year (%, 95% CI)[1]
0	0 (0-0)
1	0.6 (0.0-3.4)
2	1.6 (0.3-4.7)
3	3.9 (1.7-7.6)
4	1.9 (0.5-4.9)
5	3.2 (0.7-9.0)
6	3.6 (0.4-12.3)
7	8.0 (1.0-26.0)
8	11.1 (0.3-48.3)
9	100 (2.5-100)

[1]Based on initial validation cohort reported by Lip et al actual rates of stroke in contemporary cohorts may vary from these estimates (R10-5332).

10.2 STUDY DRUG START, THROMBOSIS PROPHYLAXIS AND TRANSITION TO NON-STUDY MEDICATION

10.2.1 When to start study drug following treatment with parenteral anticoagulants, Vitamin K antagonists, or antiplatelets

The following recommendations are provided for guidance only:

Parenteral anticoagulant pre-treatment (e.g. Heparins)

UFH or LMWH/injectable anticoagulant (if given) should be stopped prior to the first dose of study drug. Study drug should be initiated with the following suggested time windows:

- Continuous UFH/other continuous i.v. anticoagulants: initiate study drug at the time the UFH/ other continuous i.v. anticoagulant is stopped
- Bolus of UFH: initiate study drug 6 hours after the bolus injection of UFH
- Low-molecular Weight Heparin/other subcutaneous (s.c.) injectable anticoagulants: initiate study drug 0-2 hours prior to the time that the next dose of the LMWH/other s.c. injectable anticoagulant would be due.

Vitamin K antagonists (VKAs)

- The Vitamin K antagonist should be stopped. Study medication can be given as soon as the INR is < 2.0.

Antiplatelet pre-treatment
(i.e. ASA, clopidogrel, ticlopidine, prasugrel, ticagrelor, dipyridamole, dipyridamole+ASA, at any labeled maintenance dosage)

- Non-study antiplatelets should be stopped prior to the first dose of study drug. Study drug can be initiated *at any time-point* after discontinuation of the non-study antiplatelet, with one exception: After a loading dose of ticagrelor, clopidogrel or prasugrel has been taken, a minimum of 2 hours should elapse before the first dose of study medication can be given.

  Please note that ASA (commercial drug/over the counter medication) ticagrelor, clopidogrel, dypyridamole, dypyridamole+ASA and prasugrel are restricted medications and may not be taken during treatment with study drug. (Note: optional concomitant ASA assigned by IRT may be given, see Section 4.1.1*).*

10.2.2 Thrombosis prophylaxis or temporary requirement for parenteral anticoagulant or antiplatelet(s)

Immobilization or intervention may require temporary thrombosis prophylaxis with e.g. UFH or LMWH or antiplatelet(s). Certain interventions may require the use of parenteral anticoagulants.

The following rules should apply, if thrombosis prophylaxis/parenteral anticoagulants are considered temporarily necessary by the Investigator:

- Temporarily stop study medication. It is recommended to wait 12 hours after the last dose of study medication before switching to a parenteral anticoagulant (e.g. UFH, LMWH). Antiplatelet(s) can be started at any time after last dose of study drug.

The period of thrombosis prophylaxis should be kept to a minimum. For recommendations how to switch back to study drug (DE or ASA) see Section 10.2.1.

10.2.3 Transition to non-study antithrombotic treatment with early study drug discontinuation or at the end of the trial

Patients actively taking study drug at their final treatment visit and patients who stop study medication early may need to switch to a non-study antithrombotic treatment at the Investigator`s discretion. The following recommendations are provided for guidance only

- If the non-study treatment will be antiplatelet agent(s), this medication can be initiated at any time-point after last intake of study medication.
- If the non-study treatment will be DE or another NOAC (such as rivaroxaban, apixaban or edoxaban), the first dose of DE (or other NOAC) should be taken at the time that the next dose of study medication would have been due.
- If the non-study treatment is a Vitamin K antagonist, the starting time of the VKA should be adjusted according to the patient´s CrCl as follows:
  - CrCl ≥ 50 mL/min: start VKA 3 days before discontinuing study drug
  - CrCl ≥ 30-< 50 mL/min: start VKA 2 days before discontinuing study drug

