Clinical Trial Protocol

Doc. No.:
c02214385-09

EudraCT No.:	2013-003201-26
BI Trial No.:	1160.186
BI Investigational Product(s):	Pradaxa®, dabigatran etexilate
Title:	A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting **(RE-DUAL PCI)**
Clinical Phase:	IIIb
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax:
Co-ordinating Investigator:	[redacted] Phone: [redacted] Fax:
Status:	Final Protocol (Revised Protocol (based on global Amendments 1, 2 and 3))
Version and Date:	**Version: 4.0** **Date: 21 July 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: 26 March 2014	**Trial number:** 1160.186		**Revision date:** 21 July 2016
Title of trial:	A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting. **(RE-DUAL PCI)**		
Co-ordinating Investigator:	[redacted]		
Trial sites:	Multi-centre trial		
Clinical phase:	IIIb		
Objectives:	The main objective is to compare a dual antithrombotic regimen of 110mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (110mg DE-DAT) and 150mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (150mg DE-DAT) with a triple antithrombotic therapy (TAT) of warfarin plus clopidogrel or ticagrelor plus aspirin (warfarin-TAT) in patients with non valvular atrial fibrillation (NVAF) that undergo a PCI with stenting. The study aims to show non-inferiority of each dose of DE-DAT when compared to Warfarin-TAT in terms of safety. Safety is determined by bleeding events, assessed using the modified International Society of Thrombosis and Haemostasis (ISTH) classification of Major Bleeding and Clinically Relevant Non-Major Bleeding Events (CRNMBE).		
Methodology:	This is a prospective, randomised, open label, blinded endpoint (PROBE), active comparator (warfarin) trial. The study will employ a time to event analysis and all patients will remain on study treatment until the last patient entered has completed at least six months of treatment. The patients will be stratified by age (<80 or ≥80 years old) and region (EU/ROW or USA).		
No. of patients: **total entered:**	2502*		

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each treatment:	834* * These are approximations. As this is an event driven trial the actual number of patients entered may increase or decrease based on actual event rates. Sites will be notified when recruitment ends.
Diagnosis :	Patients with NVAF that undergo a successful PCI with stenting (elective or due to an acute coronary syndrome (ACS)).
Main criteria for inclusion:	1. Male or female patients aged ≥18 years 2. Patients with NVAF that have been receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) or treatment naïve prior to PCI 3. Patient with NVAF presenting with: • ACS that was successfully treated by PCI and stenting (either BMS or DES) or • Stable Coronary Artery Disease with at least one lesion eligible for PCI that was successfully treated by elective PCI and stenting (either BMS or DES)
Test products:	Dabigatran etexilate
dose:	110mg and 150mg (b.i.d.)
mode of admin.:	Oral
Comparator products:	Warfarin
dose:	1mg, 3mg and 5mg
mode of admin.:	Oral
Duration of treatment:	The minimum duration of study treatment is six months

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Criteria for efficacy:	The primary endpoint for this trial is a safety endpoint, please see below.
	The secondary efficacy endpoints (all time to first event) are:
	• A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG
	• A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)
	• Individual outcome events:
	  • All death (Cardiovascular death, Non-cardiovascular death, Undetermined),
	  • MI
	  • Stroke
	  • SE
	  • Stent Thrombosis
	• Composite endpoint of death + MI + stroke
	• Unplanned revascularisation by PCI/CABG

Criteria for safety:	The primary endpoint for this trial is time to first ISTH Major or Clinically Relevant Non-Major Bleeding Event.
Statistical methods:	The stratified Cox proportional hazards regression model will be used to analyse time-to-event endpoints. To control the Type I error rate at a one-sided 0.025 level, a hierarchical procedure for multiple testing will be used to test the safety hypotheses. Additional testing for safety and efficacy endpoints will also be included in this hierarchical procedure.

FLOW CHART

Trial Periods	***Screening[1]***	***Randomisation[1]***	***Treatment***								***EOT[2]***	***Follow up[3]***	***Final Visit[4]***
Visit	**1**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8[5]**	**9, 11**	**10, 12[5]**	**970[6]**	**980**	**990**
Days since Randomisation	**-5 to 0**	**0**											
Months since Randomisation			**1**	**3**	**6**	**9**	**12**	**15**	**18, 24**	**21, 27**	**6-30**	**EOT + 4 weeks (+7 days)**	
Time window (days)		**0**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**			
Informed Consent[7]	X												
Check Eligibility	X	X											
Demographics	X												
Medical History	X												
Physical Examination	X[8]										X		
Vital Signs (PR/BP)	X	X[9]	X	X	X		X		X		X		
Weight	X				X		X		X		X		
ECG[10]	X				X		X		X		X		
Haematology Laboratory Evaluations[11]	X[12]	X	X	X	X	X	X		X		X		
Chemistry Laboratory Evaluations[11]	X[12]	X	X		X		X				X		
Creatinine Clearance[13]	X[12]	X	X	X	X	X	X		X		X		
Pregnancy Test[14]	X		X	X	X	X	X		X		X	X	

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Time window (days)		**0**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**			
Troponin[11]		X		X									
INR/Warfarin dose adjustment[15]		X	every 2 weeks – monthly [16]										
Randomisation via IRT		X											
Dispense Trial Medication		X		X	X	X	X		X				
First Admin of Trial Medication		X[17]											
Drug Accountability			X[18]	X	X	X	X		X		X		
Bleeding Assessment		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Reporting of Outcome Events			In an expedited fashion – reporting timelines the same as for SAEs										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Termination of Trial Medication											X[19]		
End of Patient Participation												X[20]	X[20]

[1] Screening and randomisation will occur after successful PCI.

[2] End of treatment (EOT) procedures to be completed by all patients at the time of study drug discontinuation. For patients who discontinue early, the EOT visit should be performed instead of the scheduled trial visit at time of discontinuation.

[3] For patients that complete all scheduled visits or discontinue treatment early, follow up visit to be conducted four weeks after EOT.

[4] For patients that discontinue treatment early, the final visit will take place at the time trial conclusion is declared.

[5] To be conducted by telephone.

[6] This event driven trial is expected to take place over 30 months, however, the trial can conclude earlier if an adequate number of events is reported sooner. It can conclude later (or enrol additional patients) if more time is needed to observe the minimum number of required events. If it continues beyond 30 months, follow-up visits (with same assessments as required at visits 9 and 11) will occur every 6 months with telephone visits (with the same assessments as required at visits 10 and 12) in between. At the time of trial conclusion (when adequate number of events were reported), all patients would be notified of study conclusion and have an EOT and follow up visit (patients that complete all scheduled visits) or final visit (premature treatment discontinuation) scheduled. Patients who discontinue study treatment early should continue to attend regularly scheduled visits. Refer to (Section 6.2.2) for details on management of patients that wish to reduce study participation for any reason. Collection of vital status and endpoints for all patients at the end of the trial is important and described in Section 6.2.3.

[7] All patients must sign an informed consent form consistent with ICH-GCP guidelines prior to any trial-related procedures including screening tests.

[8] Includes height at Visit 1.

[9] If Visit 1 and Visit 2 occur within 24 hours then vital signs do not need to be repeated at Visit 2.

[10] ECGs must be performed at baseline and every six months until EOT. If additional ECGs are performed during the course of the trial as part of patient normal care and demonstrate a change from baseline or a new pathology develops this should be documented in the eCRF.

[11] Standard safety lab panel (haematology and chemistry, including renal function and liver function tests (LFTs)) and troponin will be performed by the central laboratory at the visits indicated, except the screening visit.

[12] Will be performed locally, only those parameters required to verify eligibility are required at screening, standard of care local results taken within 7 days prior to screening can be used to verify eligibility.

[13] Renal function: creatinine clearance (CrCl) will be calculated based on serum creatinine using the Cockcroft-Gault equation.

[14] Urine pregnancy test required for all women of child bearing potential. In addition women of child bearing potential will be supplied with pregnancy tests and instructed to perform pregnancy testing every 4 weeks. 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.

[15] All patients will have a baseline INR. Follow-up INRs will be performed only in those patients randomised to warfarin. All INR measurements conducted locally.

[16] At least two-weekly INR measurements for the first three months in patients who are commencing warfarin for the first time and monthly subsequently– all other patients at least monthly. More frequently if required.

[17] Study drug should be administered between 6 hours after sheath removal and preferably within 72 hours post PCI (refer to section 6.2.2), with haemostasis assured, however up to 120 hours post PCI is allowed.

[18] Patients randomised to Warfarin only.

[19] Patients switching to a non-study VKA from dabigatran etexilate may continue on study medication (dabigatran etexilate) after this visit for 2-3 days to assist bridging.

[20] Patients that complete all scheduled visits will conclude participation at the follow up visit, patients who discontinue treatment early will conclude participation at the final visit.

TABLE OF CONTENTS

ABBREVIATIONS

ACS	Acute Coronary Syndrome
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASA	Aspirin
AST	Aspartate transaminase
AUC	Area under the Curve
BARC	Bleeding Academic Research Consortium
b.i.d.	Twice a day
BI	Boehringer Ingelheim
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form
CRNMBE	Clinically Relevant Non Major Bleeding Event
CT	Computed Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DAPT	Dual Antiplatelet Therapy
DAT	Dual Antithrombotic Therapy
DE	Dabigatran Etexilate
DES	Drug Eluting Stent
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DTE	Death or Thrombotic Event
dTT	diluted Thrombin Time

eCRF	Electronic Case Report Form
ECT	Ecarin Clotting Time
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	Gastrointestinal
HR	Hazard Ratio
IB	Investigator's Brochure
IAC	Independent Adjudication Committee
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISTH	International Society of Thrombosis and Haemostasis
i.v.	Intravenous
LBBB	Left Bundle Branch Block
LFTs	Liver Function Tests
LMWH	Low Molecular Weight Heparin
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
MR	Magnetic Resonance
NVAF	Non Valvular Atrial Fibrillation
OPU	Operative Unit
OAC	Oral Anticoagulation
OE	Outcome Event
p.o.	per os (oral)
PD	Pharmacodynamic
PCI	Percutaneous Coronary Intervention
P-gp	P-glycoprotein

PK	Pharmacokinetic
PPI	Proton Pump-Inhibitor
PROBE	Prospective, Randomised, Open Label trial with Blinded Endpoint
q.d.	quaque die (once a day)
RDC	Remote Data Capture
REP	Residual Effect Period
SAE	Serious Adverse Event
s.c.	Subcutaneous
SPAF	Stroke Prevention in Atrial Fibrillation
SE	Systemic Embolism
SmPC	Summary of Product Characteristics
TAT	Triple Antithrombotic Therapy
TCM	Trial Clinical Monitor
TIMI	Thrombolysis In Myocardial Infarction
TSAP	Trial Statistical Analysis Plan
TT	Thrombin Time
TTR	Time in Therapeutic Range
UA	Unstable Angina
UFH	Unfractionated Heparin
ULN	Upper Limit Normal
URL	Upper Reference Limit
VKA	Vitamin K Antagonist

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The current estimate of the prevalence of atrial fibrillation (AF) in the developed world is approximately 1.5–2% of the general population. The arrhythmia is associated with a five-fold increase in the risk of stroke and a three-fold increase in the incidence of congestive heart failure and higher mortality. This arrhythmia is a major cardiovascular challenge in modern society and its medical, social and economic aspects are all set to worsen over the coming decades. Chronic anticoagulant treatment is mandatory in the great majority of the patients with AF [P10-14910, P12-11192].

Twenty to thirty percent of non valvular AF (NVAF) patients have concomitant coronary artery disease [R13-4127, P10-07397, P11-09369]. Revascularisation treatment by primary percutaneous coronary intervention (PCI) has reduced morbidity and mortality in patients with acute and chronic coronary artery disease [R13-4128, P13-11665, R13-4138].

Worldwide over 1,000,000 anticoagulated patients are candidates for a PCI each year [P10-07397]. In patients undergoing PCI, the addition of clopidogrel to aspirin (ASA) reduces death, myocardial infarction (MI) and stroke [R13-4128, P13-11665, R13-4138]. Dual antiplatelet treatment with ASA and clopidogrel also reduces recurrences and the risk of stent thrombosis and is a routine treatment in patients undergoing PCI with stent regardless of indication [R13-4128, P13-11665, R13-4138]. Therefore, when patients with AF that are receiving anticoagulant treatment have to undergo a PCI with stenting, there is an indication for concomitant treatment with ASA and clopidogrel (triple antithrombotic therapy (TAT)) to prevent stent thrombosis [R13-4127, P10-07397, P11-09369].

Rigorous antithrombotic treatment invariably raises the risk of bleeding, adding to a poorer prognosis with an estimated five-fold mortality increase following MI. Major bleeding in patients with acute coronary syndromes (ACS) treated with an early invasive strategy confers an increased risk for both short-term and mid-term mortality [P11-09951, R13-4129, R13-4130]. An acceptable bleeding risk while maintaining a lower ischaemic event rate is considered a must in the post-PCI setting [P10-07397, P11-09369, R13-4128, P13-11665, R13-4138, P11-09951, R13-4129].

In a large registry of patients undergoing PCI (CathPCI Registry - 386 688 procedures performed in the United States between 2004 and 2011), post procedural bleeding events were associated with increased risk of in-hospital mortality, with an estimated 12.1% of deaths related to bleeding complications [R13-4130]. It has been increasingly recognised that the adverse consequences of peri-procedural bleeding extends beyond the hospitalisation for the procedure and can continue for up to three years [P11-09951, R13-4129, R13-4130].

In patients with ACS or undergoing PCI, the presence of AF raises a therapeutic challenge because treatment with both anticoagulant and antiplatelet therapies is preferred to prevent stroke and further coronary events. In the absence of data derived from randomised clinical trials, the management of these patients remains unclear. An analysis of the patient subpopulation that was receiving warfarin at the time of hospital admission enrolled in

CRUSADE showed that current physician practices vary with regard to the perceived optimal antithrombotic strategy at time of hospital discharge [R13-4132]. Existing recommendations are based on small, single-centre, studies that mostly include patients treated with PCI with stent implantation. Overall, it has been concluded that further research is needed to guide patient care.

Several retrospective analyses using patients that participated in observational registries and patient populations enrolled in clinical trials have assessed outcomes and have shown that there might be a potential benefit with the implementation of a dual antithrombotic therapy (DAT) regimen (anticoagulant plus clopidogrel) in comparison with a TAT regimen (anticoagulant plus clopidogrel plus ASA) in NVAF that have undergone PCI [R13-4133, R13-4134, P13-11669, P11-01097, R13-4135].

A nationwide registry in Denmark that comprised a total of 12,165 AF patients hospitalised with MI and/or undergoing PCI between 2001-2009 assessed the risk of MI, coronary death, ischaemic stroke and bleeding according to the antithrombotic treatment regimen. Within one year, MI or coronary death, ischaemic stroke and bleeding events occurred in 18.5%, 5.6% and 6.3% of patients, respectively. Relative to triple therapy (oral anticoagulation (OAC) + ASA + clopidogrel), no increased risk of recurrent coronary events was seen for the dual regimens with OAC + clopidogrel, OAC + ASA, or ASA + clopidogrel. When compared to triple therapy, bleeding risk tends to be reduced (non-significantly reduced for OAC + clopidogrel and significantly reduced for dual therapy with OAC + ASA and ASA + clopidogrel) [R13-4136].

Since blockade of P2Y12 receptor-mediated signalling with clopidogrel is associated with greater platelet inhibitory effects than cyclooxygenase-1 inhibition with ASA and the established role that P2Y12 receptor blockade has on recurrent thrombotic events, clopidogrel might be expected to be more effective at reducing stent thrombosis, but with increased bleeding [P11-09369]. One small observational study observed a lower incidence of stent thrombosis with clopidogrel plus warfarin as compared with ASA plus warfarin [P11-09369].

Other retrospective reports and case-control studies of patients after coronary stenting with an indication for long-term OAC also found more favourable outcomes for clopidogrel than ASA in combination with OAC [R13-4136]. Significant differences in the rate of stent thrombosis have been reported between different antithrombotic drug combinations. The incidence of stent thrombosis has been reported to be higher in patients receiving a combination of warfarin plus ASA in comparison to a dual antiplatelet therapy (DAPT) regimen, a DAT regimen of warfarin plus clopidogrel and a TAT regimen of warfarin plus clopidogrel plus ASA [R13-4136, P07-06963]. The rate of stroke has been observed to be higher in patients receiving a DAT regimen without anticoagulation [P07-06963].

The observations from the retrospective and case-control studies reinforce a concept that is well known and validated in prospective clinical trials; anticoagulant therapies are more beneficial for the prevention of thromboembolism in patients with AF and DAT regimens including a P2Y12 inhibitor are of greater benefit compared to dual antithrombotic regimens comprising warfarin plus ASA for the prevention of ischaemic events, including stent thrombosis, in patients undergoing PCI [P10-07397, P11-09369]. Recommendation of the

European and North American Consensus of using triple therapy for patients with recent MI and/or PCI and concurrent AF is established because of OAC being indicated for AF patients with stroke risk factors and DAT being indicated after ACS or PCI [P10-07397, P11-09369]. The WOEST results have been reflected in some of the recent guidelines for NVAF patients undergoing PCI with stenting [P14-05384, P14-12794, P16-02545] which recommend to consider the use of DAT in certain patients. Non randomised studies on triple therapy showed a protection from ischaemic events with no clear excess bleeding, compared to other regimens, but the studies all have limitations of being potentially underpowered, performed in single centre settings and only including patients after stent implantation [P10-07397, P11-09369]. The main finding of the nationwide Danish registry was that in AF patients after MI/PCI, the combination of OAC plus clopidogrel is comparable with the recommended triple therapy in respect to the prevention of thromboembolic outcomes of MI/coronary death and ischaemic stroke while the risk of bleeding was similar [R13-4136]. Notably, the risk of all-cause mortality was similar between OAC plus clopidogrel and triple therapy but markedly increased for other therapies, namely, OAC plus ASA and DAPT therapy. No beneficial effect was evident for adding ASA to OAC plus clopidogrel treatment, which challenges current recommendations that favours triple therapy for this population. The data from the nationwide Danish registry is consistent with other retrospective reports and suggest that the favoured antiplatelet to be used in combination with OAC should be clopidogrel and this combination may well be used in AF patients after recent MI and/or PCI [R13-4136, P07-06963].