10.4 HANDLING OF OUTCOME EVENTS (BLEEDS AND MORTALITY/MORBIDITY EVENTS)

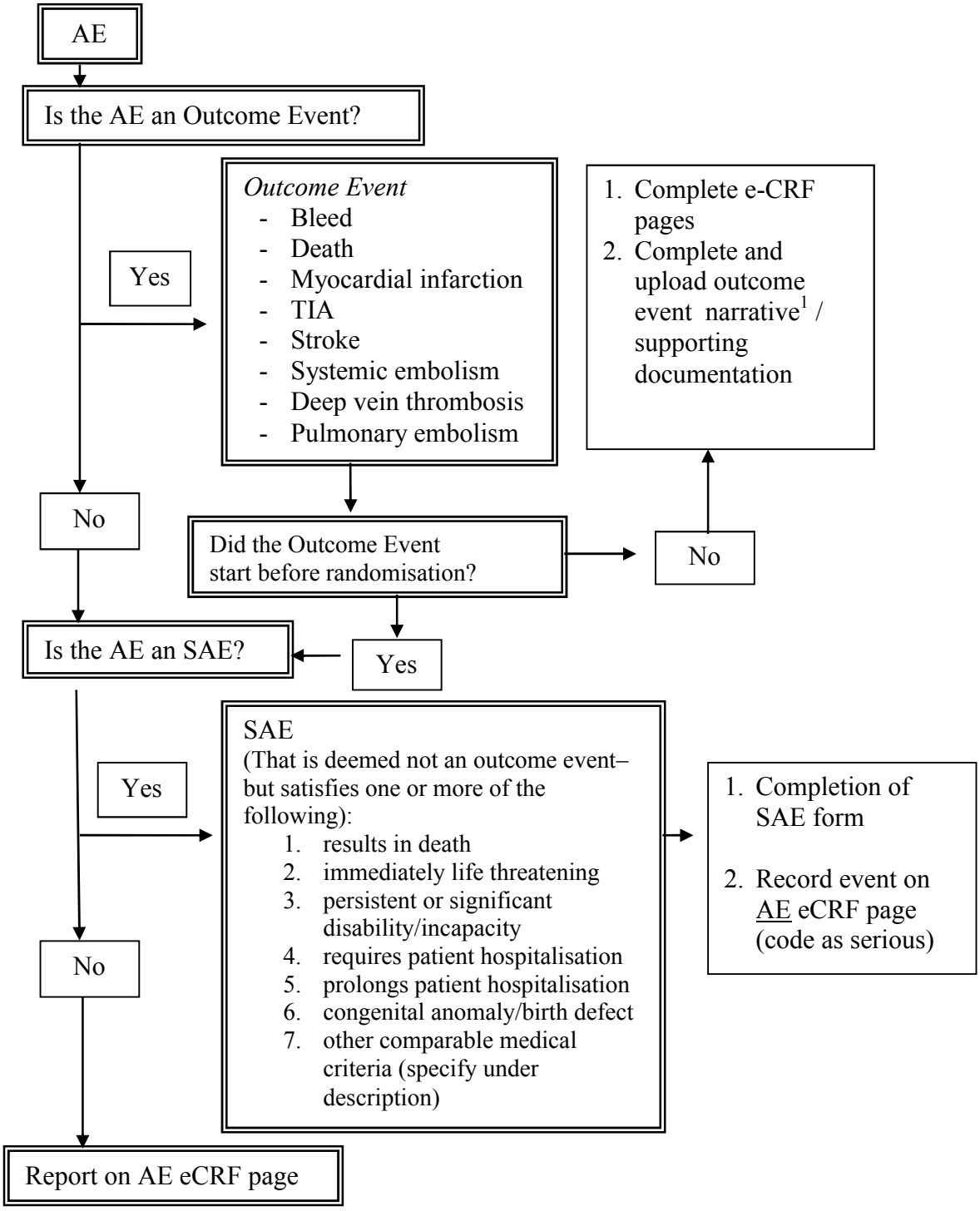

Figure 10.4.1 Hierarchical algorithm of reporting Events

[1]A narrative will only be requested if needed

10.5 NATIONAL INSTITUTE OF HEALTH STROKE SCALE

1a.Level of consciousness	**0**	Alert	
	1	Not alert, but arousable with minimal stimulation	
	2	Not alert, requires repeated stimulation to attend	
	3	Coma	
1b. Ask patient the month and their age	**0**	Answers both correctly	
	1	Answers one correctly	
	2	Both incorrect	
1c.Ask patient to open/close eyes and form/release fist	**0**	Obeys both correctly	
	1	Obeys one correctly	
	2	Both incorrect	
2.Best gaze (only horizontal eye movements)	**0**	Normal	
	1	Partial gaze palsy	
	2	Forced gaze deviation	
3. Visual field testing	**0**	No visual field loss	
	1	Partial hemianopsia	
	2	Complete hemianopsia	
	3	Bilateral hemianopsia (blind, incl. Cortical blindness)	
4. Facial paresis (Ask patient to show teeth or raise eyebrows and close eyes tightly)	**0**	Normal symmetrical movement	
	1	Minor paralysis (flattened nasolabial fold, asymmetry on	
	2	Partial paralysis (total or near total paralysis of lower face)	
	3	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	
5a. Motor Function - right arm	**0**	Normal (extends arm 90º or 45º for 10 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
5b. Motor Function - left arm	**0**	Normal (extends arm 90º or 45º for 10 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
6a. Motor Function -right leg	**0**	Normal (holds leg in 30º position for 5 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
6b. Motor Function -left leg	**0**	Normal (holds leg in 30º position for 5 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
7. Limb ataxia	**0**	No ataxia	
	1	Present in one limb	
	2	Present in two limbs	
8. Sensory (use pinprick to test arms, legs trunk and face, compare side to side)	**0**	Normal	
	1	Mild to moderate decrease in sensation	
	2	Severe to total sensory loss	

9. Best language (describe picture, name items)	**0**	No aphasia	
	1	Mild to moderate aphasia	
	2	Severe aphasia	
	3	Mute	
10. Dysarthria (read several words)	**0**	Normal articulation	
	1	Mild to moderate slurring of words	
	2	Near unintelligible or unable to speak	
	9	Intubated or other physical barrier	
11. Extinction and inattention (use visual double stimulation or sensory double stimulation)	**0**	Normal	
	1	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	
	2	Severe hemi-inattention or hemi-inattention to more than one modality	

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the revised protocol.

GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		*06AUG 2015*
EudraCT number		2013-003444-24
BI Trial number		*1160.189*
BI Investigational Product(s)		*Dabigatran etexilate*
Title of protocol		**R**andomized, double-blind, **E**valuation in secondary **S**troke **P**revention comparing the **E**ffica**C**y and safety of the oral **T**hrombin inhibitor dabigatran etexilate (110 mg or 150 mg, oral b.i.d.) versus acetylsalicylic acid (100 mg oral q.d.) in patients with **E**mbolic **S**troke of **U**ndetermined **S**ource (RESPECT ESUS)
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		Synopsis
Description of change		Clarified change in lower age limit from 50 years to 18 years. CTP revision date added Timing of follow-up MOCA was also clarified as follows: Change in cognitive status from Visit 1 ~~to end of~~

Number of global amendment		1
		~~treatment (EOT)~~ Final Visit ~~in all patients who are still on study medication at year 2 (or longer)~~ as assessed by Montreal Cognitive Assessment (MoCA) questionnaire
Rationale for change		Rationale for these changes is described below.
Section to be changed		Flowchart Footnote 1
Description of change		Text was revised as follows: It is preferred randomization to occur as soon as possible after confirming eligibility ~~but up to 14 days after signing informed consent is permitted~~. Informed consent will be signed any time before screening procedures.
Rationale for change		To clarify timing of consent does not need to be within 14 days of randomization.
Section to be changed		Flowchart
Description of change		"Submission of documentation for central evaluation of ESUS" for Visit 2 was added to the flowchart
Rationale for change		This will serve as clarification for sites that a copy of records of diagnostic pathway examinations should be made and sent for central collection
Section to be changed		Flowchart, 3.3.2, 6.2.2, 6.2.3.2
Description of change		CARDIAC MONITORING DURING THE TRIAL "Documentation of Cardiac Monitoring" has been added to the flowchart for visits 1-6, 8, 10, 12, EOT, and FINAL VISIT. The following text was also added to flowchart footnote 8: "Additional cardiac monitoring (e.g. Holter-ECGs) may be performed at the discretion of the Investigator according to local standard of care. Where this is done, the results of these cardiac monitoring efforts will be documented in the eCRF." Section 3.3.2 Inclusion 4 Footnote 4 previously stated:

Number of global amendment		1
		~~"If there is an increased risk of AF and the Investigator determines extended ECG monitoring is warranted, cardiac monitoring for more than 24 hours is acceptable, but all monitoring efforts must be completed prior to randomization. Cardiac telemetry is not sufficient, unless the data of telemetry had been recorded and summarized results are available."~~ Section 3.3.2 Inclusion 4 Footnote 4 now states: "Cardiac telemetry is not sufficient, unless the data of telemetry had been recorded and summarized results are available. Cardiac monitoring efforts (beyond minimum required per Inclusion 4) may continue after randomization at the Investigator or a treating physician's discretion. All cardiac monitoring data and findings collected during the trial will be recorded in the eCRF." Section 6.2.2 had the following text added: Additional cardiac monitoring (e.g. Holter-ECGs) may be performed at the discretion of the Investigator according to local standard of care. The results of these cardiac monitoring efforts will be documented in the CRF. Results obtained from implantable cardiac monitors will also be captured. Section 6.2.3.2 was updated as follows: It will be documented whether the patient had received an implantable cardiac monitor for continuous cardiac monitoring during the course of this trial, including the results from this long-term cardiac monitoring.
Rationale for change		This was added to clarify that medical chart review of cardiac monitoring efforts done as part of clinical routine throughout the trial. This should be documented on the CRF. The degree of monitoring efforts during the trial is expected to impact the amount of AF detected during the trial. There is no agreement on the optimal amount of cardiac monitoring that should be done in ESUS patients to detect AF. The recording of cardiac