A recently published small randomised controlled study (WOEST) [R13-4127], observed that bleeding and ischaemic event rates were lower in patients on DAT (warfarin + clopidogrel) compared to TAT (warfarin + clopidogrel + ASA). From previous experience it is also known that continued anticoagulation with warfarin during PCI procedures is associated with an increased risk of bleeding [P07-09550]. The WOEST study enrolled 573 patients randomly assigned in a 1:1 ratio to receive oral anticoagulation plus clopidogrel alone (DAT) or plus clopidogrel and aspirin (TAT). All patients were pretreated with a maintenance dose of 75mg clopidogrel per day for at least 5 days, a loading dose of 300mg clopidogrel at least 24 hours before PCI, or a loading dose of 600mg clopidogrel at least 4 hours before PCI. A 320mg loading dose of ASA was also given to patients who had not been taking ASA before the study. Study treatment was started promptly after randomisation. All patients received 75 mg clopidogrel daily, and those in the TAT group were also given 80 – 100mg ASA daily. One year follow up data were available for 279 (98.2%) patients assigned to receive DAT and 284 (98.3%) assigned to receive TAT. Bleeding episodes were seen in 54 (19.4%) patients receiving dual therapy and in 126 (44.4%) receiving triple therapy hazard ratio (HR) 0.36, 95% Confidence Interval (CI) 0.26–0.50, p<0·0001). In the dual-therapy group, six (2.2%) patients had multiple bleeding events, compared with 34 (12.0%) in the triple-therapy group. Eleven patients (3.9%) receiving dual therapy required at least one blood transfusion, compared with 27 (9.5%) patients in the triple-therapy group (odds ratio 0.39, 95% CI 0.17–0.84, p=0.011). The combined secondary endpoint of death, MI, stroke, target-vessel revascularisation and stent thrombosis was reported in 31 (11.1%) patients in the DAT group and in 50 (17.6%) in the TAT group. After correction for imbalance in baseline characteristics, the HR remained similar (0.56, 95% CI 0.35–0.91). Seven patients (2.5%) in the DAT group and 18 (6.3%) in the TAT had died from any cause at 1 year [R13-4127].

This study, however, was not powered for assessing efficacy and can only be considered hypothesis-generating.

As newer OACs (e.g. dabigatran etexilate, rivaroxaban, apixaban) are likely to replace vitamin K antagonists (VKA) in certain AF patients in the years to come, clinicians will soon face new treatment possibilities not explored in PCI clinical trials. In a RE-LY sub analysis focused on patients receiving concomitant antiplatelet therapy, dabigatran etexilate 110mg twice daily (b.i.d.) was non-inferior to warfarin in reducing stroke and systemic embolism (SE), whether patients received antiplatelet therapy or not. There were fewer major bleeds than with warfarin in both dabigatran etexilate 110mg b.i.d. subgroups for patients who used antiplatelets and for patients who did not [P13-00071]. In the same sub-analysis, dabigatran etexilate 150mg b.i.d. reduced the primary outcome of stroke and SE in comparison with warfarin [P13-00071]. Dabigatran etexilate, would therefore be an attractive alternative to warfarin (as part of triple therapy), particularly used at a lower dose since it appears to have less bleeding without loss of efficacy [P11-09369]. Prospective clinical data concerning the possibility of implementing triple or DAT regimens with dabigatran etexilate and other new OACs addressing their efficacy and safety in patients undergoing PCI are needed [P11-09369].

Newer P2Y12 inhibitors (e.g. ticagrelor, prasugrel) have also recently become available. Data is still lacking about both the concomitant use of ticagrelor with VKA or novel oral anticoagulant treatments and the potential use of ticagrelor as part of triple or dual antithrombotic therapy regimens [P11-09369]. The use of prasugrel is generally not recommended in patients ≥75 years of age because of the increased risk of fatal (1.0% prasugrel vs. 0.1% clopidogrel) and intracranial bleeding (0.8% prasugrel vs. 0.3% clopidogrel) and uncertain added benefit [P07-13246; R13-5262].

1.2 DRUG PROFILE

Dabigatran etexilate is the orally bioavailable prodrug of dabigatran, a novel, synthetic, direct thrombin inhibitor. Following oral administration dabigatran etexilate (prodrug) is rapidly converted to the active moiety dabigatran, which is a non-peptidic, highly potent, competitive and reversible inhibitor of thrombin [U06-1704, P08-12388].

The pharmacokinetic (PK) profile is characterised by peak plasma concentrations of dabigatran that occur approximately two hours after oral administration of the prodrug, a biexponential distribution phase and a terminal elimination half-life of 14-17 hours after multiple dose administration. Dabigatran maximum plasma concentrations and area under curve (AUC) increase in a dose proportional manner. PK steady state is reached by three days with b.i.d. dosing, pharmacodynamic (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. Dabigatran may be conjugated to form acylglucuronides, which are pharmacologically active. The absolute bioavailability of the current capsule formulation of dabigatran etexilate is approximately 6.5%.

In Phase I drug-drug interaction studies there was no significant influence of dabigatran etexilate 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 metabolised by the cytochrome P450 system and have no in vitro effects on human cytochrome P450 enzymes. There was, however, an effect on dabigatran etexilate 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.

In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran AUCτ,ss and Cmax,ss and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300mg or 600mg clopidogrel, dabigatran AUCτ,ss and Cmax,ss were increased by about 30-40 %. When comparing combined treatment and the respective mono-treatments, the coagulation measures for dabigatran's effect (Activated Partial Thromboplastin Time (aPTT), Ecarin Clotting Time (ECT) and Thrombin Time (TT)) remained unchanged and inhibition of platelet aggregation, a measurement of clopidogrel's effect, remained unchanged.

The potential for a PK interaction between ticagrelor and dabigatran was evaluated in a randomised, open-label, 2-period cross-over phase I study in 12 healthy male subjects (BI Trial No. 1160.141) [U12-2002]. In order to limit the potential bleeding risk to human volunteers, a low dose of 75mg dabigatran etexilate was administered either: alone in one trial period, or in combination with ticagrelor in a second period (i.e. one dabigatran etexilate dose on Day 1 at the same time as a loading dose of ticagrelor (180mg) and the second time on Day 4 at the same time as ticagrelor after it had been dosed at 90mg b.i.d. over 3 consecutive days with a goal of reaching steady state).

Co-administration of a loading dose of 180mg of ticagrelor on Day 1 with single dose of 75mg dabigatran etexilate in study 1160.141 [U12-2002) resulted in a 1.73-fold (90% CI 1.18 to 2.52) and 1.95-fold increase (90% CI1.26 to 3.00) in gMean AUC0-∞ and Cmax of total dabigatran, respectively. After further treatment with 90mg ticagrelor b.i.d. the increase of dabigatran gMean AUC0-∞ and Cmax after single oral administration of 75mg dabigatran etexilate on Day 4 were 1.46-fold (90% CI 1.00 to 2.12) and 1.56-fold (90% CI 1.02 to 2.38), respectively [U12-2002].

The interaction was further assessed under dabigatran steady state conditions in an open label, fixed sequence, multiple-dose, healthy volunteer study (BI study 1160.142 [U13-2049]). Multiple doses of 110mg dabigatran etexilate b.i.d were given alone and in combination with ticagrelor (i.e. on Day 4 the morning dose of the 110mg dabigatran etexilate b.i.d treatment was given at the same time as a 180mg loading dose of ticagrelor) and the second time on Day 7 at the same time as ticagrelor after it had been dosed at 90mg b.i.d. with a goal of reaching steady state (part 1). Further, the second part of the study investigated the effect of staggered administration of ticagrelor loading dose on dabigatran

exposure in steady state. The loading dose was given 2 hours after the morning dose of the 110mg dabigatran etexilate b.i.d treatment.

Concomitant administration of the loading dose of 180mg ticagrelor at the same time as the morning dose of 110mg dabigatran etexilate b.i.d. increased the gMean (adjusted for treatment) total dabigatran $AUC_{\tau,ss}$ 1.49-fold (90% CI 1.24 to 1.79) and $C_{max,ss}$ 1.65-fold (90% CI 1.34 to 2.03) compared with dabigatran etexilate given alone. Concomitant administration of the morning dose of 90mg ticagrelor b.i.d with the morning dose 110mg dabigatran etexilate increased the adjusted gMean total dabigatran $AUC_{\tau,ss}$ 1.26-fold (90% CI 1.07 to 1.49) and $C_{max,ss}$ 1.29-fold (90% CI 1.06 to 1.55) compared with dabigatran etexilate given alone. When the loading dose of 180mg ticagrelor was given 2 hours after the morning dose of 110mg dabigatran etexilate b.i.d gMean (adjusted for treatment) total dabigatran $AUC_{\tau,ss}$ increased 1.27-fold (90% CI 1.08 to 1.49) and $C_{max,ss}$ 1.24-fold (90% CI 1.03 to 1.49) compared with dabigatran etexilate given alone [U13-2049].

The finding that ticagrelor increased dabigatran exposure is consistent with the hypothesis of P-gp inhibition by ticagrelor at the intestinal wall, which could have decreased the efflux of dabigatran etexilate into the gut and increased its absorption. With staggered intake of ticagrelor 2 hours after the intake of dabigatran etexilate the increase of dabigatran exposure observed after simultaneous administration of both drugs was reduced. This was most likely due to the fact that dabigatran absorption in the gut is complete after 2 hours. A similar reduction of PK interaction effects with staggered intake has also been observed for verapamil and dronedarone [U13-2049].

Administration of dabigatran etexilate (single or multiple doses) and the co-administration of dabigatran etexilate with the ticagrelor loading dose and the multiple-dose regimen of ticagrelor was safe, i.e. it did not cause bleeding in the healthy subjects included in the trials 1160.141 and 1160.142 [U13-2049].

In summary, a PK interaction between ticagrelor and dabigatran etexilate has been shown in drug-drug interaction trials examining a single- and multiple-dose applications of dabigatran etexilate (BI studies 1160.141, 1160.142) [U12-2002, U13-2049]. The magnitude of this PK interaction under steady state conditions of dabigatran (i.e. in a clinically more relevant scenario) was lower when compared to conditions when the single dose of dabigatran etexilate was administered. Further, the interaction was also lower under the maintenance dose of ticagrelor or after a staggered intake of the ticagrelor loading dose (given 2 hours after dabigatran etexilate). The relative increase in dabigatran exposure under the various conditions presented above is expected to be of comparable magnitude when a dose of 150mg dabigatran etexilate is given, as dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400mg [U12-2002, U13-2049].

The magnitude of PK interaction was dependent upon the dose administered. Under steady state conditions of dabigatran and ticagrelor, the plasma level increase of dabigatran was in the range (approx. +26-29%) of the P-gp inhibitor clarithromycin which is considered of no clinical safety concern. Similar increases can be seen when the loading dose of ticagrelor is given 2 hours after dabigatran etexilate intake. When the loading dose of ticagrelor is given at the same time as dabigatran etexilate, the increase of dabigatran was in the range (approx.

+50-65%) comparable to the increases of Pgp inhibitors such as amiodarone or quinidine. Similar to the concomitant administration of dabigatran etexilate with amiodarone or quinidine, a dose adjustment of dabigatran etexilate is considered not necessary when ticagrelor treatment is initiated or given chronically [U12-2002, U13-2049].

It was demonstrated in the Phase III study, RE-LY (1160.26), that co-administration of P-gp inhibitors (such as amiodarone, quinidine and verapamil) in a long-term clinical trial setting had much smaller effects than those observed in Phase I studies, which were designed to show maximal possible PK effects. The greatest elevation of dabigatran exposure was observed for patients treated concomitantly with verapamil, who had on average a trough dabigatran plasma concentration increase of 16%. Concomitant administration of amiodarone or quinidine and dabigatran etexilate led to even smaller increases of plasma concentrations of dabigatran and did not appear to increase the relative risk of bleeding [U09-3249-02].

The PK and PD of dabigatran in subjects with normal renal function in comparison to subjects 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 (Creatinine Clearance (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.

No influence of hepatic impairment on the absorption and bioconversion of dabigatran etexilate to the active form dabigatran and its excretion was observed comparing healthy subjects and subjects with moderate hepatic impairment (category B of the Child Pugh classification system) [P08-12388].

Dabigatran etexilate is registered for reducing the risk of stroke and SE in patients with NVAF. The RE-LY trial was a Phase III, prospective, randomised, open-label, multinational trial of stroke prevention in subjects with NVAF at risk of stroke. A total of 18,113 subjects were randomised to one of two blinded doses of dabigatran etexilate (110mg b.i.d. or 150mg b.i.d.) or to warfarin (target International Normalised Ratio (INR) 2.0-3.0) [U09-3249-02].

RE-LY demonstrated that dabigatran etexilate, 150mg b.i.d., was superior to warfarin for the prevention of stroke and SE in subjects with NVAF and at least one risk factor for stroke. Dabigatran 150mg also resulted in reductions of intracranial haemorrhage, total bleeding and vascular mortality. Dabigatran etexilate 110mg b.i.d. was non-inferior to warfarin for the primary endpoint of stroke and SE and reduced intracranial haemorrhage, major bleeding and total bleeding.

Antiplatelet agents (ASA or clopidogrel) are known to increase bleeding. In RE-LY [U09-3249-02], the yearly major bleeding events (MBE) were about twice as high in subjects receiving additional ASA or clopidogrel, but this effect was similar to that observed when ASA or clopidogrel was administered with warfarin.

In an ACS setting, the RE-DEEM trial assessed the safety and indicators of efficacy of the novel oral direct thrombin inhibitor dabigatran etexilate in addition to DAPT (ASA plus clopidogrel). In this double-blind, placebo-controlled, dose-escalation trial of 1861 patients almost all patients (99.2%) received DAPT therapy with ASA and either clopidogrel or ticlopidine at baseline. Primary outcome was the composite of major or clinically relevant minor bleeding during the 6-month treatment period. Dabigatran etexilate, in addition to DAPT, was associated with a dose-dependent increase in bleeding events in patients with a recent MI. In addition, dabigatran etexilate 110mg b.i.d. and dabigatran etexilate 150mg b.i.d. were the doses associated with the lowest rate of the secondary composite ischaemic outcome compared to the lower doses that were tested (75mg b.i.d.; 50mg b.i.d.) and placebo [P11-05772].

Please refer to the current version of the Investigator Brochure (IB) for dabigatran etexilate for additional information on drug-drug interaction studies, studies in special patient populations and completed Phase II/III trials.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

There is uncertainty over the optimal antithrombotic management strategy for patients with NVAF undergoing PCI. The current treatment recommendations of TAT, comprising, VKA, clopidogrel and ASA [P10-07397, P11-09369] are based on limited data. There is increasing research to suggest that there might be a potential benefit with the implementation of a DAT regimen.

Dabigatran etexilate has been shown in the RE-LY trial in a NVAF setting at risk of stroke to be more effective than warfarin in the prevention of stroke and SE at a dose of 150mg b.i.d. and non-inferior to warfarin at a dose of 110mg b.i.d. With respect to bleeding risk, the 150mg b.i.d. dabigatran etexilate dose was equivalent to warfarin, whilst the 110mg b.i.d dabigatran etexilate was seen to significantly reduce the risk of intracranial haemorrhage, major bleeding and total bleeding.

Therefore the implementation of a DAT regimen with dabigatran etexilate (110mg b.i.d. or 150mg b.i.d.) plus clopidogrel or ticagrelor is likely to provide clinical benefits compared with a warfarin TAT regimen that is considered the current standard of care.

The concomitant evaluation of the dabigatran etexilate 110mg b.i.d. and 150mg b.i.d. doses will define the benefit/risk of each dose compared with warfarin in this particular NVAF patient subpopulation that have undergone PCI, that was not assessed in the RE-LY or RE-DEEM trials, and will provide treatment guidance on the optimal antithrombotic therapy in these patients.

2.2 TRIAL OBJECTIVES

The main objective of this study is to compare a DAT regimen of 110mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (110mg DE-DAT) and 150mg dabigatran etexilate b.i.d. plus clopidogrel or ticagrelor (150mg DE-DAT) with a TAT combination of warfarin plus clopidogrel or ticagrelor plus ASA ≤ 100mg once daily (q.d.) (warfarin-TAT) in patients with NVAF that undergo a PCI with stenting (elective or due to an ACS).

The study aims to show non-inferiority of each dose of DE-DAT when compared to Warfarin-TAT in terms of safety. Safety will be determined by comparing the rates of bleeding events, assessed using the modified International Society of Thrombosis and Haemostasis (ISTH) classification of Major Bleeding and CRNMBE.

See Section 5 for details of variables assessed.

2.3 BENEFIT - RISK ASSESSMENT

Anticoagulant therapies are more beneficial for prevention of thromboembolism in patients with AF and dual anti-platelet therapy regimens are of greater benefit compared to dual antithrombotic regimens comprising warfarin plus ASA for the prevention of ischaemic events, including stent thrombosis, in patients undergoing PCI [P10-07397, P11-09369]. An acceptable bleeding risk while maintaining a lower ischaemic event rate is considered a must in the post-PCI setting [P10-07397, P11-09369, R13-4128, P13-11665, R13-4138, P11-09951].

The incidence of stent thrombosis averages 1–2% over the first year but is greatest in the first month regardless of the type of stent used. The rate slowly declines to less than 0.1%/ year after the first year for Bare Metals Stents (BMS) and 0.4–0.6%/year after the first year for the first generation Drug Eluting Stents (DES). Stent thrombosis is associated with a mortality of 10–20% and a MI rate of 30–70% in those with early or late stent thrombosis. In the first year, however, meta-analyses of randomised trials have not shown any difference in stent thrombosis between BMS and DES with an incidence of 1.1% for DES versus 1.3% for BMS. The duration of DAPT, however, was shorter in these early studies and often only one month for BMS and less than six months for DES [P11-09369]. A number of studies in the 1990s demonstrated that the most effective antithrombotic regimen to prevent stent thrombosis was DAPT with ASA and a thienopyridine.

Therefore, a general principle guiding the use of TAT specified in the current guidelines is to choose a treatment strategy that is tailored to the individual patient, taking into consideration the anticipated risk of an adverse event (AE) particularly major bleeding. Although triple therapy including OAC, ASA and clopidogrel is recommended for AF patients with ACS and/or PCI, evidence stems from small observational studies of mostly single centre origin and American and European position documents categorise recommendations as Level of Evidence “C” [P10-07397, P11-09369]. Consequently, guidelines emphasise the need for individualisation of treatment in respect to careful assessment of each patient’s risk of thrombosis and bleeding to find the optimal balance between risk and benefit of treatment. A recent study showed that initiation of triple therapy is immediately associated with increased and persistent bleeding risk compared to OAC plus a single antiplatelet agent [R13-4135]. A recently communicated small randomised controlled study (WOEST) [R13-4127], observed that bleeding and ischaemic event rates were lower in patients on a DAT (warfarin + clopidogrel) compared to TAT (warfarin + clopidogrel + ASA). This study however, was not powered for assessing efficacy and can only be considered hypothesis-generating. The WOEST results have nevertheless been reflected in some of the recent guidelines for NVAF patients undergoing PCI with stenting [P14-05384, P14-12794, P16-02545] which recommend to consider the use of DAT in certain patients. However, data from clinical trials concerning the possibility of implementing DAT regimens with dabigatran etexilate and other new NOACs in this setting are needed.