Number of global amendment		1
		monitoring results will deliver an answer on the percentage of patients who develop AF.
Section to be changed		3.3.3, Exclusion 7
Description of change		7a) Major[23] surgery
Rationale for change		There was an error in the footnote numbering. This was corrected to align with the appropriate footnote.
Section to be changed		Flowchart, 6.2.1, 8.3.1, 10, Appendix 10.6
Description of change		BRAIN IMAGING SUBMISSION REMOVED FROM MAIN STUDY AND SUBSTUDY INTRODUCED In the original protocol, all sites were required to submit brain images (CT/MRI) conducted during trial conduct (including those performed as part of patient standard care) for central review. In the revised protocol, only sites that volunteer for the substudy are required to submit brain images (CT/MRI). MRIs are required to be submitted by substudy sites, if available. CTs will be submitted only in cases where MRIs are not available. Flowchart was changed from: Submission of all brain images (CT/MRI) conducted during trial conduct (including those performed as part of patient standard care[22] To: Imaging Substudy: Submission of brain images (CT/MRI) conducted during trial conduct (including those performed as part of patient standard care)[22] Flowchart footnote 21 was revised as follows: For endpoint events which require adjudication as per Section 3.1.1.4., copies of relevant source documentation (e.g. imaging reports) should be collected and submitted. ~~For recurrent stroke, this should include copies of images performed and their corresponding reports.~~ Flowchart footnote 22 was revised as follows: For sites that participate in the imaging substudy: Evaluation of brain images will include CT and/or

Number of global amendment		1
		MRI imaging analysis of index stroke, recurrent stroke and any repeat imaging done to initiate study drug. It will also include the collection of MRI images performed per standard of care during the course of this trial (i.e. not done/repeated specifically for this trial). CTs and/or MRIs (and corresponding reports) will be forwarded to the Sponsor`s designee for imaging analyses (see Appendix 10.6). Section 6.2.1 was updated as follows: For sites participating in the Imaging substudy, ~~All B~~brain images (i.e. CT, CT-angiography, MRI, MRI angiography, or other) related to the index stroke event and any imaging performed during the trial (plus corresponding reports) must be provided to Sponsor's designee where possible (see also Appendix 10.6). Section 8.3.1 was updated as follows: For sites participating in the Imaging Substudy: Magnetic Resonance Image/CT reports and images for the index event of stroke, possible re-imaging done before randomization and any imaging related to recurrent stroke will be analyzed by the Sponsor`s designee. In addition MRIs (or CTs, if MRIs are not available) performed during clinical routine (and corresponding reports) will be collected. (see Appendix 10.6). Section 10 was updated as follows: Appendix 10.6 SUBSTUDY: NEUROIMAGING ANALYSES OF INDEX EVENT AND RECURRENT STROKE Appendix 10.6 title was changed as follows: SUBSTUDY: NEUROIMAGING ANALYSES OF INDEX EVENT AND RECURRENT STROKE Appendix 10.6 was changed as follows: This sub study will be conducted in selected sites,

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		which show an interest in participating. Evaluation of brain images will include CT and MRI imaging analysis of index event (including possible repeat imaging, i.e. before randomization to study drug) and recurrent stroke. It will also include the collection of MRI images (or CT images, if MRI images are not available) performed per standard of care during the course of this trial… … All patients entered into the study at all selected sites choosing to participate should be included in the analysis of index and recurrent stroke images, providing that the transfer of images to the Sponsor's designee is technically feasible…. Some of the goals of the analysis of index and recurrent stroke images have been changed as follows: • to identify silent strokes (as judged by the Investigator) at Visit 1 and during study conduct (using MRI images performed per standard of care, or alternatively CT images, if MRI images are not available)… … Index and recurrent stroke images and their corresponding reports, made as part of patient clinical routine or during the course of the trial (i.e. CT and MRI images, with or without vascular imaging) will need to be provided to the Sponsor`s designee.
Rationale for change		Investigators have indicated that the complexity of this study is impairing recruitment. In order to keep the study feasible to recruit, some changes are being made: - collection of brain images will be from a portion of voluntary sites instead of all sites -the assessment of silent stroke will be judged by the Investigator instead of a central reviewer There is no change to collection of brain imaging reports. All sites will continue to submit these reports for index stroke and recurrent stroke for central review of index stroke and adjudication of recurrent stroke

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Section to be changed		Flowchart, 5.2.3, 6.2.1, 6.2.2
Description of change		LOCAL LAB CLARIFICATIONS Three changes are described here related to collection of labs: 1) An "(X)"[10] was added to the flowchart for Safety laboratory tests at Visit 2. An "(X)"[11] was added to the flowchart for PK tests at Visit 2. This clarifies that central lab samples can still be collected at Visit 2 prior to medication intake in case it was not drawn at Visit 1. 2) Local labs taken within 14 days of randomisation (instead of 3 days) can be used for eligibility. 3) Follow-up lab samples (including safety, PK, assay validation and biomarker samples) can also be collected prior to the study visit. Flowchart Footnote 10 text was revised to include new text as follows: …Local labs (within 14 days of randomisation) can be used to verify eligibility (in addition to collection of central labs) where it is necessary to avoid delaying the initiation of study drug. Refer to Section 5.2.3 for calculation of Creatinine Clearance (CrCl) and Section 4.1.3 for information about dose changes based upon CrCl value. Central labs must also be collected from all patients to provide a baseline for the study. This should preferably occur at Visit 1, however, it can alternatively be collected at Visit 2 prior to first study drug intake. Follow-up safety labs do not need to be drawn on the actual day of the visit. They may be drawn earlier as long as it is within the visit time window. In flowchart footnote 11, the following changes were made: In flowchart footnote 11, the following changes

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		were made regarding PK samples: Pharmacokinetic (PK) samples (for HPLC-MS/MS measurement) at trough to be drawn at Visit 1, Visit 3 and Visit 6. The ~~Visit 1~~ baseline sample must be taken prior to first intake of study medication. This should preferably occur at Visit 1, however, it can alternatively be collected at Visit 2 prior to first study drug intake. The PK blood samples for the dabigatran plasma concentration measurements must be taken when the dabigatran plasma concentration is at trough levels (last drug intake must have occurred 10:00–16:00 hours before blood sampling). Therefore, for these visits, patients should take the trial medication at the study site (after the PK blood sample has been taken) to ensure the PK sample is taken at trough, 10:00–16:00 hours after the last drug intake and prior to the next drug intake. Follow-up PK may be drawn anytime within the visit time window. The following text was added to Flowchart footnote 12: Follow-up biomarker may be drawn anytime within the visit time window The following text was added to Flowchart footnote 13: Follow-up assay validation samples may be drawn anytime within the visit time window. Section 5.2.3 was updated as follows: If local lab results are used, central laboratory samples must also be collected from all patients to provide a baseline for the study. This should preferably occur at Visit 1, however, it can alternatively be collected at Visit 2 prior to first study drug intake. ~~Visit 1 samples should additionally be collected and sent to the central lab.~~ Section 6.2.1 was updated as follows: All patients will have baseline blood samples sent to the central laboratory (preferably at Visit 1).