Because many new agents have come on the market recently, there is a wide variety of possible strategies with regard to not only the number and type of agents but also the intensity of anticoagulation and duration of the combination treatment [P13-00072]. The new oral anticoagulants (dabigatran etexilate, rivaroxaban, apixaban, edoxaban) so far tested in clinical

trials have all shown non-inferiority compared with VKAs, consistently showing a lower rate of intracranial haemorrhage (RR 0.48 [0.39-0.59]; p < 0.001) [P13-16211, R13-5082]. On this basis, the European Society of Cardiology guideline now recommends them as broadly preferable to VKA in the vast majority of patients with NVAF, when used as studied in the clinical trials performed so far [P12-11192].

In RE-LY, there was a 60% reduction in intracranial haemorrhage with both doses of dabigatran etexilate [U09-3249-02]. In a RE-LY sub analysis focused on patients receiving concomitant antiplatelet therapy (mandatory concomitant treatment in patients that underwent a PCI), dabigatran etexilate 110mg b.i.d. was non inferior to warfarin in reducing stroke and SE, whether patients received antiplatelet therapy or not. There were fewer major bleeds than with warfarin in both dabigatran etexilate 110mg b.i.d. subgroups for patients who used antiplatelets and for patients who did not [P13-00071]. In the same sub-analysis, dabigatran etexilate 150mg b.i.d. reduced the primary outcome of stroke and SE in comparison with warfarin. Major bleeding with dabigatran etexilate 150mg b.i.d. was similar to warfarin regardless of antiplatelet use.

Because the absolute bleeding risk on antiplatelet therapy was the lowest with the 110mg dose of dabigatran, regardless of the number of antiplatelet agents used, decreasing the dose of dabigatran from 150 to 110mg for the duration of additional antiplatelet therapy, especially in patients at high bleeding risk, seems to be reasonable. Because both doses are still associated with a lower risk of intracranial haemorrhage, however, continuing the 150mg twice-daily dose remains a defendable option, particularly in patients with relatively low bleeding risk and a high CHA2DS2-VASc score [P13-00072].

The implementation of a DAT regimen with dabigatran etexilate plus clopidogrel or ticagrelor is likely to provide clinical benefits compared with the warfarin TAT regimen that is considered the current standard of care for the prevention of thromboembolic and bleeding (ICH) complications in patients with NVAF following PCI. The potential benefit of dabigatran etexilate over warfarin is based on its more rapid onset and offset of action, the absence of a need for routine laboratory monitoring, its lack of drug-food interactions, its low drug-drug interaction potential and the superiority compared to warfarin demonstrated in patients with NVAF for the reduction of stroke and SE. A dual antithrombotic regimen with a NOAC is particularly appealing due to the potential benefit in terms of reduced risk of intracranial bleeding as well as due to the potential benefit of a reduced risk of major bleeding events in a post-PCI setting.

Dabigatran is eliminated primarily by the kidneys with urinary excretion accounting for approximately 80% of the dose administered intravenously. Treatment with dabigatran in patients with severe renal impairment (CrCl < 30 mL/min) is contraindicated and these patients will be excluded from participating in this trial. No dose adjustment is necessary in patients with mild renal impairment (CrCl 50 ≤ 80 mL/min) or moderate renal impairment (CrCl 30-50 mL/min). Close clinical surveillance is recommended in patients with renal impairment and CrCl will be monitored at every visit and followed up closely.

In all patients renal function will be assessed as follows:

- Calculating the creatinine clearance (CrCl) prior to initiation of treatment with dabigatran etexilate to exclude patients with severe renal impairment (i.e. CrCl < 30 mL/min)

- Renal function will also be assessed when a decline in renal function is suspected during treatment and as part of the routine follow up measures.

The method used to estimate renal function (CrCl in mL/min) during the clinical development of dabigatran etexilate was the Cockcroft-Gault method. This method is recommended, as indicated in the label, when assessing patients' CrCl prior to and during dabigatran etexilate treatment.

Guidance on the management of patients who experience a haemorrhagic complication is provided in Section 4.2.1. 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 4.2.1.7 Overdose, for more information regarding the specific reversal agent for dabigatran.

It should be mentioned that no reliable clinical data are available in NVAF patients on the combined use of an oral anticoagulant with the new P2Y12 antagonists (prasugrel and ticagrelor) either alone or with ASA. Therefore, dedicated prospective trials on this important clinical problem are definitely needed [P13-00072]. The proposed clinical trial will generate prospective data to evaluate or explore this important data gap.

The study will be conducted under the guidance of a Steering Committee and data will be scrutinised on an ongoing basis by an independent external data monitoring committee (DMC). The use of electronic data capture and a central laboratory should ensure quick turnaround times and up to date data for the independent DMC to provide an unbiased review of data. Additionally, all bleeds and thromboembolic events will be reviewed by an Independent Adjudication Committee (IAC); data will be provided in discrete patient packets, removing data which could potentially provide information on the patients drug assignment (INR values for example) in order to ensure the IAC review is conducted in a blinded fashion. For further details regarding the relevant committees please refer to Section 3.1.1. For further details regarding the relevant considerations for the DMC please refer to Section 7.3.4.

Based on the findings on the nonclinical studies with dabigatran etexilate conducted to date and in accordance with international regulatory guidelines, the inclusion of women of child bearing potential in this study is justified. To minimise the risk of unintentional exposure of an embryo or foetus to the investigational drug, woman of child bearing potential must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.

Given the above considerations, the risk benefit assessment is considered favourable 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 prospective, randomised, open label, blinded endpoint (PROBE), active comparator trial and the clinical endpoints are being adjudicated by an IAC in a blinded fashion.

This trial is designed to test the safety in NVAF patients that have undergone a successful PCI (elective or due to ACS) with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure.

Patients will be consented and screened after undergoing a successful PCI. Randomisation will occur on local laboratory results taken at the screening visit or on standard of care local laboratory results taken within 7 days prior to screening; central laboratory samples must be taken at randomisation prior to first intake of study drug. Randomisation can occur up to 120 hours post PCI, however within 72 hours is preferable. Study drug should be administered between 6 hours after sheath removal and preferably within 72 hours post PCI, with haemostasis assured, however up to 120 hours post PCI is allowed.

Patients aged < 80 years will be randomly assigned to 110mg dabigatran etexilate b.i.d., 150mg dabigatran etexilate b.i.d. or warfarin in a 1:1:1 ratio for the duration of the trial.

Patients aged ≥80 years will be randomly assigned depending on their geographical location:

- Patients aged ≥80 years in the USA will be assigned to 110mg dabigatran etexilate b.i.d., 150mg dabigatran etexilate b.i.d. or warfarin in a 1:1:1 ratio
- All other patients aged ≥80 years outside of the USA will be assigned to 110mg dabigatran etexilate or warfarin in a 1:1 ratio.

In addition to their randomised treatment:

- All patients will receive either clopidogrel (75mg q.d.) or ticagrelor (90mg b.i.d), according to the local label, for at least 12 months after randomisation. Discontinuation of clopidogrel or ticagrelor or switching to ASA (≤ 100mg q.d.) after 12 months of treatment is at the discretion of the Investigator
- Patients randomised to receive warfarin will receive ASA (≤ 100mg q.d.) for either one month in patients with a bare metal stent BMS and for three months in patients with a DES.

For details of drug administration see Section 4.1.4.

The study plan is detailed in Figure 3.1: 1.

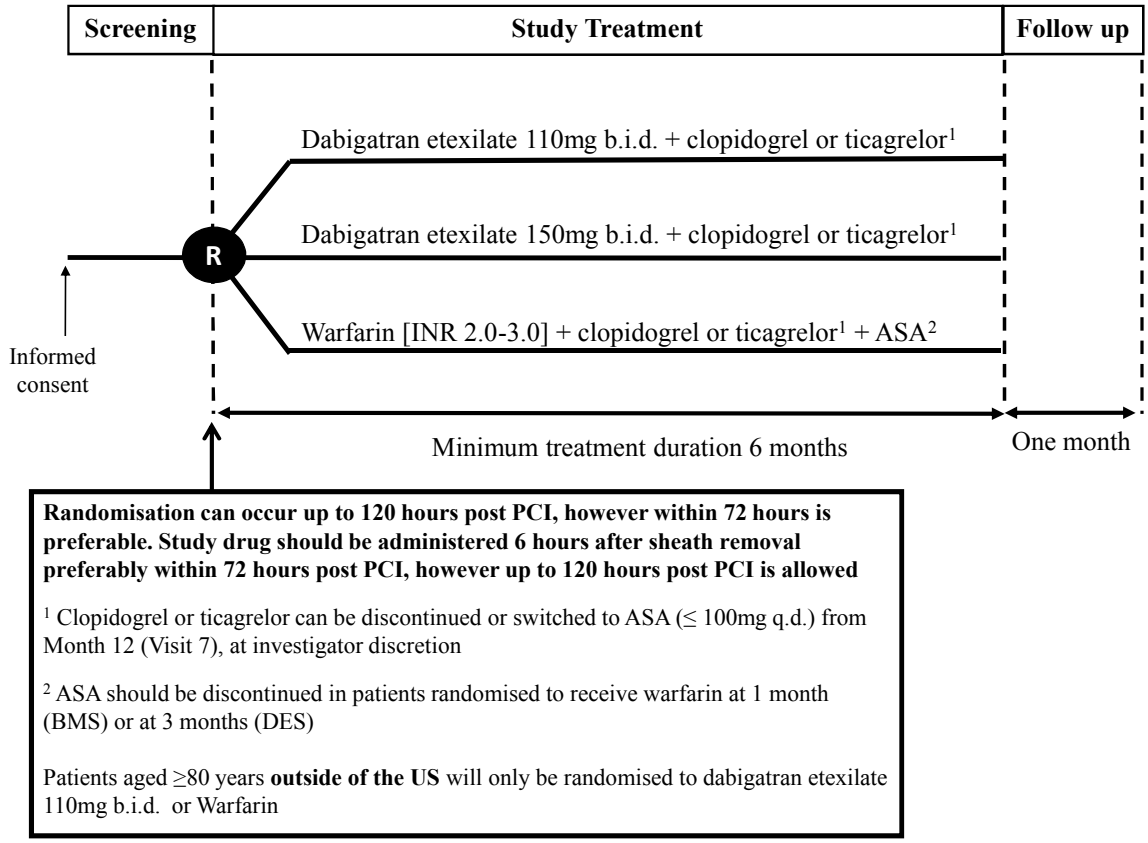

Figure 3.1: 1 Study Plan

Prior to consent, the patient's antithrombotic treatment (i.e. ASA and anticoagulant use before and during PCI, use of clopidogrel or ticagrelor loading dose) should be managed as per local standard of care. The screening period will consist of one visit (Visit 1). The patients will be randomised at Visit 2. Screening and randomisation can be conducted on the same day. The treatment period will consist of between three and 10 visits (Visits 3-12). The trial is event driven and is designed to continue until approximately 500 patients with at least one MBE or CRNMBE (in total) occur. The last patient randomised will receive at least six months of treatment and patients recruited earlier remain in the study until the time point at which this last patient has reached at least six months. Any ongoing patient, at the time the required number of events is reached will be discontinued. Following completion of the treatment period, the patients will have a follow-up visit four weeks later.

The visits scheduled at 15, 21 and 27 months (Visits 8, 10 and 12) are to be conducted by telephone. Collection of AEs, outcome events (OE) (including bleeding) and use of concomitant medication will be made.

Blood sampling for a standard chemistry safety panel (including renal function and Liver Function Tests (LFTs)) will be collected at Visits 1, 2, 3, 5, 7 and End of treatment (EOT). In addition, samples for standard haematology safety panel will be taken at all clinic visits. All

blood measurements (with the exception of INR and screening labs) will be performed by a central laboratory.

For further study procedure details see Flow Chart.

The end of the trial is defined as "last patient out", i.e. last visit completed by the last patient.

3.1.1 Administrative structure of the trial

An Executive Steering Committee, consisting of a small group of external experts and representatives from the Sponsor, will provide scientific leadership for the planning and conduct of the trial. A Steering Committee will also be formed, where in addition to these members, there will be representatives from every country participating in the trial. These committees will be chaired by the Coordinating Investigator. A charter describing the tasks and responsibilities of the Executive Steering Committee and Steering Committee will be developed.

Overall organisation will be overseen by an Operations Committee, consisting of representatives of the Sponsor and Harvard Clinical Research Institute. The Operations Committee will oversee the conduct and execution of the trial, coordinate the agenda for the Steering Committees and will be responsible for the day-to-day operations of the trial.

An independent DMC will monitor patient safety and the trial conduct. A detailed DMC charter will be written to govern the activities of this committee. The DMC analyses and operations will be formally separated from the Sponsor, the Investigators, the Steering Committees and the Operations Committee. All data (for both dabigatran etexilate and warfarin patients), both adjudicated and non-adjudicated will be reviewed by the DMC in an ongoing fashion.

An IAC will be established for the blinded adjudication of efficacy outcomes (e.g. death, stroke, MI, SE) as well as bleeding. An Adjudication Committee Charter, under which the principles of the PROBE design can be carried out, will govern their activities. The charter will provide detailed definitions of each endpoint and the processes by which adjudication will occur, including how blinding will be preserved.

The Coordinating Investigator is selected based on [redacted] expertise in this therapeutic area and reputation for being a [redacted] in [redacted] field. [redacted] will review and sign the clinical trial protocol (CTP) and relevant clinical trial report (CTR).

Physicians (e.g. cardiologists, interventionalists) managing anticoagulation may be Investigators for this trial.

An Interactive Response Technology (IRT) will perform the randomisation of patients and ensure appropriate distribution of trial medication to trial sites during the course of the trial.

A central laboratory will perform all protocol specified blood analyses with the exception of INR and screening measurements.

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

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

TAT, comprising of VKA, clopidogrel and ASA, is the current standard treatment to prevent post-PCI stent thrombosis and the recommendation by multiple international guidelines (consensus document of the European Society of Cardiology Working Group on Thrombosis that was endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) [P10-07397]; and the North American Consensus Document on Antithrombotic therapy in patients with AF undergoing coronary stenting [P11-09369]). The WOEST results have been reflected in some of the recent guidelines for NVAF patients undergoing PCI with stenting [P14-05384, P14-12794, P16-02545] which recommend to consider the use of DAT in certain patients. However, data from clinical trials concerning the possibility of implementing DAT regimens with dabigatran etexilate and other new NOACs in this setting are needed.

Therefore, an active control group is required for any study in patients who have undergone PCI with stenting. Warfarin, the most widely used VKA, was chosen as the active control in this study.

The trial is event driven; therefore all patients will remain in the trial until the required number of events have occurred. Individual patient participation will vary from approximately 6 months to 2.5 years or longer (estimated average duration 18 months).

Double-blind, double-dummy trials in anticoagulation have limitations due to potential unavoidable deviations from routine clinical procedures [R08-4453]. This trial will use the PROBE design. The PROBE approach has been used in several trials of anticoagulation comparing against VKAs, e.g. in patients with AF.

The following procedures will be implemented to reduce the potential for bias in the reporting and assessment of primary and secondary events.

1. Clearly defined objective outcomes:
   The primary and secondary outcomes of the study are clinically relevant events for which objective documentation will be obtained. Standard, widely accepted definitions are to be used that rely on objective documentation.

2. Blinded IAC:
   All OEs will be adjudicated by blinded adjudication experts. Blinding of all event documentation will be performed by trained specialists. The role of the IAC will be to oversee and perform the blinded adjudication of all outcome events. This Committee will report to the Executive Steering Committee and DMC.

3. Bleeding Questionnaire:

A questionnaire querying patients for signs and symptoms of bleeding will be administered at each visit. The goal is to reduce the possibility of under-reporting of events. All symptoms will be evaluated and if potentially consistent with an outcome event will be referred to the IAC.

4. Review of Data for Clinical Events:
   Any AE that indicates potential loss of neurological function, such as unilateral weakness, loss of vision or sensory disturbance will trigger a request for more information from the centre for event adjudication if potentially consistent with an outcome event. Any decrease in haemoglobin of >2g/dL will be similarly investigated.

5. Data Handling:
   Patients will be randomly allocated to the treatment arms via IRT. Wherever feasible, data management will be undertaken without knowledge of patient treatment allocation. Special procedures to handle data with the potential for unblinding, such as INRs, will be specified. By treatment data tabulations will not be reviewed during the course of the trial and the data management personnel will not have access to the randomisation code.

By implementing these appropriate measures to avoid bias, the PROBE design is an acceptable [R14-0530] and preferred approach for this study.

3.3 SELECTION OF TRIAL POPULATION

In order to test the two combined efficacy-safety hypotheses in NVAF patients that have undergone a successful PCI, at least 834 patients per treatment group are estimated to be required (see Section 7.6).

Approximately 550 trial centres worldwide will participate in the trial. The enrolment target for each site is a minimum of one patient every two months. Enrolment will be competitive and the trial will be terminated when the total number of events has been observed, regardless of enrolment at individual centres. If enrolment is delayed, additional study centres 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.

3.3.1 Main diagnosis for study entry

3.3.2 Inclusion criteria

The patient must meet all the inclusion criteria:

1. Male or female patients aged ≥18 years

2. Patients with NVAF that have been receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant), or were treatment naïve prior to PCI. AF may be paroxysmal, persistent or permanent, and not secondary to a

reversible disorder such as MI, pulmonary embolism, recent surgery, pericarditis or thyrotoxicosis, unless long term oral anticoagulation is planned

3. Patient presenting with:

   - An ACS (STEMI, NonSTEMI [NSTEMI] or unstable angina [UA]) that was successfully[1] treated by PCI and stenting (either BMS or DES)

   Or

   - Stable Coronary Artery Disease with at least one lesion eligible for PCI that was successfully[1] treated by elective[2] PCI and stenting (either BMS or DES)

4. The patient must be able to give informed consent in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local legislation and/or regulations.

3.3.3 Exclusion criteria

The patient must not meet any of the exclusion criteria:

1. Patients with a mechanical or biological heart valve prosthesis

2. Cardiogenic shock during current hospitalisation

3. Patients who have used fibrinolytic agents within 24 hours of randomisation that, in the opinion of the Investigator, will put the patient at high risk of bleeding

4. Stroke within 1 month prior to screening visit

5. Patients, who in the opinion of the Investigator, have had major surgery within the month prior to screening

6. Patient has received an organ transplant or is on a waiting list for an organ transplant

7. History of intraocular, spinal, retroperitoneal or a traumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery)

8. Gastrointestinal (GI) haemorrhage within one month prior to screening, unless, in the opinion of the Investigator, the cause has been permanently eliminated (e.g. by surgery)

[1] Successful treatment with PCI is defined as achievement of < 30 % residual diameter stenosis of the target lesion assessed by visual inspection or quantitative coronary angiography and no in-hospital major adverse cardiac events (MI or repeat coronary revascularisation of the target lesion).
[2] Indication for elective PCI should be based upon the ACCF/SCAI/STS/AATS/AHA/ASNC [R14-1287] and ESC guidelines [P10-12773].

9. Major bleeding episode (reduction in the haemoglobin level of at least 2g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ) including life-threatening bleeding episode (symptomatic intracranial bleeding, bleeding with a decrease in the haemoglobin level of at least 5g/dL or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery) in one month prior to screening visit

10. Haemorrhagic disorder or bleeding diathesis (e.g. von Willebrand disease, haemophilia A or B or other hereditary bleeding disorder, history of spontaneous intra-articular bleeding, history of prolonged bleeding after surgery/intervention)

11. Anaemia (haemoglobin <10g/dL) or thrombocytopenia including heparin-induced thrombocytopenia (platelet count $<100 \times 10^9$/L) at screening (Visit 1)

12. Severe renal impairment (estimated CrCl calculated by Cockcroft-Gault equation) <30mL/min at screening (Visit 1)

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

    - Prior and persistent alanine aminotransferase (ALT) **or** Aspartate transaminase (AST) **or** alkaline phosphatase (AP) >3 × upper limit of normal (ULN)[1]
    - Known active hepatitis C
    - Known active hepatitis B
    - Known active hepatitis A

14. Recent malignancy or radiation therapy (≤6 months) unless, in the opinion of the Investigator, the estimated life expectancy is greater than 36 months

15. Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, St. John's Wort. See Section 4.2.2

16. Patients who, in the Investigator's opinion, need continuous treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

17. Patients with a known allergy to dabigatran etexilate or to the excipients used for the capsule of the drug

18. Patients with a known allergy to warfarin tablets or to the excipients

19. Patients who, in the Investigator's opinion, should not be treated with OAC

20. Patients with a contraindication to clopidogrel, ticagrelor or ASA

[1] Clinical judgement of whether ALT/AST enzyme elevation is due to active liver disease or due to ACS, should be made by the Investigator following evaluation the of the clinical characteristics of the patient and the laboratory findings.

21. Pre-menopausal women (last menstruation ≤1 year prior to screening) who:

    - Are pregnant or breast feeding or
    - Are not surgically sterile or
    - Are of child bearing potential and not practising two acceptable methods of birth control, or do not plan to continue practising an acceptable method of birth control throughout the trial. Acceptable methods of birth control are 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, intrauterine device or intrauterine system, double-barrier method of contraception (condom and occlusive cap or condom and spermicidal agent), male sterilisation and complete sexual abstinence (if acceptable by local authorities). Periodic abstinence is not an acceptable method of contraception.

22. Patients who have participated in another trial with an investigational drug or device within the past 30 days preceding the screening visit or are participating in another trial (patients participating in an observational study only will not be excluded)

23. Patients not willing or able to comply with the protocol requirements or considered unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, who have a life expectancy less than the expected duration of the trial due to concomitant disease, or who have any condition which in the opinion of the Investigator, would not allow safe participation in the study (e.g. drug addiction, alcohol abuse).

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from the trial if:

- The patient withdraws consent, without the need to justify the decision

Treatment with study drugs should be discontinued if:

- The patient needs to take concomitant drugs that interfere with the investigational product or other study medication(s)
- The patient is no longer able to take trial medication for other medical reasons (e.g. surgery, AEs, or other diseases)
- The patient is persistently noncompliant with study drug administration
- If a patient becomes pregnant during the trial the investigational drug will be stopped, the patient will be discontinued from the trial medication and the patient will be followed up 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.

- Patients on dabigatran etexilate who are found to have a CrCl <30mL/min during the course of the trial, should have study medication stopped and a parenteral anticoagulant can be started according to local practice (see Appendix 10.1 for switching to a parenteral anticoagulant). CrCl laboratory testing should be repeated as soon as feasible, ideally within 48 hours. If this second measurement confirms a CrCl <30mL the patient should be permanently discontinued from dabigatran etexilate, unless the concomitant clinical condition is expected to allow recovery of the renal function within 7 days from the initial CrCl reduction. A patient should also be permanently discontinued from study drug, if CrCl drops to <30mL/min at two different occasions during the trial

- 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)

- The patient elects to stop taking study drug (the patient should be encouraged to resume study drug per the protocol).

Patients who discontinue treatment prematurely will be followed up until the end of the study (for further details please see Sections 6.2.2 and 6.2.3).

Patients who drop out during the screening phase prior to randomisation (Visit 2) will be considered a screen failure. They have to be recorded as screen failures in the electronic Case Report Forms (eCRFs), along with the reason for failing screening, and no further follow-up is required.

Patients who discontinue or withdraw from the study after randomisation (Visit 2) will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the eCRFs. The data will be included in the trial database and will be reported.

Patients who withdraw or discontinue from the trial after randomisation will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Advice of the independent DMC, decision by an Independent Ethics Committee (IEC) /Institutional Review Board /(IRB) or Competent Authority (CA)
2. Failure to meet expected enrolment goals overall or at a particular trial site
3. Emergence of any efficacy/safety information that could significantly affect continuation of the trial
4. Violation of GCP, the CTP, or the contract by a trial site or Investigator, disturbing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and comparator products

The investigational product dabigatran etexilate and the comparator warfarin will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. The composition of these drugs capsules are detailed in Table 4.1.1: 1 and Table 4.1.1:2.

Table 4.1.1: 1 Dabigatran etexilate (Investigational drug)

Substance: Brand name:	Dabigatran etexilate Pradaxa®
Pharmaceutical formulation:	Capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	110mg and 150mg
Total Daily dose	220mg; 300mg 1 x 110mg capsule b.i.d. (total daily dose 220mg) 1 x 150mg capsule b.i.d. (total daily dose 300mg)
Route of administration:	*p.o.*

The main excipients of the dabigatran capsule include tartaric acid, acacia, hypromellose, dimeticone, talc, hydroxypropylcellulose, HPMC (hydroxylpropylmethylcellulose) 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 Warfarin (active comparator)

Substance:	Warfarin
Pharmaceutical formulation:	Tablet
Source:	Teva UK Limited, UK
Total Daily dose	1mg; 3mg; 5mg As needed to maintain a target INR of 2.0- 3.0 (2.0-2.5 if feasible)
Route of administration:	*p.o.*

For easy identification warfarin tablet strengths will have a different colour label.

The warfarin sodium tablets are composed of lactose monohydrate, starch (pregelatinised, maize), dispersed erythrosine lake, sodium starch glycolate and magnesium stearate.

Patients will take the warfarin q.d.. The individual doses will be titrated without splitting of the tablet as needed to maintain a target INR of 2.0 - 3.0. If feasible, an INR of between 2.0 – 2.5 should be targeted. INR will be measured at least every two weeks for the first three months in patients newly commencing warfarin, otherwise at least every month throughout the study (more frequently immediately after initiation of warfarin therapy or if required, according to clinical judgement).

All patients will also take clopidogrel (75mg q.d.) or ticagrelor (90mg b.i.d.) according to the local label for at least 12 months after randomisation (in addition to either dabigatran etexilate or warfarin). After 12 months of treatment the clopidogrel or ticagrelor can be discontinued or switched to ASA (≤ 100mg q.d.) at the discretion of the Investigator.

For patients randomised to receive warfarin:

Patients randomised to receive warfarin will receive ASA (≤ 100mg q.d.) for either one month in patients with a BMS and for three months in patients with a DES.

Warfarin and dabigatran etexilate supplies will be managed using the IRT system.

4.1.2 Method of assigning patients to treatment groups

Inclusion and exclusion criteria should be assessed at screening to ensure inclusion of eligible patients. After having signed the informed consent form, patients should complete the screening visit including specified procedures (see the Flow Chart).

Eligible patients who meet all inclusion and none of the exclusion criteria at Visit 2 will be randomised to receive either dabigatran etexilate 110mg, dabigatran etexilate 150mg or warfarin (see Section 3.1). In addition, patients will be stratified by age (<80 or ≥80 years

old) and region (Europe (EU)/Rest of World (ROW) or USA). This stratification will be performed dynamically by the IRT.

The dose of warfarin for the patient will be adjusted to ensure the INR for the patient is maintained at a level of 2.0 – 3.0. If feasible, an INR of between 2.0 – 2.5 should be targeted.

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 will be described in a user guide/manual, a copy of which will be available in the ISF.

The IRT will assign the correct kit number for dabigatran etexilate for the patients at each time point, but for the warfarin patients, individual management will be by the Investigator.

4.1.3 Selection of doses in the trial

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

4.1.4 Drug assignment and administration of doses for each patient

Each patient will be randomised at Visit 2 to receive either dabigatran etexilate (110mg or 150mg b.i.d.) or warfarin. The first dose of trial medication will be taken, between 6 hours after sheath removal and preferably within 72 hours post PCI, with haemostasis assured, however up to 120 hours post PCI is allowed.

Patient randomised to receive dabigatran etexilate:
It is permitted for patients to receive bridging therapy with a parenteral anticoagulant according to local practice before switching to dabigatran etexilate. Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of parenteral anticoagulant would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous (i.v.) unfractionated heparin (UFH)). See Appendix 10.1 for guidance how to switch from an anticoagulant to dabigatran etexilate.

Dabigatran etexilate capsules should be taken in the morning and in the evening (one at each timepoint), at the same time every day with a full glass of water. The capsules must not be crushed, nor opened and can be taken with or without food. If dyspeptic symptoms occur, the Investigator should consider adding a proton pump-inhibitor (PPI) or H2-blocker to the concomitant therapy of the patients.

The interval between doses should be as close to 12 hours as possible.

If a dose of dabigatran etexilate is missed for any reason, the forgotten dose may still be taken up to six hours prior to the next scheduled dose. From six hours prior to the next scheduled

dose on, the "missed" dose should be omitted. A double dose to make up for missed individual doses must not be taken.

Any patient that decides to discontinue study medication should be considered for a switch to an appropriate (non-study) anticoagulant according to local practice. For patients receiving dabigatran etexilate, continuation of study drug for 2-3 days to assist bridging may be appropriate. For recommendations on how to switch from dabigatran etexilate to other anticoagulants see Appendix 10.2).

Patient randomised to receive warfarin:
Anticoagulant bridging therapy (according to local practice) is at the discretion of the Investigator (see Appendix 10.1).

Warfarin compliance will be monitored by means of the INR rather than by pill counts as it is a more accurate and biologic measure of pharmacodynamic effect than pill counts. Warfarin patients will usually be managed by their Investigator. However, Investigators will also be able to assign INR monitoring to a local anticoagulation clinic. All dose adjustment will be done according to usual clinical practice. The Investigator will be responsible for reporting INR results and the dose of warfarin prescribed.

For patients initiating warfarin, INR should be measured at least every two weeks for the first three months to obtain target INR as soon as possible and to avoid over- or under-dosing. Thereafter, minimum acceptable intervals for INR measurements are every month. More frequent INR measurements will be done as necessary at the discretion of each Investigator or anticoagulation clinic.

To aid Investigators, a validated normogram, will be provided which will indicate recommended dose changes and INR re-testing times for different INR values. This normogram requires more frequent INR monitoring after out-of-range INR values have occurred.

Numerous factors, alone or in combination, may influence the patient's response to anticoagulants. Thus to ensure adequate control it is recommended that additional INR measures are done when other medications are initiated, discontinued or taken irregularly and/or diet changes. All patients should be educated about potential interactions with other medications, herbal preparations and foods and about the importance of monitoring. INR measurements can be performed independently from the scheduled study visits (see Flow Chart and Section 6), however all available INR values should be entered into the eCRF. It is critical to obtain the best possible level of INR control.

Regular study treatment will be completed with the last dose of trial medication being taken on the evening before or the morning of the EOT visit. If the trial medication is to be terminated the patient should switch to an appropriate (non study) anticoagulant according to the local practices.

For recommendations on switch from dabigatran etexilate and study warfarin to other anticoagulants see Appendix 10.2.

Clopidogrel or ticagrelor
All patients will also receive clopidogrel or ticagrelor for at least 12 months following randomisation. The decision as to whether the patient should receive clopidogrel or ticagrelor is at the discretion of the Investigator. This background medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

ASA:
Patients who require ASA treatment as detailed in Section 4.1.1 will also receive ASA (≤100mg per day). This background medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label trial; treatment allocation to the Investigators and patients will not be concealed throughout the study. The eCRF will contain information on randomised treatment. Trial medication will be identified by a medication code number. Despite the trial being open label, all activities conducted by the trial team will be performed in a blinded manner until database lock.

For justification of the PROBE design chosen for this study see Section 3.2.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

Dabigatran etexilate will be provided in kits. Each kit will contain four bottles that each contains 60 capsules of either 110mg or 150mg dabigatran etexilate. The number of kits provided to the patient will vary depending on the time between visits.

Patients on warfarin will receive the required combination of 1mg, 3mg and 5mg tablets in bottles or blister packs according to their actual needs as defined by the measured INR value. Each warfarin bottle will contain 66 tablets. Each blister pack will contain 70 tablets. Warfarin supplies should be checked at each visit to ensure the patient has sufficient quantity and that expiry dates will not be compromised prior to the next clinic visit.

Supply and re-supply will be managed by the IRT.

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 dabigatran etexilate 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 Investigator / pharmacist / investigational drug storage manager 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 process outlined in the ISF should be followed.

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 authorised 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, blisters and outer boxes (empty or filled) must be either returned to the Sponsor, or, following written authorisation 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

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 / IEC,
- 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. competent authority,
- availability of the curriculum vitae of the Principal Investigator,
- availability of a signed and dated CTP or immediately imminent signing of the CTP (in exceptional cases, medication could already be sent to the site, before its activation via IRT)
- availability of the proof of a medical licence for the Principal Investigator, if applicable
- 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 product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates and the unique code numbers assigned to the investigational product(s) 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 product(s) received from the sponsor.

At the time of return to the sponsor, the Investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

For non-investigational medicinal products (NIMPs), a system allowing traceability will be implemented (please refer to Section 4.2.1 for the definition of a NIMP in this trial). This will include the following:

- documentation of intake of the NIMP in the source data (e.g. name of NIMP, how much and when it was taken [but no unit count will be necessary])

- documentation of intake of NIMP in the eCRF.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Any additional drugs considered necessary for the patient's welfare may be given at the discretion of the Investigator and with due consideration of the information provided below.

Comprehensive details of concomitant medication of special interest (e.g. antiplatelet medication, parenteral anticoagulant, thrombolytic agent, GPIIb/IIIa antagonist, VKA, therapies for bleeding management, novel direct oral anticoagulant) administered to the patient from 30 days prior to Informed Consent until the patient completes follow-up should be recorded in the eCRF. Abbreviated information will be collected for any other concomitant therapy.

Certain concomitant therapies (e.g. fibrinolytics, anticoagulants other than warfarin/ dabigatran etexilate) or surgery/intervention may require the temporary discontinuation of warfarin or dabigatran etexilate. Study medication should be restarted as soon as safely possible. In case of a temporary interruption, bridging therapy with a parenteral anticoagulant is allowed at the discretion of the Investigator (see Appendix 10.1 for guidance on bridging therapy). 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 dose.

The concomitant administration of PPIs is strongly recommended in patients without clinical contraindications for those agents, to reduce the risk of GI bleeding. In patients receiving clopidogrel, PPIs that do not interact with the CYP2C19 (lanzoprazole, pantoprazole, etc.) should be used.

4.2.1 Rescue medication, emergency procedures, and additional treatments

In this trial clopidogrel, ticagrelor and ASA are considered a NIMP. This means that in the event of a serious adverse event (SAE), the Investigator will assess the causal relationship of the SAE to the NIMP. Further details regarding SAE reporting can be found in Section 5.2.2.3.

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies that may occur during the study.

4.2.1.1 Major Bleeds

Dabigatran Etexilate Treated Group:
If a patient experiences major bleeding, the study medication should be temporarily stopped and the source of bleeding investigated and treated. This will generally involve coagulation testing (e.g. aPTT, TT, ECT), platelet count, and possibly transfusion, diagnostic procedures and/or surgical haemostasis.

The recommendations given below are derived from guidelines to manage bleeding with dabigatran etexilate. See Section 4.2.1.7 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 haemostasis 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, P13-06400]. As protein binding is low, dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting. Clearance of dabigatran by haemodialysis 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. There is some experimental evidence to support the role of agents such as activated prothrombin complex concentrates (APCC, e.g. 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 long acting antiplatelet drugs have been used. All symptomatic treatment will be given according to the treating physician's judgement.

Re-administration of study medication (at the same dose as before) after the bleeding has resolved and haemostasis has been achieved, is at the discretion of the Investigator. In the case of a temporary stop of dabigatran etexilate bridging therapy with a parenteral anticoagulant with e.g. UFH or LMWH (according to local practice) is at the discretion of the Investigator. See Appendix 10.1 for additional information related to bridging.

A summary of how to manage bleedings on dabigatran etexilate is presented in Figure 4.2.1.1: 1.

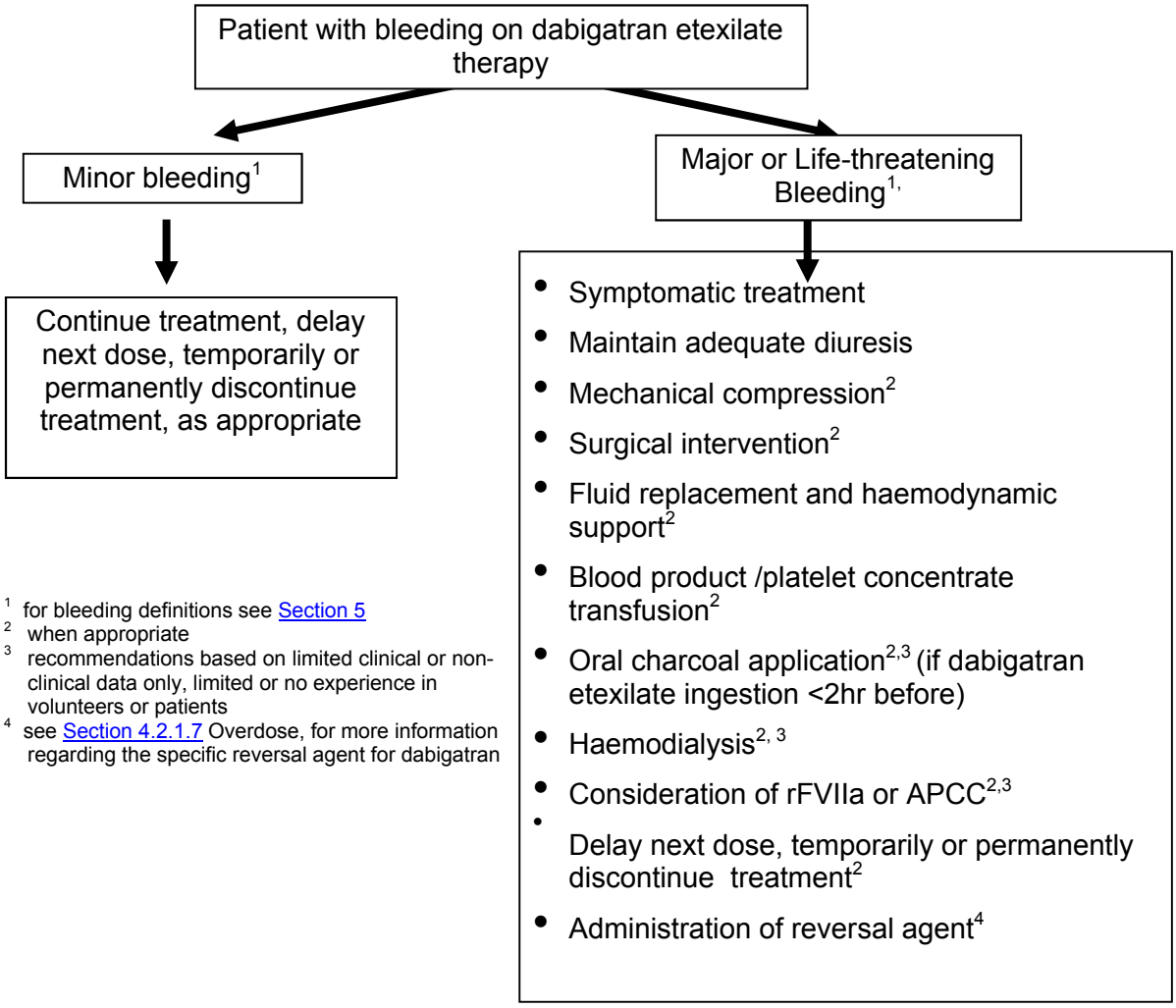

Figure 4.2.1.1: 1 Management of bleeding on dabigatran therapy [P10-03790]

Warfarin Treated Group:

If a patient experiences a major bleed warfarin should be temporarily stopped. The anticoagulant effect of VKAs can be reversed with vitamin K, prothrombin complex concentrates and/or fresh frozen plasma. Re-administration of warfarin after the bleeding has resolved and haemostasis has been achieved is at the discretion of the Investigator. Bridging therapy, e.g. UFH until the INR has returned back to the target range, is at the discretion of the Investigator (see Appendix 10.1).