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		Randomization based on central lab results is strongly encouraged and preferred. However, local laboratory test results that have been collected within 14 ~~3~~ days prior to randomization can also be used to verify eligibility (blood must additionally be collected and sent to central lab for analysis). Section 6.2.2 was updated with the following new text: Labs do not need to be drawn on the actual day of the visit. They may be drawn earlier as long as it is within the visit window.
Rationale for change		This change allows for local labs to be used with the same flexibility as central labs. This is particularly helpful when recent local labs reports are already available. Collecting labs ahead of the visit is preferred by some investigators to allow them to review study results on the day of the visit. This flexibility is also applicable to PK, biomarker and assay validation samples to avoid multiple blood draws for the patient.
Section to be changed		Flowchart, 5.1.1, 5.1.2.7, 5.3.2, 6.2.3.2, 7.3.2.1
Description of change		MOCA ASSESSMENTS Timing of MOCA follow-up was changed in the flowchart. Previously, it was at Visit 1 and Visit 10 for patients still on treatment, now it is at Visit 1 and Final Visit for all patients regardless of treatment status. Flowchart footnote 15 was revised as follows: The follow-up MoCA assessment is ~~only~~ required for all patients (regardless of study drug status) ~~still on study medication at Visit 10 (or later). For these patients, there needs to be one final assessment of the MoCA test~~ at their ~~End of Treatment~~ Final visit. Section 5.1.1 was updated as follows: Further efficacy endpoint are…:

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		-…..Change in cognitive status from Visit 1 to Final Visit ~~EOT in all patients who are still on study medication at year 2 (or longer)~~ as assessed by MoCA questionnaire Section 5.1.2.7 was updated as follows: The MoCA questionnaire to assess cognitive status will be performed in all patients at Visit 1 and at the Final Visit. ~~A follow-up MoCA assessment is required for patients still on study medication at Visit 10 or later (i.e. 24 months after randomization, or later). In these patients, there needs to be one final assessment of the MoCA test at their End of Treatment (EOT) visit (i.e. at the time point of study drug discontinuation or shortly thereafter).~~ Section 5.3.2 was updated as follows: The MoCA test (R13-4024) will be used to assess cognitive status at Visit 1 and ~~in patients who are still taking study medication~~ at the Final Visit ~~10 or later (i.e. at least 24 months after randomization, or later). In these patients, there needs to be one final assessment of the MoCA test at their End of Treatment (EOT) visit (i.e. at the time point of study drug discontinuation or shortly thereafter)~~. The MoCA questionnaire will be performed in countries where a validated translation is available. Section 6.2.3.2 was updated as follows: Refer to Flow Chart for list of required assessments at the final visit. For ~~a~~ patients that are on treatment at the end of the trial, the EOT and Final Visit assessments can be done at the same visit. The MoCA test will also be performed. Section 7.3.2.1 was updated as follows: Change in MoCA scores from Visit 1 to ~~EOT~~ final visit will be analyzed using Analysis of covariance (ANCOVA) with fixed effects of treatment, Visit 1 MoCA, and country. The percentage of patients with cognitive impairment (defined by MoCA < 26) at Visit 1 and ~~EOT~~ final

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		visit will be presented as descriptive statistics. All time-to-event further efficacy analyses will be performed on the RS population for the full follow-up period. ~~MoCA analyses will be performed on the TS for the on-treatment period.~~
Rationale for change		MoCA follow-up will be performed in all patients irrespective of study drug continuation status to allow for a full analysis of MoCA (and in order to also cover e.g. patients who stopped medication due to recurrent stroke)
Section to be changed		Abbreviations
Description of change		Abbreviations for CKD-EPI and CK-MB were switched
Rationale for change		This was a correction
Section to be changed		1.1
Description of change		The novel oral anticoagulant (NOAC) dabigatran etexilate (DE) has been demonstrated to be effective against cardioembolic stroke related to AF with significantly reduced risk of intracranial hemorrhage compared to warfarin.
Rationale for change		The abbreviation DE has been clarified.
Section to be changed		1.1
Description of change		The following text was added to provide explanation for early study drug start in this study: Patients are at highest risk of recurrent stroke in the first days after index stroke as demonstrated by the CHANCE trial (R15-2975). The RE-SPECT ESUS study will assess the effectiveness and safety of DE versus ASA with study medication started early during this high risk period. Providing cerebral hemorrhage is ruled out, study drug can be started as early as one day after index stroke. For details on recommended earliest study drug start according to stroke severity, refer to Table 4.1.4: 1.
Rationale for change		There is not a standard guideline for when to start treatment after stroke. Guidance is provided for the earliest study drug start within this clinical

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		trial (see Table 4.1.4: 1). The rationale for starting study drug soon after stoke is clarified here for common understanding.
Section to be changed		2.3, 4.2.1
Description of change		REVERSAL AGENT DATA COLLECTION "Antidote" was changed to " specific reversal agent" in Section 2.3 and 4.2 Section 2.3 was revised as follows: ~~There is currently no specific treatment (specific reversal agent) available to reverse the anticoagulant effects of dabigatran should a life-threatening bleeding arise.~~ Standard management for bleeding (such as transfusion of blood products, etc.) needs to be applied as described in Section 4.2.1 and in Figure 4.2.1: 1. A specific reversal agent (idarucizumab) has been developed and is currently being reviewed for registration in various countries. When clinically indicated and available, it can be given to a patient in the context of a clinical trial (e.g. BI trial 1321.3) or from commercial supply when it becomes approved. See section 4.2.1 Overdose, for more information regarding the specific reversal agent for dabigatran. Text was added to Section 4.2.1 Emergency Procedures as follows: See section 4.2.1- Overdose, for more information regarding the specific reversal agent for dabigatran. Section 4.2.1 Major Bleeds was revised as follows: The recommendations given below are derived from guidelines to manage bleeding with DE, however, with the exception of recommendations on the specific reversal agent for dabigatran, they can be applied to all patients in this trial irrespective of assigned study medication (i.e. DE or ASA). ~~There is currently no specific antidote to~~

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		~~counteract the antithrombotic activity of dabigatran.~~ See section 4.2.1 Overdose, for more information regarding the specific reversal agent for dabigatran. Text was removed from Section 4.2.1 Overdose with DE as follows: ~~To date, there is no specific reversal agent to counteract the antithrombotic activity of dabigatran, although there is one in development (P13-05131)~~ A section was added to Section 4.2.1 as follows: Specific reversal agent to dabigatran A specific reversal agent (idarucizumab) has been developed and is currently being reviewed for registration in various countries. When clinically indicated and available, it can be given to a patient in the context of a clinical trial (e.g. BI trial 1321.3) or from commercial supply when it becomes approved. If the specific reversal agent for dabigatran is given, information surrounding the clinical circumstances, treatment and clinical outcome will be collected on the CRF of the appropriate trials.
Rationale for change		To clarify terminology and allow collection of information regarding use of the reversal agent.
Section to be changed		3.3
Description of change		RESCREENING The following text was added to Section 3.3 at the bottom: If a patient is deemed ineligible for a reason which later resolves and all eligibility criteria can be met (e.g. time since an exclusionary event), patients can be rescreened up to one time provided it is still within 3 months since index stroke (within 6 months for select patients). Patients cannot be re-screened if any of the following exclusions were met: # 4, 7e, 8, 9, 19, 20, or 21; during the initial screening.
Rationale for change		To explicitly clarify that rescreening of patients is permitted, if they become eligible within the