4.2.1.2 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 be stopped in these cases.

4.2.1.3 Emergency and Elective Surgery

Dabigatran Etexilate Treated Group:
Preoperative Phase:

Emergency Surgery
In the case of emergency surgery, study medication should be discontinued. If possible, surgery should be postponed until 12 hours, or longer in case of renal failure, 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 or diluted TT (where available), activated partial thromboplastin time (aPTT) or the ECT. For further details on results of coagulation times expected with dabigatran, see section on elective surgery below.

See Section 4.2.1.7 Overdose, for more information regarding the specific reversal agent for dabigatran.

Elective Surgery

Physicians may consider the following information regarding dabigatran etexilate 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 4.2.1.3: 1]. Serum creatinine should normally be checked 1-2 weeks before surgery and the CrCl should be calculated using the Cockcroft-Gault formula (Section 5.2.3). Patients with a CrCl <30mL/min during the course of this study should not be receiving study medication (see Section 3.3.4.1).

The following is a guide to the discontinuation of dabigatran etexilate (under special consideration of the half-life of dabigatran depending on renal function) before surgery taking renal function and additional risk factors into account. In patients with normal renal function, discontinuation of two doses of dabigatran etexilate will decrease plasma levels to approximately 25% of steady state trough levels and discontinuation of four doses will decrease dabigatran plasma levels to approximately 5-10% of steady-state trough levels.

Table 4.2.1.3: 1 Recommendations on cessation of study drug in relation to the timing of major surgery

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

[1] CrCl can be estimated using serum creatinine by the Cockcroft-Gault formula (see Section 5.2.3). Patients who develop CrCl <30mL/min during the course of the trial should have study medication stopped (see Section 3.3.4.1).

[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 anaesthesia may also require complete haemostatic function.

In patients at high risk of bleeding, including those in whom severe renal dysfunction may occur in the course of the trial (<30mL/min CrCl), an elevated thrombin clotting time (TT) or diluted thrombin time ((dTT); only in countries where this assay is approved)) 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 TT/dTT should be performed 6-12 hours before elective surgery and a normal result as defined by the local lab should be obtained before a patient undergoes surgery. A persistently prolonged thrombin time (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.

In patients receiving chronic therapy with dabigatran etexilate 110mg b.i.d., the median peak aPTT is approximately 57 sec [U09-3249-02]. Assuming the baseline range of normal is between 22 to 40 sec (aPTT assay as used in RE-LY) this peak aPTT prolongation corresponds to approximately 2 times control [U11-1855-01]. Twelve hours after the last dose, the median aPTT is approx. 1.7 times control [U09-3249-02], (median trough aPTT prolongation for patients receiving 110mg BID in RE-LY: 48 sec) given adequate renal function, with less than 10% of patients exceeding 2.4 times control [U11-1855-01,U09-3249-02], (90th percentile trough aPTT prolongation for patients receiving 110mg b.i.d. in RE-LY: 69 sec). ECT shows a close linear correlation with the plasma concentrations of direct thrombin inhibitors, including dabigatran. Median ECT ratios over baseline of approx.1.8 at trough and 2.5 [U11-1855-01] at peak, have been observed after intake of dabigatran etexilate 110mg b.i.d. Coagulation times should be interpreted in relation to the timing of last drug intake of study medication (peak versus trough dabigatran levels). The

current version of the IB should be referenced for further information about dabigatran etexilate.

Post Procedural Period:
With the exception of cardiac surgery, dabigatran etexilate will be initiated as soon as the patient is haemodynamically stable and haemostasis is achieved. If oral medication is not feasible, bridging therapy with i.v. or subcutaneous (s.c.) UFH or s.c. Low Molecular Weight Heparin (LMWH) should be considered at the discretion of the Investigator (see Appendix 10.1).

Note: In patients where renal function is impaired or procedures undertaken which may temporarily compromise renal function, a serum creatinine should be performed and CrCl calculated based on the Cockcroft-Gault formula. In patients receiving dabigatran etexilate, if CrCl drops to <30mL/min during the course of the study, study medication should be stopped and bridging therapy may be considered. Study drug dabigatran etexilate can be re-started if CrCl recovers to ≥30mL/min within seven days; otherwise it should be permanently discontinued for the duration of the trial and the patient followed until the trial completes. A patient should also be permanently discontinued from study drug, if CrCl drops to <30mL/min at two different occasions during the trial. See Section 3.3.4.1.

WarfarinTreated Group:
Preoperative Phase:
Bridging therapy with a parenteral anticoagulant should be considered depending on the length of study drug interruption. Bridging therapy is at the discretion of the Investigator and can be performed according to local practice (see Appendix 10.1 for guidance).

Post Procedural Period:
Anticoagulation can be started as soon as clinically feasible with i.v. (unfractionated) or s.c. LMWH and simultaneously with study warfarin until the INR is ≥2.0. Parenteral bridging therapy should be stopped when target INR is achieved (see Appendix 10.1 for guidance).

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture

Dabigatran and Warfarin Treated Group:

Procedures such as spinal anaesthesia may require complete haemostatic function. See Table 4.2.1.3: 1 for recommendations on when to stop dabigatran before spinal/epidural anaesthesia. For patients randomised to Warfarin, INR measurements should be performed to ensure that coagulation is under control.

The risk of spinal or epidural haematoma 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 haemostasis is achieved, but at minimum an interval of at least one hour should elapse for all patients. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

4.2.1.4 Stroke

Patients with documented or suspected stroke should be managed according to usual clinical practice. It is anticipated that in most cases study drug will be withheld until a computed tomography (CT) or magnetic resonance (MR) imaging scan has been obtained.

Ischaemic stroke:
For ischaemic stroke, ASA and/or clopidogrel, or ASA/dipyridamole (the latter in lieu of clopidogrel) may be administered as indicated according to usual clinical practice. Anticoagulation with the study drug can be continued at the discretion of the local Investigator, in the absence of evidence of bleeding [P13-06400].

Fibrinolytics may be considered for ischaemic stroke, if a normal aPTT, ECT or TT test is obtained for patients receiving dabigatran etexilate, or if the INR is ≤ 1.7 in patients receiving warfarin.

Haemorrhagic stroke:
For haemorrhagic stroke or other intracranial bleeding, consultation with a coagulation expert and a neurosurgeon is recommended.

See Section 4.2.1.1 and Figure 4.2.1.1: 1 for details relating to how to manage bleeding on dabigatran etexilate or warfarin.

Reintroduction of study treatment following a stroke:

Dabigatran Etexilate Treated Group:
The decision about restarting dabigatran etexilate following a stroke is at the discretion of the Investigator. The following recommendations on when to restart dabigatran etexilate are provided for guidance only.

Table 4.2.1.4: 1 Recommendations on restarting dabigatran etexilate following a stroke [P12-02400]

Stroke Severity	**Restart of Dabigatran etexilate**
TIA	as soon as imaging has excluded a cerebral haemorrhage
Mild Stroke	3-5 days after stroke onset
Moderate Stroke	5-7 days after stroke onset
Severe Stroke	2 weeks after stroke onset

Warfarin Treated Group:
The decision about restarting study warfarin following a stroke and its exact timing is at the discretion of the Investigator.

4.2.1.5 Acute Coronary Syndrome

In patients with documented or suspected ACS, study drug should be temporarily discontinued if other anticoagulants (e.g. UFH) are deemed necessary. ASA, clopidogrel and glycoprotein IIb/IIIa inhibitors may be administered according to usual clinical practice.

Dabigatran Etexilate Treated Group:
In patients receiving dabigatran etexilate, unfractionated or low-molecular-weight heparin should be withheld until at least 12 hours have passed since the last dose of dabigatran etexilate or the aPTT is less than 1.5 x ULN.

- If the aPTT is between 1.2 and 1.5 x ULN, UFH may be commenced with or without a loading dose at the discretion of the physician and LMWH may be commenced at the usual therapeutic dose (without an i.v. loading 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.

Warfarin Treated Group:
Unfractionated or low-molecular-weight heparin (or other anticoagulants) may be administered in warfarin treated patients according to usual clinical practice.

4.2.1.6 Other Medical Intervention

Percutaneous Coronary Intervention (PCI):

Dabigatran etexilate should be discontinued in advance and bridging anticoagulation administered according to local practice. ASA, clopidogrel or ticagrelor use is permitted according to usual clinical practice.

For patients randomised to Warfarin, refer to Section 4.2.1.3.

Study medication can be reintroduced between 6 hours after sheath removal with haemostasis assured, as considered appropriate by the Investigator.

Coronary Artery Bypass Graft (CABG) Surgery:

Dabigatran etexilate should be discontinued in advance and bridging anticoagulation administered according to local practice. Usual priming therapies for cardiovascular surgical procedures are allowed. Patients with renal dysfunction may have elevated concentrations of dabigatran due to longer half-lives of active drug (see Table 4.2.1.3: 1). If bypass surgery is to start during elevated plasma concentrations of dabigatran etexilate 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 dTT/TT measurements. For further advice on

emergency and elective cardiac surgery see Section 4.2.1.3 and corresponding Table 4.2.1.3: 1.

For patients randomised to Warfarin, refer to Section 4.2.1.3.

Cardioversion:

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Other Minor Procedures:

In the case of other elective procedures or minor surgery, dabigatran etexilate can be continued until 24 hours before the procedure.

For patients randomised to Warfarin, refer to Section 4.2.1.3.

Reintroduction following medical intervention:
Dabigatran etexilate can be re-commenced at the cessation of parenteral anticoagulant treatment according to the same regimen as at randomisation, provided clinically indicated and in accordance with the recommendations in Appendix 10.1.

For patients randomised to Warfarin, refer to Section 4.2.1.3.

4.2.1.7 Overdose

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. In cases of suspected overdose it may be advisable to assess the anticoagulation status of a patient. A TT measure with the calibrated Hemoclot® thrombin inhibitor assay indicating a dabigatran plasma concentration of >200ng/mL (approximately >65 seconds) prior to the next drug intake after 150mg twice-daily dosing (trough measure, i.e. 10-16 hours after the last drug intake) may be associated with an increased risk of bleeding. An aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT > 2-fold ULN at trough, i.e. when the next dose is due, may be associated with a higher risk of bleeding.

For a summary how to manage bleeding events on dabigatran etexilate see also Section 4.2.1.1 and corresponding Figure 4.2.1.1: 1.

Specific reversal agent to dabigatran

A specific reversal agent (idarucizumab) has been developed and is currently available in many countries and being reviewed for registration in various other 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 eCRF of the appropriate trials.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Corticosteroids or NSAIDs may be used if clinically indicated according to current treatment guidelines but it is strongly recommended to avoid these if possible. It should be noted that the use of any of these agents with warfarin or dabigatran etexilate is likely to increase the risk of bleeding.

The following treatments should not be taken during the active treatment phase of the trial:

1. Treatment with ticlopidine or prasugrel

2. Fibrinolytic agents (see Section 4.2.1.4 for exception)

3. GPIIb/IIIa antagonists (e.g. abciximab, tirofiban)

4. Treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone and rifampicin, phenytoin, carbamazepine or St. John's Wort

5. Diypyridamole, rivaroxaban, apixaban and edoxaban, or other oral anticoagulants (e.g. VKAs)

6. ASA - except where specified in the protocol for patients randomised to the warfarin arm or in both treatment arms after 12 months of treatment if clopidogrel or ticagrelor is switched to ASA (≤ 100mg q.d.) at Investigator discretion. The patients should be advised to not use additional ASA-containing over-the-counter medications.

The Investigator is alerted to the use of concomitant administration of moderate to strong P-gp inhibitors (e.g. such as amiodarone, verapamil, quinidine, nelfinavir, posaconazole, ritonavir, saquinavir and tipranavir+ritonavir or lopinavir+ritonavir) or P-gp inducers in this study due to a potential risk of higher or lower plasma levels of dabigatran and consequent exaggerated or reduced pharmacodynamic effect of dabigatran etexilate (notably bleeding risk). Concomitant use of such drugs is not prohibited in this study *per se* (except for treatment with ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus dronedarone, rifampicin, phenytoin, carbamazepine or St. John's Wort), but should be used with caution or, at Investigator discretion, switched to a suitable alternative.

In the RE-LY study, patients treated concomitantly with verapamil had on average at trough and two hours post-dose dabigatran plasma concentrations increased by only 16% and 20%, respectively. Accordingly, the annualised bleeding rates in patients who had used verapamil at least once together with warfarin, dabigatran etexilate 110mg b.i.d. or 150mg b.i.d. were 3.33%, 3.09% and 3.92%, respectively. If verapamil is initiated during the course of this trial in a patient randomised to receive dabigatran etexilate 150mg b.i.d, consideration to separate the timing of administration of dabigatran etexilate and verapamil should be given.

If dabigatran etexilate is given at least two hours before verapamil for the first three days, the increase of dabigatran exposure will be reduced compared to taking verapamil and dabigatran etexilate at the same time-point.

In the RE-LY study, concomitant administration of amiodarone or quinidine and dabigatran etexilate did not increase the relative risk of bleeding compared to patients on warfarin and amiodarone or quinidine. Therefore, no dose adjustment of dabigatran etexilate is considered necessary in this study for patients receiving amiodarone or quinidine as co-medications.

The strong P-gp inducer rifampicin (and potentially also carbamazepine, phenytoin or St. John's Wort) is associated with a potential risk of lower plasma levels of dabigatran (in a Phase I trial rifampicin decreased total dabigatran peak plasma concentration and total exposure (AUC) by 65.5% and 67%, respectively) and consequent reduced pharmacodynamic effect of dabigatran etexilate (notably increased thromboembolic risk) and should therefore not be taken during the course of this trial.

A list of common P-gp inhibitors will be provided in the ISF.

The concomitant use of dabigatran etexilate with the following treatments has not been studied and may increase the risk of bleeding: UFHs (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, apixaban, edoxaban, prasugrel, direct thrombin inhibitors, VKAs and the P-gp inhibitors itraconazole, tacrolismus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (U11-1642-01) or selective serotonin norepinephrine re-uptake inhibitors (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 GI bleeding, increases.

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

4.2.2.2 Restrictions on diet and life style

Dabigatran etexilate can be taken with or without food. There are no specific dietary restrictions with dabigatran etexilate, whereas patients randomised to VKA need to follow dietary instructions regarding their vitamin K intake. They must also be aware of the potential risk of over- or under dosing with changes of co-medications (e.g. use of antibiotics) or concomitant diseases (e.g. diarrhoea).

4.3 TREATMENT COMPLIANCE

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

Dabigatran Etexilate:
Based on capsule counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100.

Doses taken on the current visit day will be excluded from the count and doses taken on the previous visit day will be included in the count.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}^{1}}$$

A patient will be considered as non-compliant if the number of doses taken is not between 80-120% of the expected number of doses. If compliance does not meet this range the patient should be asked to provide an explanation and re-informed about the purpose and conduct of the trial. Non-compliance should be discussed with BI.

General principles regarding the evaluability of non-compliant patients are outlined in Section 7.3. Decisions about evaluability of patients will be made at the Blinded[2] Report Planning Meeting (BRPM) and at the latest prior to database lock.

Warfarin:
Warfarin compliance will be monitored by means of the INR rather than by pill counts as it is a more accurate and biologic measure of pharmacodynamic effect than pill counts. Investigators will be able to assign INR monitoring to a clinic outside the investigational site and dose adjustments will be made according to usual clinical practice. However, the Investigator will be responsible for reporting INR results, dose management of the patient and drug accountability of the warfarin prescribed. Patients must have the INR measured at least every two weeks for first three months, when commencing warfarin for the first time, otherwise at least monthly measurement are required. More frequent INR measurements may be done as necessary at the discretion of each Investigator or anticoagulation clinic. To aid Investigators, a validated nomogram, will be provided in the ISF, which will indicate recommended dose changes and INR re-testing times for different INR values. This nomogram requires more frequent INR monitoring after out-of-range INR values have occurred.

The quality of warfarin therapy for each patient will be assessed by reporting the number of INR values within the indicated therapeutic target range (2.0 – 3.0 and 2.0 – 2.5) as well as those above and below this range. The Rosendaal method [R08-1695] will be used to evaluate the percentage of time that a patient's INR is in range (i.e. time in therapeutic range

[1] The number of tablets which should have been taken should take into account any temporary interruptions in study drug
[2] Despite the trial being open label, the trial team will be blinded during medical quality review.

(TTR)). For each calendar month, the mean of all INR values will be reported. This will be calculated for each patient, for each centre, for each country and for the whole study. The mean percentage of time of INR in range will be calculated for each centre and each country during the trial conduct to monitor the INR control. The percentage of time of INR in range for each country and for the trial will be reported at study end.

Analyses from clinical trial data for SPAF have identified a minimum threshold of TTR of at least 60%, below which warfarin may be considered as no more effective than DAPT [P07-02268]. The goal for the study is that the INR control should be at least as good as that achieved for anticoagulation in the historical control studies. The mean TTR [INR 2.0-3.0] for warfarin in RE-LY was 64% (median 67%) [U09-3249-02].

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints of efficacy

The primary endpoint for this trial is a safety endpoint. See section 5.2.1. There are no primary efficacy endpoints.

The secondary efficacy endpoints (all time to first event) are:

1. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG

2. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)

3. Individual outcome events:
   - All death
     - Cardiovascular death
     - Non-cardiovascular death
     - Undetermined
   - MI
   - Stroke
   - SE
   - Stent thrombosis

4. Composite endpoint of death + MI + stroke

5. Unplanned revascularisation by PCI/CABG

See Section 7.3.1 for details of the analyses.

5.1.2 Assessment of efficacy

These endpoints will be adjudicated by the IAC using criteria outlined in its charter governing the adjudication process.

5.1.2.1 Death

Death from any cause includes cardiovascular death, non-cardiovascular-death and undetermined cause of death, as classified by adjudication [R13-4874, R15-0010].

Cardiovascular death

Cardiovascular (CV) death '*/71+%(+%)#$&%(17#'*2&,9)*)/1#%<!4 (1++%*/)&+')/ +%)#$4 +%)#$-1%#, $%)&'#)'71&4%+%)#$ +1% #, (#&,=%4 +%)#$.>1%5&„/%+1&%(%)#$-1%#, .> $)%9,&&$)2%* + +%)#$-1%#, ,#$%& /)1(%(;

Non-cardiovascular death

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- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune
- (including autoimmune)
- Haemorrhage that is neither cardiovascular bleeding or a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose
- Neurological (non-cardiovascular)
- Malignancy
- Other non-CV (to be specified)

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.

Further details on death classification will be specified in the adjudication charter.

5.1.2.2 Myocardial infarction

Criteria for acute MI [R13-4872]:

The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia.

Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

    - Symptoms of ischaemia

    - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)

    - Development of pathological Q waves in the ECG

    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

    - Identification of an intracoronary thrombus by angiography or autopsy

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased

- PCI related MI is arbitrarily defined by elevation of cTn values > 5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values ≥20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL

- CABG related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for fatal MI

Death due to Acute MI refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. Acute MI (for criteria see above) should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (e.g.

PCI, CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI [R15-0010].

Silent MI

Silent myocardial infarction will be retrospectively diagnosed by the appearance of significant new Q-waves on an ECG performed after randomisation. In such cases, the date of the event is recorded as the midpoint between the ECG with new Q-waves and the prior normal ECG.

Criteria for prior MI [R13-4872]:

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause
- Pathological findings of a prior MI.

5.1.2.3 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 haemorrhage or infarction [DEF@ GHI@R15-0010J.

Ischaemic Stroke

Ischaemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Haemorrhage may be a consequence of ischaemic stroke. In this situation, the stroke is an ischaemic stroke with haemorrhagic transformation and not a haemorrhagic stroke.

Haemorrhagic stroke

Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage.

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 haemorrhage or infarction but with insufficient information to allow categorisation as ischaemic or haemorrhagic 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 modified Rankin Scale (mRS) at the onset of stroke and at 3 months after recurrent stroke, if this time frame falls anytime within the study participation. Disabling stroke is defined as a stroke with mRS ≥4 at 3 months (see Appendix 10.3 for definition of mRS).

5.1.2.4 Systemic embolism

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

5.1.2.5 Stent Thrombosis

There will be three categories of evidence to define stent thrombosis:

1. Definite Stent Thrombosis

A definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation [R13-4874, R15-0010]:

- Angiographic confirmation of stent thrombosis[1]
  - The presence of a thrombus[2] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
    - Acute onset of ischaemic symptoms at rest
    - New ischaemic ECG changes that suggest acute ischaemia
    - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
    - Non-occlusive thrombus

    Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of

[1] The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
[2] Intracoronary thrombus

contrast material within the lumen, or a visible embolization of intraluminal material downstream

- Occlusive thrombus

Thrombolysis In Myocardial Infarction (TIMI) 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

- Pathological Confirmation of Stent Thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

2. Probable Stent Thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

3. Possible Stent Thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

5.1.2.6 Repeated revascularisation by PCI/CABG

Repeated revascularisation due to objectively documented recurrent ischaemia, stent thrombosis or ACS. Unplanned revascularisation is any repeated revascularisation not planned prior to informed consent. These cases will undergo adjudication for confirmation of whether the event was unplanned, the type of procedure, the indication and if it is a target lesion revascularisation.

All details of documentation required for adjudication will be provided in the ISF.

5.2 SAFETY

5.2.1 Endpoints of safety

The primary endpoint for this trial is time to first ISTH MBE or CRNMBE. For definition of CRNMBE see section 5.2.2.1.

Other safety endpoints are:

1. Major bleeding (ISTH)

2. CRNMBE (for definition see section 5.2.2.1)

3. Clinically relevant bleeding measured using the following definitions:

   - Bleeding Academic Research Consortium (BARC) ≥3
   - TIMI group - Major and Minor

4. Minor and total bleeding (ISTH, BARC and TIMI)

5. Intracranial haemorrhage

5.2.2 Assessment of adverse events

5.2.2.1 Assessment of Bleeding events

Patients should be carefully assessed for signs and symptoms of bleeding. Bleeding will be classified as major, Clinically Relevant Non Major Bleeding Event (CRNMBE) or minor. Major bleeds will be further sub classified as life-threatening and other major bleeds. The location of the bleeding including the specific critical area or organ into which the bleeding occurred and whether or not it prolongs hospitalisation will be recorded. The following definitions are specified for bleeds:

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 haemoglobin 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

- Fatal bleed

Definition of a CRNMBE
A clinically relevant non-major bleeding event is a clinically overt bleed that does not meet

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

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 for bleeding

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 minor bleed
Minor bleeds are clinical bleeds that do not fulfil the criteria for major bleeds. Minor bleeds will be further divided to those that are CRNMBE, (see above) and those that are not.

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 haemoglobin of at least 5g/dL; transfusion of at least four units of blood or packed cells, associated with hypotension requiring the use of i.v. inotropic agents; necessitated surgical intervention.

Definition of intracranial haemorrhage (ICH)
Intracranial haemorrhage (ICH) comprises the subtypes of intracerebral bleeds, subdural bleeds, epidural bleeds and subarachnoid bleeds and will be recorded.

Definition of a fatal bleeding
Fatal bleeding is defined as a bleeding event that the IAC determines is the primary cause of death or contributes directly to death.

Total bleeds
This is the sum of all major and minor bleeds.

In addition to the specified primary definition to be used for major bleeds in this trial (according to ISTH criteria, see above), components of the further bleeding definitions will be prospectively collected. It will be the responsibility of the IAC to categorise investigator-reported bleeding events according to the following pre-specified secondary classifications:

- **BARC** (R13-4065, R13-4066)
- **TIMI** (P07-10190)

TIMI Classification of Bleeding

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

The TIMI definition of bleeding uses four categories: major, minor, minimal and none, with definitions of the first three as follows:

- Major
  Intracranial haemorrhage or a ≥ 5g/dL decrease in haemoglobin concentration or a ≥ 15% absolute decrease in haematocrit

- Minor
  Observed blood loss: ≥ 3g/dL decrease in haemoglobin concentration or ≥ 10% decrease in haematocrit.
  No observed blood loss: ≥ 4g/dL decrease in haemoglobin concentration or a ≥ 12% decrease in haematocrit

- Minimal
  Any clinically overt sign of haemorrhage (including imaging) associated with a < 3g/dL decrease in haemoglobin concentration or < 9% decrease in haematocrit.

BARC Definition for Bleeding[1]

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation

Type 3:

- Type 3a
  - Overt bleeding plus haemoglobin drop of 3 to < 5 g/dL* (provided haemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding

[1] Footnotes to BARC definition:
CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL haemoglobin).
†Cell saver products are not counted.

- Type 3b
  - Overt bleeding plus haemoglobin drop ≥ 5 g/dL* (provided haemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
  - Bleeding requiring i.v. vasoactive agents

- Type 3c
  - Intracranial haemorrhage (does not include microbleeds or haemorrhagic
  - transformation, does include intraspinal)
  - Subcategories confirmed by autopsy or imaging or lumbar puncture
  - Intraocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 hour
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-hour period†[1]
- Chest tube output ≥ 2L within a 24-hour period

Type 5: fatal bleeding

- Type 5a
  - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

- Type 5b
  - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

The protocol specified study definitions will be used by the Adjudication Committee as outlined in its Charter governing the adjudication process.

5.2.2.2 Definitions of AEs

AE

[1] Footnotes to BARC definition:
CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL haemoglobin).
†Cell saver products are not counted.

An 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.

SAE

An 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 hospitalisation, 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of AE

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.

Outcome Events

Since efficacy and safety endpoints can also be SAEs, they can be treated as disease-related. These events 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 remit of the independent DMC is to protect patient safety by monitoring the incidence and clinical relevance of safety data collected throughout the conduct of this study.

In addition, for the safety parameters of primary interest, namely any bleeding event (see Section 5.2.2.1) and for the major mortality/morbidity clinical endpoints of interest (see

Section 5.2.2.2 and Section 5.1.2), a blinded IAC will be in place with the responsibility to confirm and classify all such events.

Any OE that occurs prior to randomisation and fulfils the criteria of an SAE will be reported in the standard expedited fashion as an SAE; however, if the patient has been randomised, these events will not be reported as SAEs, but entered in the eCRF as OEs.

OEs are therefore defined as follows:

- Any bleed
- All deaths
- All MIs
- All strokes
- All SE
- All TIAs
- All stent thromboses

The Investigator (or designee) will enter these OEs (even if they meet the criteria of an SAE) in the corresponding pages in the eCRF within 24 hours of awareness, as well as providing any defined supporting documentation (including imaging e.g. MR, CT, angiography). This will be provided by the Sponsor to the DMC and IAC, as defined in their respective charter. This procedure is defined in more detail in Appendix 10.4.

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.

Protocol-specified Adverse Events of Special Interest (AESI)

No AESIs are defined for this trial.

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 is defined as 6 days after last intake of trial medication.

5.2.2.3 Adverse event and serious adverse event reporting

Except where noted in Section 5.2.2.2, all AEs, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase) will be collected, documented and reported to the sponsor by the Investigator on the appropriate eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

For each AE, 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 a causal relationship assessment made by the Investigator.

The Investigator also has the responsibility to report any AEs occurring in the four weeks after a patient completes the trial. Any AEs reported to the sponsor during this phase must be documented in the safety database.

The Investigator does not need to actively monitor patients for AEs once the clinical trial has ended. However, if the Investigator becomes aware of an SAE that occurred after the patient has completed the clinical trial (including the REP and follow-up period), the Investigator should report it to the sponsor if the Investigator considers it relevant to BI investigational product.

The Investigator must report the following events via fax immediately (within 24 hours or the next business day, whichever is shorter) to the sponsor: SAEs and non-serious AEs relevant to the SAE.

BI has set up a list of AEs which are defined to be always serious. In order to support the Investigator with the identification of these "always serious AEs", if a non-serious AE is identified to be serious per BI definition and does not meet the definition of an OE, 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 an SAE 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 any further information to these events, a follow-up SAE report has to 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 ISF). 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). Congenital anomalies are always considered to be SAEs.

5.2.3 Assessment of safety laboratory parameters

Blood samples will be taken at the screening visit for those parameters required to verify eligibility (haemoglobin, platelets, ALT and / or AST, AP and creatinine (the latter to calculate CrCl according to the Cockcroft-Gault formula)) and will be analysed by a local laboratory. If standard of care local blood results are available, taken within 7 days prior to screening, these can be used to verify eligibility. From Visit 2 (randomisation) onwards, an abbreviated haematology panel and chemistry panel including liver and renal function testing (defined in Table 5.2.3:1) will be analysed by the central laboratory at the specific time points indicated in the flowchart. Central laboratory samples must be taken at the randomisation visit, prior to first intake of study medication.

The central laboratory will provide the required materials for processing the samples (except INRs and local testing at screening) 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.

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.

All blood samples can be taken in a non-fasting condition.

Table 5.2.3:1 Safety laboratory parameters

Chemistry	**Haematology**
ALT (SGPT)	Erythrocyte
AST (SGOT)	Haemoglobin
Alkaline Phosphatase	Haematocrit
Bilirubin total, fractionated if increased	Platelet Count
GGT	WBC
LDH	
Albumin	
Creatinine	
Creatinine Clearance*	
Glucose	
Potassium	
Sodium	
Total Protein	
Urea	

* According to Cockcroft-Gault formula

Pregnancy Testing
A urine pregnancy test will be performed locally on all women of child bearing potential at all clinic visits. In additional women of child bearing potential will be supplied with pregnancy tests and instructed to perform pregnancy testing every 4 weeks. Urine pregnancy tests will be provided.

Renal Function Measurements
CrCl will be calculated using the Cockcroft-Gault formula, as follows:

- For creatinine in µMol/L:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \times 1.23\ (\times 0.85 \text{ if female})}{\text{serum creatinine [µMol/L]}}$$

- For creatinine in mg/dL:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]}\ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$$

Please refer to Section 3.3.4.1 for guidance if a patient's CrCl is <30mL/min.

5.2.4 Electrocardiogram

All ECGs will be collected on standardised devices and stored at a central digital database provided by a central ECG service. At each visit as indicated in the Flow Chart a 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded. The ECGs will be evaluated by the Investigator or a designate for immediate investigation or treatment. In addition, the central ECG vendor will provide manual reading results which will be communicated to the Investigator for [redacted] further judgment and will be stored in the central database of the vendor.

Additional ECGs recorded outside the Investigator's facilities may be collected by the Investigator and transferred to the central database for safety reasons.

Upon receipt of an alert from the ECG vendor, the Investigator or designate is expected to review, sign and date the findings, record their clinical judgement in the source documents. Agreement with the findings should result in a reported OE or (S)AE, if judged to be clinically relevant. If the Investigator does not agree with the ECG reviewer's findings, a note should be made in the source regarding the review of the alert. Clinically relevant changes in the ECG will be reported as AEs.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical Examination

A cardiovascular focused physical examination will be performed by medical qualified personnel according to the flowchart. Documentation of and findings from the physical examination, must be part of the source documents available at the site. All 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 the EOT physical examinations will be recorded as AEs on the appropriate eCRF page, if judged clinically relevant by the investigator. In the event that clinically relevant findings are observed in the physical examination at the end of treatment, the patient should be followed by the Investigator until resolution of the event, or an agreement has been made with the Sponsor that follow-up is sufficient on that patient.

5.2.5.2 Vital Signs and Weight

BP and PR will be performed at every visit after resting for at least five minutes. For each patient, all BP recordings shall be made using the same type of instrument (i.e. manual BP recording vs. automatic digital vital signs monitor) on the same arm. Weight will be measured at the visits indicated in the flow chart in order to calculate CrCl according to Cockcroft-Gault. Any new clinically relevant findings that are identified will be reported as AEs.

5.3 OTHER

5.3.1 Other endpoint(s)

Transient Ischaemic Attacks will be collected and adjudicated. TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction [R13-4874, R15-0010]. All details of documentation required will be provided in the ISF.

5.4 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint for this study is a safety endpoint using the ISTH definition for major bleeding and CRNMBEs which are similar endpoints to those used in other contemporary clinical trials in the same setting (ClinicalTrials.gov: NCT01830543 and NCT02415400).

In order to allow bleeding incidence in this trial, to be compared to published data with other antithrombotic combinations, key components of the BARC bleeding classifications will be prospectively collected. Classifications of bleeding events (to various different scales and major/minor) will be confirmed by the IAC and provided on an on-going basis to the DMC.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study will consist of three sequential periods, Screening/Baseline Period of up to 5 days, a Treatment Period of up to approximately 30 months and a Follow up Period of four weeks. The maximum treatment duration is expected to be 30 months, however, the trial can conclude earlier, if adequate number of events are reported sooner or it can conclude later (or enrol 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 (Day 1). 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 (i.e. no permission can be granted by the Sponsor 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 (i.e. constituting a protocol violation) will be assessed prior to analysing the data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

No study procedures may be initiated prior to the patient signing the informed consent in compliance with ICH-GCP and local legislation.

6.2.1 Screening and run-in period(s)

6.2.1.1 Screening Visit (Visit 1)

Screening will be performed after successful PCI. All tests as detailed in the Flow Chart must be performed.

Screened patients should be registered in IRT. Only patients meeting the study criteria will be randomised. Patients who fail screening will not be followed up. Patients who fail screening should be registered as a screen failure in IRT.

6.2.2 Treatment period(s)

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 done, Visit 2 can be conducted including randomisation via IRT. Screening and randomisation can be on the same day, depending on the availability of the screening laboratory results.

Randomisation can occur immediately after successful screening and up to 120 hours post PCI, however, randomisation within 72 hours is preferable. The first dose of trial medication

will be taken between 6 hours after sheath removal and preferably within 72 hours post PCI (end of intervention i.e. when the last catheter used for PCI is removed), with haemostasis assured, however randomisation up to 120 hours post PCI is allowed.

Treatment visits will take place approximately every three months for the first 12 months of treatment and every six months thereafter. After month 12, phone calls will be conducted in between regular clinic visits. These calls are designed to encourage accurate and timely event reporting and continued engagement of patients.

As this is an OE driven trial, patients will remain in the treatment period until the necessary number of OEs is reached. 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 patients who discontinue treatment 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 (as indicated in the Flow Chart) ECGs will be performed and the collection of AEs, OEs (including completion of the bleeding questionnaire) and use of concomitant medication will be made.

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 permit collection of 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.

The patient will be asked to choose the most rigorous follow-up they are willing to comply with.

For patients who withdraw consent no more data on their medical information will be requested, see Section 3.3.4.1.

The site must make periodic documented attempts (approximately every three months) to locate patients who are lost to follow up.

6.2.3 End of trial and follow-up period

6.2.3.1 End of treatment

All patients will remain on study treatment until the last patient entered has completed at least six months of treatment. Based on the number of OEs, the operations committee will declare the end of the trial date and ask that all patients be brought in for their end of trial visit within a certain time period, which will be communicated by the trial team.

The EOT visit should take place for all patients when they discontinue study drug.

Patients who discontinue the study medication early should be registered as "withdrawn" and patients who complete the full treatment period should be registered as completed in the IRT.

After termination of study drug the patient should be switched to an appropriate non study anticoagulant and antiplatelet regimen (if required) according to the local practices. See Appendix 10.2.

Assessments should be performed as mentioned in the Flow Chart.

6.2.3.2 Follow up visit

All patients should have a follow-up visit performed four weeks after EOT. During this visit, concomitant medications, AEs, SAEs and OEs (including signs and symptoms of bleeding) during the 4 week period after last dose of study drug will be collected.