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		allowed time window since index stroke (up to 3 months before randomization, or up to 6 months before randomization in patients that are ≥60 years plus at least one additional risk factor for recurrent stroke- see stroke risk factors a-f as outlined in Inclusion 1).
Section to be changed		3.3
Description of change		# of countries increased from approximately 35 to 40 Section 3.3 was updated as follows: An estimated 6,000 patients will be randomized at approximately 550 sites in approximately ~~35~~ 40 countries.
Rationale for change		There is a potential to conduct the study in additional countries.
Section to be changed		Table 3.3.1: 1, Section 3.3.2 Inclusion 4, 3.3.4.1, 4.2.2.1, 6.2.1
Description of change		MINIMUM AMOUNT OF CARDIAC MONITORING REQUIRED FOR ENTRY A minimum of 20 hours (instead of 24 hours) of cardiac monitoring is required to rule out atrial fibrillation prior to study entry. Additionally, it is clarified that cardiac monitoring with interruption is acceptable within the boundaries described in the protocol. Table 3.3.1: 1 Step 4 was updated as follows: 4. Cardiac monitoring for ≥20 ~~24~~ hours with automated rhythm detection Table 3.3.1: 1 footnote 2 has new text: Eligible patients can be enrolled with a minimum of 20 hours of cardiac monitoring completed and results demonstrate < 6 min AF. Cardiac monitoring with interruption is acceptable, if the total recording time of at least 20 hours is completed within the same hospital stay or within consecutive 10 days. Section 3.3.2 Inclusion 4 was updated as follows: As evidenced by cardiac monitoring for ≥ 20 ~~24~~

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		hours with automated rhythm detection, there is absence of AF > 6 minutes in duration (within a 20 ~~24~~ hour period, either as single episode or cumulative time of multiple episodes). Section 3.3.4.1 was updated as follows: (An individual patient is to be discontinued from study drug if the following occurs…): Atrial fibrillation (with duration exceeding 6 minutes, either as single episode or cumulative time of several episodes recorded within 20 ~~24~~ hours, or as per Investigator discretion), or atrial flutter Section 4.2.2.1 was updated as follows: If AF is identified during follow-up and the duration of AF exceeds 6 minutes (either as single episode or cumulative time of several episodes within 20 ~~24~~ hours), trial treatment must be discontinued (but the treatment assignment blind should not be broken), and the patient should be switched to standard of care treatment for stroke prevention in atrial fibrillation (SPAF) (e.g. DE or other) according to local label recommendations. Section 6.2.1 was updated as follows: The investigations outlined in Table 3.3.1: 1 are to be completed and documented per standard of care as a prerequisite to consideration for study participation. (Note: a minimum of 20 hours cardiac monitoring is required for enrollment).
Rationale for change		During the early part of trial conduct, it was realized that in clinical practice what is referred to as a "24 hour" holter monitor does not necessarily mean that the holter device would be connected to the patient for a full 24 hour time period. 20 hours more reasonably reflects routine clinical practice and it is considered the minimum required monitoring time needed to rule out AF.
Section to be changed		3.3.2 Inclusion criterion 1
Description of change		MINIMUM AGE FOR ENTRY 3.3.2 Inclusion criterion 1 was updated to allow enrollment of patients as young as 18 years old

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		(instead of 50). The change is as follows: Age 18 ~~50~~ -59 years
Rationale for change		To allow enrollment of younger patients that have ESUS. Assuming 10% of patients enrolled under the age of 50 would have reduced recurrent stroke rate of 2.1% (compared to 4.1% for all other patients), power calculations estimate that the length of the trial may have to be increased by 6 weeks to observe the 353 recurrent strokes, if all estimates are correct. Because of the potential impreciseness of these estimates and the fact that the actual number of recurrent strokes will be actively monitored, it is not necessary to change the estimated length of the trial at this time.
Section to be changed		Section 3.3.2 Inclusion criterion 2
Description of change		REFORMATING OF INCLUSION 2 Section 3.3.2 Inclusion criterion 2 was revised as follows: 2) 2a) ~~Acute~~ Ischemic stroke with ~~an anatomically appropriate~~ a brain lesion visualized by neuroimaging (either brain CT[1] or MRI). The visualized stroke is a non-lacunar infarct , ~~i.e.~~ e.g. involving the cortex or >1.5 cm (>2.0 cm if measured on MRI diffusion-weighted images) in largest diameter if exclusively subcortical. Visualization by CT usually requires delayed imaging >24-48 hours after stroke onset. See Exclusion 21 for definition of lacunar stroke. 2b) The index stroke ~~It~~ must have occurred either: a. up to 3 months before randomization (mRS ≤3 at randomization) OR b. up to 6 months before randomization (mRS ≤3 at randomization) in selected patients that are ≥ 60 years plus at least one additional risk factor for recurrent stroke (see stroke risk factors

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		a - f as outlined in Inclusion 1).
Rationale for change		Dividing Inclusion criterion 2 into 2a and 2b clarifies there are two prerequisites that must be met. 2a (to describe eligible infarct size, location) and 2b (to define time since ESUS). Reference to inclusion criteria 2b was also updated in 6.2.2. Inclusion criterion 2 is amended to clarify that non-lacunar strokes in certain other locations of the brain (e.g. brain stem) do not need to meet size requirements outlined for exclusively subcortical infarcts. A reference to new Exclusion 21 (definition of lacunar stroke) is also provided.
Section to be changed		3.3.2 Inclusion criterion 3
Description of change		The following text was added to footnote 3: Cases with acute full artery occlusion deemed by Investigator to be of embolic origin are allowed.
Rationale for change		To allow for inclusion of certain patients with full occlusion due to an embolus of unknown origin (e.g. in cases where imaging done prior to ESUS index stroke demonstrated absence of relevant large vessel disease and no occlusion or the occlusion appears embolic in nature). This change is in line with the embolic source concept of the study.
Section to be changed		3.3.2 Exclusion criterion 6, Table 4.1.4: 1, 5.2.2.1
Description of change		MICROBLEED DEFINED Exclusion criterion 6 footnote 2 was updated as follows: A hemorrhagic transformation of a primarily ischemic stroke may be included as per Investigator`s judgment. Sporadic microbleeds may be included as per Investigator`s judgment. As a general recommendation, a cerebral microbleed is considered to ~~be < 0.5 cm~~ ≤ 5mm, but sometimes up to 10mm, in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences. ~~MRI (criteria may vary depending on MRI imaging modalities).~~ Any blood visualized

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		on a CT will be classified as a macrobleed. A macrobleed is an exclusion criterion for the trial. Table 4.1.4: 1 Foot note 1 was updated as follows: … Sporadic microbleeds may be included as per Investigator`s judgment. As a general recommendation, a cerebral microbleed is considered to be in general ≤ 5mm, but sometimes up to 10 mm, in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences. Microbleeds are incidental findings that do not constitute an exclusion criterion. ~~< 0.5 cm in greatest diameter on gradient recalled echo (GRE) MRI (criteria may vary depending on MRI imaging modalities).~~ In patients with hemorrhagic transformation or microbleeds, the Investigator may choose to delay the start of study medication. Any blood visualized on a CT will be classified as a macrobleed. In patients with macrobleeds, study medication should not be started. Section 5.2.2.1 was updated as follows: Intracranial hemorrhage comprises the subtypes of intracerebral bleeds, subdural bleeds, epidural bleeds and subarachnoid bleed and will be recorded in eCRF. Microbleeds (for definition see below) do not qualify as ICH, except when they are symptomatic. • Definition of a microbleed: A cerebral microbleed is in general ≤ 5mm, but sometimes up to 10 mm, in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences (R15-2999). Any blood visualized on a CT will be classified as a macrobleed. Asymptomatic microbleeds are incidental findings that do not constitute an exclusion criterion. Irrespective of size, any cerebral bleed that causes focal neurologic symptoms and/or signs does not constitute a microbleed, but will be reported as a stroke endpoint (hemorrhagic stroke) and bleeding event (intracerebral