Patients who discontinue the study medication early should return to their original visit schedule after this follow up visit (see Section 6.2.2).

6.2.3.3 Final Visit

The final visit will be conducted in all patients who discontinue study treatment early at the time the trial conclusion is declared. Assessments will be done according to the flowchart.

6.2.3.4 Vital Status and Outcome Event Collection

It is important to record the vital status and OEs of all randomised patients at the end of the trial.

If a site has difficulty contacting a patient at the end of the trial, site staff should make a minimum of three documented attempts to contact the patient using different methods (i.e. phone, email, certified letter, other). 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 thrombotic events and major bleeds (where possible).

6.2.3.5 Withdrawal of consent

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

If the patient is not willing to continue in the trial and withdraws consent refer to Section 3.3.4.1.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a prospective, randomised, open label, blinded endpoint (PROBE), active comparator trial and the clinical endpoints are being adjudicated by an IAC in a blinded fashion. The study will employ a time to first event analysis (using a stratified Cox proportional hazards regression model) and it is assumed that all patients will remain on study treatment until the last patient entered has completed at least six months of treatment (up to an anticipated maximum duration of approximately 30 months for the first patient entered). The trial will be monitored by an independent DMC.

This study is designed to test a safety hypothesis in NVAF patients that have undergone a successful PCI (elective or due to ACS) with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure.

The primary outcome is stated in Section 5.2.1.

1. ISTH MBE and CRNMBE

7.2 NULL AND ALTERNATIVE HYPOTHESES

Two safety hypotheses (110mg Dabigatran Etexilate (DE-DAT) vs. warfarin-TAT and 150mg DE-DAT vs. warfarin-TAT) will be tested:

1. 110mg DE-DAT is non-inferior to warfarin-TAT with respect to MBE/CRNMBE over the duration of the trial

2. 150mg DE-DAT is non-inferior to warfarin-TAT with respect to MBE/CRNMBE over the duration of the trial.

To control the Type I error rate at a one-sided 0.025 level, a hierarchical procedure for multiple testing will be used to test the above hypotheses. Additional testing for safety and efficacy endpoints will also be included in this hierarchical procedure. The following hierarchical procedure will be applied:

Step 1 – Non-inferiority of 110mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

Step 2 – Non-inferiority of 150mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

Step 3 – Non inferiority of 150mg DE-DAT and 110mg DE-DAT combined to warfarin-TAT in DTE and unplanned revascularisation by PCI/CABG is met at the one-sided 0.025 level of significance

Step 4 –Superiority of 110mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

Step 5 – Non inferiority of 150mg DE-DAT and 110mg DE-DAT combined to warfarin-TAT in DTE is met at the one-sided 0.025 level of significance

Step 6 – Superiority of 150mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

If any of the steps above fail to meet statistical significance, the testing procedure will stop at that step and subsequent tests will not be performed.

The Non-Inferiority (NI) margin used for MBE/CRNMBE will be 1.38 (on the relative HR scale). See Section 7.6 for a clinical justification of this margin. The upper bound of the Wald confidence interval (CI) of the HR of DE-DAT vs. warfarin-TAT (one-sided 97.5%) will be compared to this NI margin for the NI testing.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary endpoint (measured from date of randomisation to end of observation period) is:

- Time to first MBE/CRNMBE

as determined by the IAC. It will be analysed using the stratified Cox proportional hazards regression model including factors for age (<80 or ≥80 years old) and treatment arm (110mg DE-DAT vs warfarin-TAT and 150mg DE-DAT vs warfarin-TAT). Models will be fitted for each comparison separately.

The primary analysis will be performed under the intention-to-treat framework on the full analysis set of patients (FAS) that includes all randomised patients (regardless of whether they have received treatment). Patients who discontinue study medication will be followed until the end of the trial. Patients who are lost to follow-up for vital status will be censored for the primary endpoint at the time of their last known vital status. All patients will be analysed according to the treatment arm to which they were randomised.

For the comparison of 110mg DE-DAT vs warfarin-TAT, patients of all ages and geographical regions will be included. For the comparison of 150mg DE-DAT vs warfarin-TAT, patients from the EU/ROW who are ≥80 years old will be excluded from the warfarin-TAT arm (as patients who are ≥80 years old from the EU/ROW are not randomised to 150mg DE-DAT).

The robustness of the primary analysis will be assessed by an on-treatment analysis. This on-treatment analysis will only count events that occur while a patient is taking study medication (including the REP of 6 days – see Section 5.2.2.2). It will also analyse patients by the actual treatment that was being taken while the event occurred.

In addition, a sensitivity analysis will be performed that censors patients who switch from dabigatran to non-study warfarin or from study warfarin to non-study NOAC, at the time of the switch. The proportional hazards assumption will be investigated.

Kaplan-Meier curves will also be presented.

Subgroup analyses are planned and will be specified in the Trial Statistical Analysis Plan (TSAP).

7.3.2 Secondary analyses

Secondary efficacy endpoints (all time to first event, measured from date of randomisation to end of observation period) are:

- A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI /CABG
- A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)
- All death
    - Cardiovascular death
    - Non-cardiovascular death
    - Undetermined
- MI
- Stroke
- SE
- Stent thrombosis
- Composite of death + MI + stroke
- Unplanned revascularisation by PCI /CABG

Time to first event endpoints will be analysed using the same methods as for the primary endpoint. No multiplicity adjustments are planned for secondary endpoints (apart from those mentioned in the hierarchy, see Section 7.2). Nominal one-sided p-values will be reported for descriptive purposes.

All secondary analyses will be performed on the FAS. The robustness of these analyses will be assessed by on-treatment analyses (see Section 7.3.1).

TIA (further endpoint, see Section 5.3.1) will be analysed using the same approaches as above.

7.3.3 Safety analyses

Safety endpoints are defined in Section 5.2.1.

These endpoints will be analysed using the same methods as the primary endpoints. No multiplicity adjustments are planned for safety endpoints (apart from those mentioned in the hierarchy, see Section 7.2).

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 AEs. All AEs with an onset after the first dose of study medication up to the end of the REP of 6 days (see Section 5.2.2.2) after the last dose of study medication will be assigned to the treatment period for evaluation. Other adverse events will be assigned either to the screening or post study period as appropriate.

On-treatment analyses will be performed for AEs.

7.3.4 Interim analyses

No interim analysis is planned, but blinded sample size re-calculations may be performed. The conduct of the trial will be monitored by a DMC. The DMC will hold regular meetings to monitor imbalance in endpoints, with the focus on MBE/CRNMBE. The DMC's objectives and working practices are documented in the DMC charter.

The DMC may recommend terminating the study at any time for DE-DAT safety concerns. Further details will be included in the DMC charter.

The DMC will have unblinded safety reviews every 2 months.

7.3.5 Pharmacokinetic analyses

Not applicable.

7.3.6 Pharmacodynamic analyses

Not applicable.

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

A major goal of the trial is to obtain virtually complete follow-up of vital status. 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.

The CTR will contain a summary of the number and proportion of patients with (and without) complete follow-up of vital status in each treatment group.

Partial dates will be imputed for the primary and secondary endpoints. Specific imputation rules will be documented in the TSAP.

7.5 RANDOMISATION

Patients aged <80 years old will be randomly assigned to 110mg DE-DAT, 150mg DE-DAT or warfarin-TAT in a 1:1:1 ratio for the duration of the trial.

Patients aged ≥80 years old will be randomly assigned depending on their geographical region:

- Patients aged ≥80 years old in the USA will be assigned to 110mg DE-DAT, 150mg DE-DAT or warfarin-TAT in a 1:1:1 ratio

- All other patients aged ≥80 years old (i.e. EU/ROW) will be assigned to 110mg DE-DAT or warfarin-TAT in a 1:1 ratio.

Patients will be randomised in permuted blocks, dynamically stratified by age (<80 or ≥80 years old) and region (EU/ROW or USA) using an IRT. Dynamic stratification allocates blocks of randomisation numbers according to the strata of the first randomised patient within that block. For example, if the first patient randomised to the first block is <80 years old and from the USA, other randomisation numbers within this block will only be allocated to patients <80 years old from the USA (until there are no more randomisation numbers left to allocate within this block). BI will arrange for the packaging and labelling of study medication. The randomisation list will be generated using a validated system and 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

This is an event-driven trial where it is assumed that the first patient recruited into the study will be followed up for a maximum of approximately 30 months and the last patient recruited into the trial will be followed up for a minimum of 6 months. It is assumed that patient accrual will be approximately uniform over the 24 month recruiting period.

The proportion of patients with at least one MBE/CRNMBE at one year is estimated to be 14% based on current blinded trial data.

A relative NI margin for the original co-primary endpoint (DTE) was chosen in analogy to recent SPAF trials with primary endpoints of stroke/SE, where 1.38 was used by the FDA for ximelagatran, apixaban, rivaroxaban and dabigatran to preserve at least 50% of the relative reduction (on the log scale) in the risk associated with warfarin in six previous (historical), randomised, controlled trials. See publication by Jackson K, Gersh BJ, Stockbridge N, et al. [R08-2662]. The same NI margin has been applied to MBE/CRNMBE as it was considered the most clinically relevant available reference in the absence of any other type of data.

The overall sample size is driven by the non-inferiority comparison of MBE/CRNMBE between 110mg DE-DAT or 150mg DE-DAT and warfarin-TAT. With alpha=0.025 (one-sided) and 14% of patients with at least one event at one year, 334 patients with at least one MBE/CRNMBE in each pair of treatment groups (i.e. 167 patients with MBE/CRNMBE per treatment group) are required to achieve 83.6% power for this endpoint, yielding a final sample size estimated at 834 patients in each treatment group (i.e. 2502 randomised patients in total). Therefore approximately 500 patients with at least one MBE/CRNMBE are required in total across the three treatment groups.

As described in Section 7.3.1, for the comparison of 150mg DE-DAT vs warfarin-TAT, patients from the EU/ROW who are ≥80 years old will be excluded from the warfarin-TAT arm (as patients who are ≥80 years old from the EU/ROW are not randomised to 150mg DE-DAT). The actual number of patients entered may increase or decrease based upon actual event rates. As this is an event-driven trial, the trial can conclude earlier, if an adequate number of events are reported sooner or later, if more events are needed. Because the last patient entered must be followed up for a minimum of 6 months and to avoid accruing too many events, recruitment will need to be stopped before the required number of events are observed. Blinded event rates will be monitored closely by BI (and the Executive Steering Committee) to predict the time at which recruitment should be stopped. Sites will be notified when recruitment ends.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for 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 subjects against any immediate hazard and also of any serious breaches of the protocol/ICH GCP and in Japan, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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.

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 competent authority (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 authorised the Local Clinical Monitors or Clinical Research Associate (CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

eCRFs for individual patients will be provided by the sponsor, via RDC. 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; also current medical records must be available.

For eCRFs all data must be derived from source documents.

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. eCRFs 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. FDA). The CRA / on site monitor and auditor may review all eCRFs and written informed consents. An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest risk which have the most potential to impact subject safety and data quality will be utilised**.** The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records - Japan

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 sites to retain the source documents and the 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 fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE 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 dabigatran etexilate this is the current version of the IB (U98-3208). For the comparator (Warfarin) this is the current UK Summary of Product Characteristics (SmPC). The current versions of these reference documents are to be provided in the ISF. For the NIMPs the reference documents are the UK SmPC for ticagrelor, the UK SmPC for clopidogrel and the US Package Insert for ASA. No AEs are classified as listed for study design or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (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, i.e. the CA.

8.6 COMPLETION OF TRIAL

For Japan: 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 EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, 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 subjects 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

APPENDIX 10.1 STUDY DRUG START AND BRIDGING RULES

10.1.1 When to start dabigatran etexilate following treatment by other anticoagulants

Heparins
UFH or LMWH/injectable anticoagulant (if given) should be stopped prior to the first dose of dabigatran etexilate. Dabigatran etexilate should be initiated with the following suggested time windows:

- UFH/other continuous i.v. anticoagulants: initiate dabigatran etexilate at the time the UFH/other continuous i.v. anticoagulant is stopped

- LMWH/other s.c. injectable anticoagulants: initiate dabigatran etexilate 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
Patients already on VKA, should start dabigatran etexilate once the INR is <2.0. If the INR is ≥2.0, study medication can be dispensed but the patient will be instructed not to start it until notified. Follow-up INR testing will be performed in 1-2 day intervals until INR falls below 2.0, at which time the patient will be instructed to start taking the study medication.

Novel Oral Antiocagulants
Patients taking apixaban, edoxaban,rivaroxaban or dabigatran etexilate can be initiated at the time the next dose of the novel oral anticoagulant would have been due. As there is no clinical experience for switching from other novel oral anticoagulants to dabigatran etexilate, the decision must be taken based on clinical considerations and recommendations [P13-06400].

10.1.2 When to start warfarin following treatment by other anticoagulants or VKAs

Parenteral anticoagulants
Warfarin can be initiated at the same time as the patient is taking parenteral anticoagulants (for recommendations on how to dose warfarin see the nomogram provided in the ISF). Parenteral bridging therapy (e.g. UFH, LMWH) should be stopped when target INR is achieved.

Vitamin K antagonists
For recommendations on how to switch a patient from another VKA to warfarin and for maintenance of warfarin therapy see the nomogram provided in the ISF.

Novel Oral Anticoagulants
An overlapping therapy with both novel oral anticoagulant and warfarin should not be performed for patients randomised to warfarin. It is recommended to use bridging therapy with a parenteral anticoagulant instead while initiating warfarin.

The novel oral anticoagulant should be discontinued and the parenteral anticoagulant should be started at the time of the next scheduled dose of the novel oral anticoagulant (in line with the respective novel oral anticoagulant label).

10.1.3 Bridging Therapy (e.g. for temporary interruptions of study drug due to interventions)

The use of bridging therapy depends on the thomboembolic risk status of the patient and the length of the planned interruption. It is at the discretion of the investigator whether to use a parenteral anticoagulant for bridging purposes or not.

Due to the short off- and onset of action, the majority of interventions in patients receiving dabigatran etexilate may not require the use of bridging therapy. If bridging therapy is deemed necessary for patients in the dabigatran etexilate arm, it is recommended to wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant.

Patients in the warfarin arm should be treated at the discretion of the investigator. In general, a parenteral anticoagulant may be considered when the INR is below the target INR. For recommendations how to switch back to study drug (dabigatran etexilate or warfarin) see Sections 10.1.1 and 10.1.2.

APPENDIX 10.2 SWITCHING FROM STUDY TREATMENT AT EOT

At the end of the study or if a patient discontinues early, continued anticoagulant therapy will usually be required because the patients has NVAF.

Investigators should plan for each subject's transition to standard of care taking into consideration the individual patient's risk profile and previous experience with non-study VKA.

As patients have different risk profiles, optimal approaches might differ between patients and not all possible approaches are described below.

OPTION 1: STARTING WARFARIN PRIOR TO DABIGATRAN ETEXILATE DISCONTINUATION

Start warfarin at the EOT visit and continue on dabigatran etexilate for 2-3 days after the EOT visit[1]. In patients with CrCl >50mL/min who discontinue dabigatran but still require anticoagulation, dabigatran should be continued for three more days. For patients with moderate renal dysfunction (CrCl ≥30 to <50mL/min), as measured in the visit before EOT, dabigatran can be stopped after two days of concomitant VKA.

Many physicians will want to see warfarin naïve patients before starting warfarin. There is no special need to measure the CrCl before starting warfarin. If the INR is checked on the day of the EOT visit, Investigators should recognise that the presence of dabigatran could elevate the INR. Because dabigatran etexilate can increase the INR, the INR will better reflect warfarin's effect only after dabigatran etexilate has been stopped for at least 24 hours.

OPTION 2: BRIDGING WITH LMWH

Patient comes in on the day of the EOT visit, dabigatran etexilate is stopped and non-study VKA is started. LMWH can be used to bridge the patient until the INR becomes therapeutic. The LMWH can be started 12 hours after the last dose of dabigatran etexilate. This approach is an alternative to Option 1 described above.

The decision to use bridging therapy is at the discretion of the investigator (see Appendix 10.1).

Please consult local guidelines for the starting dose of the respective VKA.

Although there are large differences in the plasma half-lives of the various VKAs in clinical use, apart from the selection of the starting dose, the half-life of the VKA will have no impact on the transition from dabigatran etexilate.

[1] The date of final intake of dabigatran etexilate must be documented in the eCRF.

APPENDIX 10.3 DEFINITION OF DISABLING STROKE BY MODIFIED RANKIN SCALE

Grade 0: no symptoms at all

Grade 1: no significant disability despite symptoms;
able to carry out all usual duties and activities

Grade 2: slight disability:
unable to carry out all previous activities but able to look after own affairs without assistance

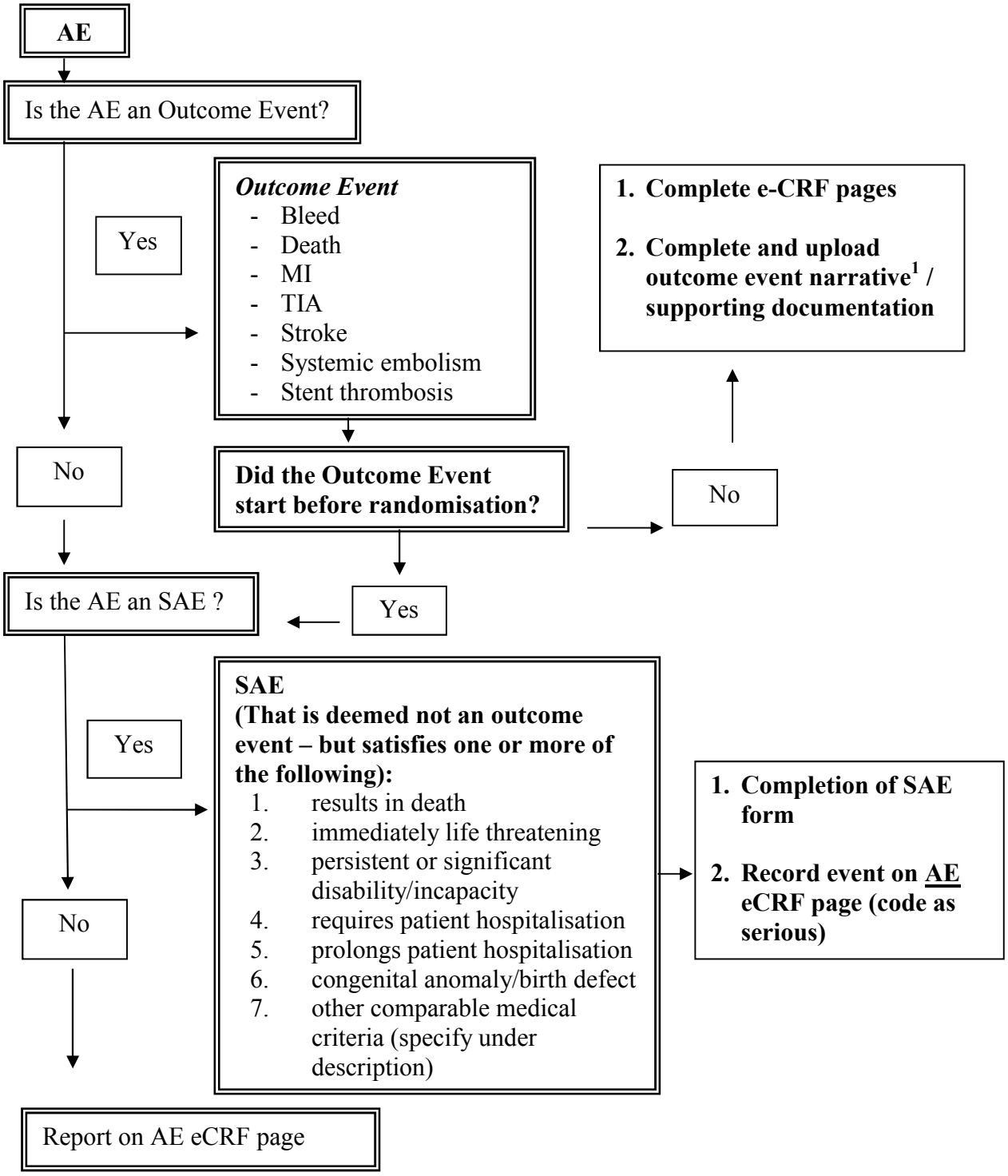
Grade 3: moderate disability:
requiring some help but able to walk without assistance

Grade 4: moderate severe disability:
unable to walk without assistance and unable to attend to own bodily needs without assistance

Grade 5: severe disability:
bedridden, incontinent and requiring constant nursing care and attention.