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		hemorrhage).
Rationale for change		Definition added for cerebral microbleeds for common implementation as it relates to eligibility and reporting of outcome events, specifically intracranial hemorrhage. Clarification added that asymptomatic microbleeds do not qualify as intracranial hemorrhage.
Section to be changed		3.3.3 Exclusion criterion 7e
Description of change		3.3.3 Exclusion criterion 7e was revised as follows: platelet count < ~~100,000/ml~~ <100 x10^3/µl at screening
Rationale for change		Correction of units
Section to be changed		3.3.3 Exclusion criterion 7h
Description of change		Exclusion criterion 7h was added as follows: 7h) Any history of intracranial aneurysm (unless it was permanently resolved with either clipping or coiling at least one year prior to the study entry).
Rationale for change		This exclusion criterion was added to exclude patients at high risk for future intracranial hemorrhage.
Section to be changed		3.3.3 Exclusion criterion 8
Description of change		Clarification to state that patients with history of symptomatic non-traumatic intracranial hemorrhage could be eligible if the Investigator deems patient is not at risk for recurrent ICH. Exclusion criterion 8 was revised as follows: 8. History of symptomatic nontraumatic intracranial hemorrhage with risk of recurrence according to Investigator judgment.
Rationale for change		If according to the Investigator`s judgment the risk for recurrent ICH is not increased despite a history of symptomatic non-traumatic intracranial hemorrhage, there is no safety reason to exclude the patient.
Section to be changed		3.3.3 Exclusion 15
Description of change		Exclusion 15 was revised as follows:

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		Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) (R15-5904) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. ~~Acceptable methods of birth control include a) complete sexual abstinence, b) intra uterine devices/systems (IUDs/IUSs), c) oral or parenteral (patch, injection, implant) hormonal contraception, which has been used continuously for at least one month prior to the first dose of study medication, d) condom and occlusive cap (diaphragm or cervical caps) or condom with spermicidal agent (also referred to as double barrier methods), or e) male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. If this method is chosen, WOBCP must attest that they are in a monogamous relationship).~~
Rationale for change		To align the protocol with the ICH M3 (R2) guideline (R15-5904) regarding highly effective methods of birth control and with the company's latest guidance on contraception in Clinical Trials.
Section to be changed		3.3.3 Exclusion criterion 16
Description of change		Clarification to make clear how past involvement in a clinical trial can impact eligibility. Exclusion criterion 16 was updated as follows: Patients who participated in another trial within 14 days prior to screening. Patients with residual effect from another investigational product remaining at time of screening. ~~Patients who have participated in another trial with an investigational drug or device within the past 14 days preceding the screening visit or are participating in another trial assuming no clinical effect from the investigational drug or device used in the previous study remains~~. Patients participating in a purely observational study will not be excluded.

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Rationale for change		Clarification was necessary to guide Investigators on the eligibility of patients previously or currently involved in other studies (including observational studies) for better understanding
Section to be changed		3.3.3 Exclusion criterion 17
Description of change		New text was added as follows: Patients considered unreliable by the Investigator concerning the requirements for follow-up during the study or at the end of the study (e.g. not able to comply with regular medication intake)
Rationale for change		Clarified that if a patient was not able to comply with regular medication intake, they would not be eligible to avoid enrolling patients where noncompliance with study drug intake could be foreseen by the Investigator. Regular study medication intake is considered a prerequisite for overall compliance, trial follow-up and completion.
Section to be changed		3.3.3 Exclusion criterion 18, 3.3.4.1
Description of change		Exclusion criterion 18 was updated as follows: Any condition the Investigator believes would not allow safe participation in the study, e.g. other neurological condition that would complicate assessment of outcomes (e.g. severe dementia, high propensity for falls where Investigator deems a patient's potential risk for bleeding exceeds the potential benefits of study drug). 3.3.4.1 was updated as follows: At the discretion of the Investigator/patient, an individual patient may be discontinued from study drug if….in the opinion of the Investigator, continuation on the study drug is not in the patient's best interest, if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at trial assessments, and reason to be recorded in the electronic Case Report Form (eCRF)) or if the patient develops a high propensity for falls where Investigator deems a patient's potential risk for bleeding exceeds the potential benefits of study drug.

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Rationale for change		To clarify that the Investigator should consider the potential risks associated with falls prior to inclusion of the patient. A patient could be excluded if they had a high propensity for falls where Investigator deems a patient's potential risk for bleeding exceeds the potential benefits of study drug. If this risk develops during the trial for a patient on study drug, the Investigator can stop study drug if they deem it appropriate.
Section to be changed		3.3.3 Exclusion criterion 21, Table 1.1: 1
Description of change		LACUNAR STROKE DEFINED Exclusion criterion 21 was added as follows: Lacunar stroke. Lacunar infarcts of restricted size in the deep parts of the brain in the territories of small penetrating arteries. They are absent from the cerebral and cerebellar cortex. On brain CT and MR images they are <1.5 cm in largest diameter or <2.0 cm if measured on MRI diffusion sequences. In several pathological studies, sites of predilection included the lenticular nucleus, thalamus, central white matter, internal capsule, centrum ovale, corpus callosum, basis pontis, and, rarely, the cerebellum, midbrain and medulla. Infarcts <1.5 cm in largest diameter, or <2.0 cm if measured on MRI diffusion sequences, in the dorsal or lateral areas of the brainstem, in the territory of circumferential, rather than deep penetrating, arteries are not lacunar infarcts. (note: history of lacunar stroke is not exclusionary). Table 1.1: 1 footnote 2 was revised as follows: Lacunar ~~defined as subcortical infarct ≤ 1.5 cm (≤ 2.0 cm on MRI diffusion-weighted images) in largest dimension, and in the distribution of the small, penetrating cerebral arteries; visualization by CT usually requires delayed imaging > 24-48 hours after stroke onset.~~ is defined in Section 3.3.3 exclusion criterion 21
Rationale for change		To clearly provide a definition of lacunar stroke. Index strokes must meet ESUS criteria (part of

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		which requires the stroke be non-lacunar). However, this also clarifies that a history of a lacunar stroke (other than ESUS stroke) is not exclusionary.
Section to be changed		3.3.4.1
Description of change		A statement was added: Guidelines for transitioning to non-study antithrombotic medications are provided in Section 10.2.2.
Rationale for change		To clarify that additional information can be referenced in case study drug needs to be stopped for patients who have reduced renal function
Section to be changed		4.1.1
Description of change		"Concomitant use of ASA is at the discretion of the Investigator" was removed.
Rationale for change		Correction to original protocol: Concomitant use of ASA is not allowed while taking study drug except for patients with CAD and where blinded ASA is dispensed by IRT.
Section to be changed		4.1.4
Description of change		Text was changed as follows: Breaking or chewing of the tablets or capsules, or emptying the contents of the capsules is not ~~recommended~~ permitted.
Rationale for change		This correction was to clarify that breaking or study medication is not permitted.
Section to be changed		Table 4.1.4: 1 revised, 4.2.1, Table 4.2.1: 2 was removed, 6.2.1, 6.2.2
Description of change		STARTING/RESTARTING STUDY DRUG AFTER STROKE - reformatted Table 4.1.4: 1 was entitled Recommendations on starting study medication after index event of stroke (mRS $\leq$ 3 at time of randomization) Table 4.2.1: 2 was entitled Recommendations on re-starting study medication following a stroke