Grade 6: dead

APPENDIX 10.4 HANDLING OF OUTCOME EVENTS (BLEEDS AND MORTALITY / MORBIDITY EVENTS), SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS



[1]A narrative will only be requested if needed

Figure 10.4: 1 Hierarchical algorithm for reporting OEs, SAEs and AE.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		16 September 2015
EudraCT number		2013-003201-26
BI Trial number		1160.186
BI Investigational Product(s)		Pradaxa®, dabigatran etexilate
Title of protocol		A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DU**AL antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting **(RE-DUAL PCI)**
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		Cover Page Fax number
Description of change		Fax: [redacted] Has been changed to Fax: [redacted]

Number of global amendment		1
Rationale for change		To reflect update of fax number
Section to be changed		Flow Chart
Description of change		Visit 1 visit window updated from: -3 to 0 days To -5 to 0 days
Rationale for change		To facilitate patient recruitment and to operationally simplify where possible.
Section to be changed		Flow Chart
Description of change		Physical examination Footnote added at Visit 1: Includes height at Visit 1 Subsequent footnotes have been re-numbered.
Rationale for change		To add clarity that height is part of the physical examination at Visit 1
Section to be changed		Flow Chart
Description of change		Vital Signs (PR/BP) Footnote added at Visit 2: If Visit 1 and Visit 2 occur within 24 hours then vital signs do not need to be repeated at Visit 2 Subsequent footnotes have been re-numbered.
Rationale for change		To clarify that no additional vital sign measurement is needed when Visit 1 and Visit 2 both occur within 24 hours
Section to be changed		Flow Chart
Description of change		INR/Warfarin dose adjustment[13]

Number of global amendment		1
		every 2 - 4 weeks[14] Has been changed to: every 2 weeks – monthly[14]
Rationale for change		To be consistent with section 4 of the protocol.
Section to be changed		Flow Chart
Description of change		Footnote 12 (previously footnote 10) Will be performed locally, only those parameters required to verify eligibility are required at screening. Has been changed to: Will be performed locally, only those parameters required to verify eligibility are required at screening, **standard of care local results taken within 7 days prior to screening can be used to verify eligibility.**
Rationale for change		To minimise blood samples that need to be taken from patient and the use of standard of care local laboratory results taken within 7 days prior to screening is considered acceptable.
Section to be changed		Flow Chart
Description of change		Footnote 17 (previously footnote 15) Study drug should be administered between 6 hours after sheath removal and up to 72 hours post PCI, with haemostasis assured. Has been changed to: Study drug should be administered between 6 hours after sheath removal and **preferably within** 72 hours post PCI **(refer to section 6.2.2),** with haemostasis assured**, however up to 120 hours post PCI is allowed.**
Rationale for change		To facilitate patient recruitment and to operationally simplify where possible.

Number of global amendment		1
Section to be changed		Flow Chart
Description of change		Drug Accountability Footnote added at Visit 3: Patients randomised to Warfarin only
Rationale for change		Clarification. At Visit 2 patients randomised to Dabigatran receive a 3 month kit, therefore drug accountability does not need to be performed at Visit 3 for patients randomised to dabigatran etexilate.
Section to be changed		1.1 Medical Background
Description of change		The bold text below has been added: A recently published small randomised controlled study (WOEST) [R13-4127], observed that bleeding and ischaemic event rates were lower in patients on DAT (warfarin + clopidogrel) compared to TAT (warfarin + clopidogrel + ASA). From previous experience it is also known that continued anticoagulation with warfarin during PCI procedures is associated with an increased risk of bleeding [P07-09550]. The WOEST study enrolled 573 patients **randomly assigned in a 1:1 ratio to receive oral anticoagulation plus clopidogrel alone (DAT) or plus clopidogrel and aspirin (TAT). All patients were pretreated with a maintenance dose of 75mg clopidogrel per day for at least 5 days, a loading dose of 300mg clopidogrel at least 24 hours before PCI, or a loading dose of 600mg clopidogrel at least 4 hours before PCI. A 320mg loading dose of ASA was also given to patients who had not been taking ASA before the study. Study treatment was started promptly after randomisation. All patients received 75mg clopidogrel daily, and those in the TAT group were also given 80–100 mg ASA daily.**
Rationale for change		To provide details in relation to the pre-PCI antithrombotic regimens used in the WOEST study.
Section to be changed		2.3 Benefit – Risk Assessment

Number of global amendment		1
Description of change		Excessive anticoagulation may require interruption of dabigatran treatment. There is currently no specific antidote to dabigatran available on the market. Guidance on the management of patients who experience a haemorrhagic complication is provided in Section 4.2.1. Has been changed to: Guidance on the management of patients who experience a haemorrhagic complication is provided in Section 4.2.1. **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.**
Rationale for change		To clarify terminology and allow collection of information regarding use of the reversal agent if administered to patient.
Section to be changed		2.3 Benefit – Risk Assessment
Description of change		The following text has been deleted Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.
Rationale for change		See rationale for change in section 5.2.2.2 Definitions of AEs
Section to be changed		3.1 Overall Trial Design And Plan
Description of change		Patients will be consented and screened after undergoing a successful PCI. Randomisation will occur on local laboratory results taken at the screening visit; however central laboratory samples must be taken at randomisation prior to first intake of study drug. Randomisation can occur up to 72

Number of global amendment		1
		hours post PCI. Study drug should be administered between 6 hours after sheath removal and up to 72 hours post PCI, with haemostasis assured. Has been changed to: Patients will be consented and screened after undergoing a successful PCI. Randomisation will occur on local laboratory results taken at the screening visit **or on standard of care local laboratory results taken within 7 days prior to screening**; central laboratory samples must be taken at randomisation prior to first intake of study drug. Randomisation can occur up to **120** hours post PCI, **however within 72 hours is preferable**. Study drug should be administered between 6 hours after sheath removal and **preferably within** 72 hours post PCI, with haemostasis assured, **however up to 120 hours post PCI is allowed.**
Rationale for change		To minimise blood samples that need to be taken from patient and the use of standard of care local laboratory results taken within 7 days prior to screening is considered acceptable. To facilitate patient recruitment and to operationally simplify where possible.
Section to be changed		3.1 Overall Trial Design And Plan
Description of change		In addition to their randomised treatment: • All patients will receive either clopidogrel (75mg q.d.) or ticagrelor (90mg b.i.d), according to the local label, for at least 12 months after randomisation. Discontinuation of clopidogrel or ticagrelor after 12 months of treatment is at the discretion of the Investigator Has been changed to: In addition to their randomised treatment: • All patients will receive either clopidogrel (75mg q.d.) or ticagrelor (90mg b.i.d), according to the local label, for at least 12 months after randomisation. Discontinuation of clopidogrel or

Number of global amendment		1
		ticagrelor **or switching to ASA (≤ 100mg q.d.)** after 12 months of treatment is at the discretion of the Investigator Figure 3.1: 1. also updated to reflect this change and increase of time window for randomisation to 120 hours.
Rationale for change		To allow the switch of antiplatelet therapy (clopidogrel or ticagrelor to ASA) after month 12 as per Investigator discretion.
Section to be changed		3.1 Overall Trial Design And Plan
Description of change		The screening period will consist of one visit (Visit 1). The patients will be randomised at Visit 2. Has been changed to: **Prior to consent the patient's antithrombotic treatment (i.e. ASA use during PCI, use of clopidogrel loading dose) should be managed as per local standard of care.** The screening period will consist of one visit (Visit 1). The patients will be randomised at Visit 2.
Rationale for change		To clarify that before consent the patient should be treated per local standard of care.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion 2 Patients with NVAF that have been receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant), or were treatment naïve prior to PCI. AF may be paroxysmal, persistent or permanent, but must not be secondary to a reversible disorder such as MI, pulmonary embolism, recent surgery, pericarditis or thyrotoxicosis Has been changed to: Patients with NVAF that have been receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant), or were treatment naïve prior to PCI. AF may be paroxysmal, persistent or permanent, **and** not

Number of global amendment		1
		secondary to a reversible disorder such as MI, pulmonary embolism, recent surgery, pericarditis or thyrotoxicosis, **unless long term oral anticoagulation is planned**
Rationale for change		To allow inclusion of patients who are a candidate for long term oral anticoagulation.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Footnote added to exclusion 13: Active liver disease as indicated by at least one of the following: • Prior and persistent alanine aminotransferase (ALT) or Aspartate transaminase (AST) or alkaline phosphatase (AP) >3 × upper limit of normal (ULN)[1] • Known active hepatitis C • Known active hepatitis B • Known active hepatitis A **[1] Clinical judgement of whether ALT/AST enzyme elevation is due to active liver disease or due to ACS, should be made by the Investigator following evaluation of the clinical characteristics of the patient and the laboratory findings.**
Rationale for change		To provide clarification to exclusion criterion 14 in relation to active liver disease.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion 15: Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, St. John's Wort or any cytotoxic/myelosuppresive therapy. Has been changed to: Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, St. John's Wort.

Number of global amendment		1
Rationale for change		Cytotoxic/myelosuppresive therapies are not contraindicated for patients receiving dabigatran etexilate or warfarin. Therefore patients on cytotoxic/myelosuppresive therapy do not need to be excluded.
Section to be changed		4.1.1 Identity of BI investigational product and comparator products
Description of change		All patients will also take clopidogrel (75mg q.d.) or ticagrelor (90mg b.i.d.) according to the local label for at least 12 months after randomisation (in addition to either dabigatran etexilate or warfarin). Discontinuation of clopidogrel or ticagrelor after 12 months of treatment is at the discretion of the Investigator. Has been changed to: All patients will also take clopidogrel (75mg q.d.) or ticagrelor (90mg b.i.d.) according to the local label for at least 12 months after randomisation (in addition to either dabigatran etexilate or warfarin). **After 12 months of treatment the clopidogrel or ticagrelor can be discontinued or switched to ASA (≤ 100mg q.d.)** at the discretion of the Investigator.
Rationale for change		To allow the stop or switch of antiplatelet therapy (clopidogrel or ticagrelor; switch to ASA) after month 12 as per Investigator discretion.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Each patient will be randomised at Visit 2 to receive either dabigatran etexilate (110mg or 150mg b.i.d.) or warfarin. The first dose of trial medication will be taken, between 6 hours after sheath removal and up to 72 hours post PCI, with haemostasis assured. Has been changed to: Each patient will be randomised at Visit 2 to receive either dabigatran etexilate (110mg or 150mg b.i.d.) or warfarin. The first dose of trial medication will be taken, between 6 hours after sheath removal and

Number of global amendment		1
		preferably within 72 hours post PCI, with haemostasis assured, **however up to 120 hours post PCI is allowed**.
Rationale for change		To facilitate patient recruitment and to operationally simplify where possible.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		The following text has been changed under "Patient randomised to receive dabigatran etexilate": It is permitted for patients to receive bridging therapy with a parenteral anticoagulant according to local practice before switching to dabigatran etexilate. Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of parenteral anticoagulant would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous (i.v.) unfractionated heparin (UFH)). See Appendix 10.2 for guidance how to switch from a parenteral anticoagulant to dabigatran etexilate. Has been changed to: It is permitted for patients to receive bridging therapy with a parenteral anticoagulant according to local practice before switching to dabigatran etexilate. Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of parenteral anticoagulant would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous (i.v.) unfractionated heparin (UFH)). See Appendix 10.**1** for guidance how to switch from an anticoagulant to dabigatran etexilate.
Rationale for change		Guidance updated to cover switch from oral anticoagulant aswell as parenteral anticoagulant. Appendices re-numbered due to removal of clinical evaluation of liver injury – see rationale for change to section 5.2.2.2 Definitions of AEs.
Section to be changed		4.1.6 Packaging, labelling, and re-supply
Description of change		Patients on warfarin will receive the required combination of 1mg, 3mg and 5mg tablets in bottles

Number of global amendment		1
		according to their actual needs as defined by the measured INR value. Each warfarin bottle will contain 66 tablets. Has been changed to: Patients on warfarin will receive the required combination of 1mg, 3mg and 5mg tablets in bottles according to their actual needs as defined by the measured INR value. Each warfarin bottle will contain 66 tablets. **Warfarin bottles should be checked at each visit to ensure the patient has sufficient supplies and that expiry dates will not be compromised prior to the next clinic visit.**
Rationale for change		To facilitate medication compliance checks and ensure appropriate trial supplies available to patient
Section to be changed		4.2 Concomitant Therapy, Restrictions, and Rescue Treatment
Description of change		Details of concomitant medication administered to the patient during the course of the study should be recorded in the eCRF. This includes all concomitant therapies from time of patient informed consent until the patient completes follow-up. In addition, at the Screening Visit, information regarding specific drugs (e.g. antithrombotic medication, medications with a potential drug-drug interaction with dabigatran etexilate (P-gp inhibitors and inducers)), administered in the 30 days prior to Informed Consent will be recorded. Has been changed to: **Comprehensive details of concomitant medication of special interest (e.g. antiplatelet medication, parenteral anticoagulant, thrombolytic agent, GPIIb/IIIa antagonist, VKA, therapies for bleeding management, novel direct oral anticoagulant) administered to the patient from 30 days prior to informed consent until the patient completes follow-up should be recorded in the eCRF. Abbreviated information will be collected for any other concomitant therapy.**
Rationale for change		Clarification in relation to recording of concomitant therapy.

Number of global amendment		1
Section to be changed		4.2.1.1 Major Bleeds
Description of change		There is no specific antidote currently available on the market to counteract the antithrombotic activity of dabigatran etexilate. Has been changed to: **The recommendations given below are derived from guidelines to manage bleeding with dabigatran etexilate. See section 4.2.1.7 Overdose, for more information regarding the specific reversal agent for dabigatran.**
Rationale for change		To clarify that the recommendations apply to the management of bleeding with dabigatran etexilate treatment and to introduce the reversal agent for dabigatran.
Section to be changed		4.2.1.3 Emergency and Elective Surgery
Description of change		The following text has been added: **See section 4.2.1.7- Overdose, for more information regarding the specific reversal agent for dabigatran.**
Rationale for change		To allow collection of information regarding use of the reversal agent.
Section to be changed		4.2.1.6 Other Medical Intervention
Description of change		<u>Percutaneous Coronary Intervention (PCI):</u> …… Study medication can be reintroduced between 6 hours after sheath removal and up to 72 hours post PCI with haemostasis assured. Has been updated to say: <u>Percutaneous Coronary Intervention (PCI):</u> …… Study medication can be reintroduced between 6 hours after sheath removal with haemostasis assured, **as considered appropriate by the Investigator**.

Number of global amendment		1
Rationale for change		To allow Investigator's medical discretion when to re-introduce study medication.
Section to be changed		4.2.1.7 Overdose
Description of change		The following text has been added: **<u>Specific reversal agent to dabigatran</u>** **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		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		ASA >100mg per day, corticosteroids, or NSAIDs may be used if clinically indicated according to current treatment guidelines but it is strongly recommended to avoid these if possible. The patients should be advised to not use additional ASA-containing over-the-counter medications on a regular basis. It should, however, be noted that the use of any of these agents with warfarin or dabigatran etexilate is likely to increase the risk of bleeding. Has been changed to: Corticosteroids or NSAIDs may be used if clinically indicated according to current treatment guidelines but it is strongly recommended to avoid these if possible. It should be noted that the use of any of these agents with warfarin or dabigatran etexilate is likely to increase the risk of bleeding. Additional text added to section –

Number of global amendment		1
		The following treatments should not be taken during the active treatment phase of the trial: 1. …….. **6. ASA - except where specified in the protocol for patients randomised to the warfarin arm or in both treatment arms after 12 months of treatment if clopidogrel or ticagrelor is switched to ASA (≤ 100mg q.d.) at Investigator discretion. The patients should be advised to not use additional ASA-containing over-the-counter medications.**
Rationale for change		Clarification of the restrictions of ASA use in order to comply with the clinical trial objectives.
Section to be changed		5.1.2.1 Death 5.1.2.3 Stroke 5.1.2.5 Stent Thrombosis 5.3.1 Other endpoints
Description of change		Inclusion of reference R15-0010
Rationale for change		Updated publication released. However, the endpoint definitions within these sections of the protocol are not affected.
Section to be changed		5.1.2.2 Myocardial infarction
Description of change		The following definitions have been added: **<u>Criteria for fatal MI</u>** **Death due to Acute MI refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. Acute MI (for criteria see above) should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (eg PCI, CABG), or to treat a complication resulting from MI, should also be considered death due to acute**

Number of global amendment		1
		MI (R15-0010). **<u>Silent MI</u>** **Silent myocardial infarction will be retrospectively diagnosed by the appearance of significant new Q-waves on an ECG performed after randomisation. In such cases, the date of the event is recorded as the midpoint between the ECG with new Q-waves and the prior normal ECG.**
Rationale for change		Sub classifications of MI that were not previously included.
Section to be changed		5.1.2.3 Stroke
Description of change		The following definition has been added: **<u>Fatal stroke</u>** **Fatal stroke is defined as death from any cause within 30 days of stroke.**
Rationale for change		Additional definition not previously included in error.
Section to be changed		5.1.2.3 Stroke
Description of change		<u>Severity of recurrent stroke</u> Severity of recurrent stroke will