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		during the trial Tables 4.1.4: 1 and 4.2.1: 2 have been combined into Table 4.1.4: 1 which is now named: Recommendations on starting study medication after index event of stroke (mRS ≤ 3 at time of randomization) and for reintroduction of study treatment after recurrent stroke (mRS ≤ 3 at time of study medication restart) Table 4.1.4: 1 first column is now updated to Header of left column updated as follows: Stroke Severity (at time of ~~stroke~~ randomization / at time of study medication restart after recurrent stroke) Row for Modified Rankin Scale = 3 updated with this additional text: Please take note: This category includes patients with an initial Modified Rankin Scale of 4 at time of stroke, who have improved to a Modified Rankin Scale of 3. Patients with Modified Rankin Scale of 4 at time of randomization are excluded. Patients with Modified Rankin Scale of 4 cannot restart study medication unless their Modified Rankin Scale improves to 3. Header of right column updated as follows: Earliest start of Study Medication after ~~Index Event~~ Stroke Row for MRS 1 or 2 was updated as follows: 3-5 days after most recent stroke onset Row for MRS 3 was updated as follows: 5-7 days after most recent stroke onset Table 4.1.4: 1 Footnote 1 was also updated as follows: If starting study medication within 10 days of

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		~~index~~ most recent stroke in patients with mRS of 1,2, or 3, re-imaging of the brain is required to rule out bleeding into the brain.... Section 4.2.1 text was revised as follows: Reintroduction of study treatment following a stroke (i.e. after recurrent stroke) The decision about when to restart study medication following a recurrent stroke is at the discretion of the Investigator (with the exception of strokes with mRS of 4 or higher, where restart is not allowed, unless the patient improves to a mRS of 3). Table 4.1.4: 1~~4.2.1:2~~ shows recommendations (P12-02400) on the earliest possible time point to ~~restart~~ start study medication. These recommendations in Table 4.1.4:1 also apply to restarting study medication after recurrent stroke. Cerebral hemorrhage must be excluded before study drug is restarted. If restarting study medication within 10 days of stroke in patients with mRS of 1, 2 or 3, re-imaging is required to rule out bleeding into the brain (for details see footnote of Table 4.1.4:1 ~~4.2.1:2~~). Table 4.2.1:2 was removed from this section as noted above. Section 6.2.1 text was revised as follows: Patients with mRS of 1,2 or 3 at time of randomization who are scheduled for initiation of study medication within 10 days of index event require repeat imaging of the brain to rule out bleeding into the brain (per Exclusion #6). This repeat imaging must occur prior to randomization. Section 6.2.2 was revised as follows (some text was moved into a footnote): Restricted medications as outlined in Section 4.2.2 will be stopped. Study medication will be dispensed and should be initiated as outlined in Section 4.1.4 and Table 4.1.4:1[1]. ~~As a reminder, if a patient has mRS of 1,2 or 3 and study medication is to be started within 10 days of~~

Number of global amendment		1
		~~index event, repeat imaging is mandatory to rule out bleeding into the brain. Randomization should only occur after reimaging of the brain has been performed and eligibility has been confirmed.~~ AEs, SAEs and OEs (after randomization) will be collected as described in Section 5.1 and Section 5.2. Footnote 1 was added: <u>As a reminder, if a patient has mRS of 1,2 or 3 at time of randomization and study medication is to be started within 10 days of index event, repeat imaging is mandatory to rule out bleeding into the brain. Randomization should only occur after reimaging of the brain has been performed and eligibility has been confirmed. Refer to Table 4.1.4:1 for details.</u>
Rationale for change		The two tables were combined into one table within Section 4.2.1 as recommendations on medication start after index stroke versus recurrent stroke are essentially the same. Clarification was added for patients with a mRS of 4.
Section to be changed		4.1.5.2
Description of change		Text was revised as follows: An emergency code will be available ~~to the Investigator/pharmacist/investigational drug storage manager~~ via the IRT.
Rationale for change		The unblinding module will be available to the appropriate user type within IRT.
Section to be changed		4.2.1
Description of change		The following text was added regarding Management of an elective procedure in the perioperative phase: <u>Where the Investigator becomes aware of a planned procedure/surgery, it is recommended that the study investigator contact the treating surgeon. Refer to Appendix 10.2 on transitioning to non-study medication in case bridging therapy is chosen.</u>
Rationale for change		To provide further guidance to the Investigator to facilitate a planned intervention of the patient.

Number of global amendment		1
Section to be changed		4.2.1, 10.2.2, 10.2.3
Description of change		The following text in Section 4.2.1 was revised regarding Management of an elective procedure in the perioperative phase: During a temporary interruption, thrombosis prophylaxis therapy with commercial antiplatelet(s) or a parenteral anticoagulant e.g. Low-molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) (according to local practice) is at the discretion of the Investigator depending on duration of interruption, type of intervention and individual thromboembolic risk of the patient. Section 10.2.2 Title was revised as follows: Thrombosis prophylaxis or temporary requirement for parenteral anticoagulant or antiplatelet(s) Section 10.2.2 was revised as follows: Immobilization or intervention may require temporary thrombosis prophylaxis with e.g. UFH or LMWH or antiplatelet(s). Certain interventions may require the use of parenteral anticoagulants. The following rules should apply, if thrombosis prophylaxis/parenteral anticoagulants are considered temporarily necessary by the Investigator: • Temporarily stop study medication. It is recommended to wait 12 hours after the last dose of study medication before switching to a parenteral anticoagulant (e.g. UFH, LMWH). Antiplatelet(s) can be started at any time after last dose of study drug Section 10.2.3 was revised as follows: • If the non-study treatment will be ~~an~~ antiplatelet agent(s), this medication can be initiated at any time-point after last intake of study medication.
Rationale for change		To clarify that non-study antiplatelet(s) can be

Number of global amendment		1
		used while not taking study drug
Section to be changed		4.2.1
Description of change		The section describing management of stroke was changed as follows: Patients with documented or suspected stroke should be managed according to usual clinical practice, which may include the use of fibrinolytic agents and mechanical clot removal.
Rationale for change		Mechanical clot removal was added as a patient management strategy for patients with stroke. It is increasingly used in stroke patients
Section to be changed		4.2.2.1
Description of change		Text was added as follows: In patients ≥75 years, or with previous gastritis, history of peptic ulcer disease or previous gastrointestinal bleeding, the Investigator should consider prescribing a proton-pump-inhibitor (PPI) based on the local prescribing information while receiving NSAIDs/ASA.
Rationale for change		Concomitant use of PPIs should be considered in select patients at highest risk of GI bleeding to potentially protect them from future GI bleeds. The decision to use PPIs remains at the discretion of the Investigator.
Section to be changed		5.2.2.2
Description of change		Section 5.2.2.2 was updated as follows: In addition, for the safety parameters of primary interest, namely any major bleeding event (see Section 5.2.2.1) and for the major mortality/morbidity clinical endpoints of interest (see Section 5.1.2), a blinded IAC will be in place with the responsibility to confirm and classify events as listed in Section 3.1.1.4.
Rationale for change		Clarify verbiage to make clear that major bleeds are adjudicated (but not minor bleeds).
Section to be changed		5.5.2
Description of change		The following text was added to Section 5.5.2:

Number of global amendment		1
		The PK samples will be discarded not later than 3 years following availability of the final CTR (or as dictated by local requirements).
Rationale for change		Clarify storage of PK samples
Section to be changed		5.6.2.1
Description of change		Section 5.6.2.1 was updated as follows: Blood samples of about 5 mL will be collected in ~~glass~~ tubes for biomarker analyses.
Rationale for change		This is a correction to the original protocol.
Section to be changed		5.8, 7.3.5
Description of change		CHANGES TO PK ANALYSIS Text from Section 5.8 has been revised as follows: Not applicable. ~~The relationship between dabigatran trough plasma concentrations with safety (bleeding) and efficacy events (stroke/ischemic stroke) may be explored in case the number of events will suffice for a scientifically sound analysis. Details will be outlined in the Trial Statistical Analysis Plan (TSAP).~~ Section 7.3.5 was revised as follows: …Trough plasma concentrations of total dabigatran will also be displayed for certain demographic subgroups (e.g. sex, age, race, body weight, Body Mass Index (BMI), creatinine clearance) ~~categorized by the occurrence of pre-specified events (primary endpoint: first recurrent stroke, secondary endpoint: first MBE), and displayed by use of relevant medication (e.g. P-glycoprotein inhibitors) at the time of sampling. Details on further subgroup analyses will be specified in the TSAP~~…. …Non-compartmental PK analyses will not be performed. ~~Trough concentrations may be subject to PopPK analysis using the final model derived on data from AF patients in RE-LY (U10-2017-~~

Number of global amendment		1
		~~01) to evaluate the applicability of the RE-LY model to this patient population. Results of this analysis will be reported separately.~~
Rationale for change		Analysis of the PK-PD relationship special PK analyses and of a population PK analysis has been removed. This will streamline the data analysis processes.
Section to be changed		6.2.1, 8.3.1
Description of change		INDEX SOURCE DOCUMENT COLLECTION Section 6.2.1 was updated as follows: Detailed results of the required diagnostic imaging for the index stroke (~~see~~ from diagnostic evaluations specified in Table 3.3.1:1) must be provided to the Sponsor or Sponsor`s designee ~~including the required reports of brain imaging, echocardiography, cardiac rhythm monitoring, a 12-lead ECG and vascular imaging~~. All of the required diagnostic examinations related to the index stroke~~, including extended cardiac monitoring (if deemed warranted by the investigator)~~ must be completed prior to randomization. Section 8.3.1 was updated as follows: ~~All other~~ Examination reports supporting the diagnosis of index ESUS, i.e. reports of the required examinations, including echocardiography, cardiac rhythm monitoring and vascular imaging such as imaging of the extracranial and intracranial arteries supplying the area of brain ischemia (either catheter angiography, MRI angiography, computed tomographic angiography, or cervical plus TCD ultrasonography) must be provided to the Sponsor`s designee. Copies of 12 lead ECG reports done as part of the clinical routine at the time of index stroke need not be submitted.
Rationale for change		Protocol language surrounding collection of documentation for central index source document review has been modified to reduce specificity.

Number of global amendment		1
		For example, at this time, copies of 12-lead ECGs are not required to be collected, as a baseline ECG is part of the Visit 1 procedures.
Section to be changed		9.1
Description of change		The following references were added in Section 9 and referenced where appropriate within protocol: R15-0010 (added to section 5.1.2.1, 5.1.2.4, 5.1.2.5) R15-2975 (added to section 1.1) R15-2999 (added to section 5.2.2.1) R15-5904 (added to Section 3.3.3)
Rationale for change		To update protocol to reflect latest literature
Section to be changed		Appendix 10.5
Description of change		National Institute of Health Stroke Score changed to National Institute of Health Stroke Scale
Rationale for change		Correction of terminology

GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		**21 Apr 2016**
EudraCT number		2013-003444-24
BI Trial number		1160.189
BI Investigational Product(s)		Dabigatran etexilate
Title of protocol		**R**andomized, double-blind, **E**valuation in secondary **S**troke **P**revention comparing the **E**ffica**C**y and safety of the oral **T**hrombin inhibitor dabigatran etexilate (110 mg or 150 mg, oral b.i.d.) versus acetylsalicylic acid (100 mg oral q.d.) in patients with **E**mbolic **S**troke of **U**ndetermined **S**ource (RESPECT ESUS)
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		Title Page
Description of change		Change of Trial Clinical Monitor name and contact details
Rationale for change		To reflect change of Trial Clinical Monitor and to provide current contact details.

Number of global amendment		2
Section to be changed		FLOW CHART
Description of change		Deletion of visit 2 procedure “submission of documentation for central evaluation of ESUS”.
Rationale for change		To simplify and optimize logistics of the trial and reduce operational complexity, central source data reassessment processes is cancelled. This change is related to data collection only and does neither affect patients` safety nor the integrity of the overall study. Removal of this data collection portal will optimize the feasibility of the trial.
Section to be changed		6.2.1. Screening and run-in periods
Description of change		Detailed results of the required diagnostic imaging for the index stroke (from diagnostic evaluations specified in Table 3.3.1: 1) must be provided to the Sponsor or Sponsor`s designee. Changed to: Detailed results of the required diagnostic imaging for the index stroke (from diagnostic evaluations specified in Table 3.3.1: 1) must be available in the source notes for all patients and in the case of recurrent stroke or death must also be provided to the Sponsor or Sponsor`s designee as part of the adjudication package.
Rationale for change		To simplify and optimize logistics of the trial and reduce operational complexity, central source data reassessment processes is cancelled. This change is related to data collection only and does neither affect patients` safety nor the integrity of the overall study. Removal of this data collection portal will optimize the feasibility of the trial.
Section to be changed		7.3.1. Primary analyses
Description of change		Sensitivity analyze that includes only patients whose ESUS diagnosis was confirmed by central source data reassessment performed by Sponsor`s designee is removed.
Rationale for change		Not applicable due to cancellation of central source data reassessment.

Number of global amendment		2
Section to be changed		8.3.1. Source documents
Description of change		Following text deleted: • Examination reports supporting the diagnosis of index ESUS, i.e. reports of the required examinations, including echocardiography, cardiac rhythm monitoring and vascular imaging such as imaging of the extracranial and intracranial arteries supplying the area of brain ischemia (either catheter angiography, MRI angiography, computed tomographic angiography, or cervical plus TCD ultrasonography) must be provided to the Sponsor`s designee. Copies of 12 lead ECG reports done as part of the clinical routine at the time of index stroke need not be submitted. Following text added instead: • In the case of recurrent stroke or death detailed results of the required diagnostic imaging for the index stroke must also be provided as part of the adjudication package.
Rationale for change		To simplify and optimize logistics of the trial and reduce operational complexity central source data reassessment processes is cancelled. This change is related to data collection only and does neither affect patients` safety nor the integrity of the overall study. Removal of this data collection portal will optimize the feasibility of the trial.

APPROVAL / SIGNATURE PAGE

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Title: Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate (110 mg or 150 mg, oral b.i.d.) versus acetylsalicylic acid (100 mg oral q.d.) in patients with Embolic Stroke of Undetermined Source (RESPECT ESUS)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		21 Apr 2016 14:06 CEST
Author-Trial Clinical Pharmacokineticist		21 Apr 2016 14:10 CEST
Approval-Therapeutic Area		21 Apr 2016 14:20 CEST
Approval-Team Member Medicine		21 Apr 2016 15:36 CEST
Author-Trial Statistician		26 Apr 2016 16:34 CEST
Verification-Paper Signature Completion		26 Apr 2016 16:53 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed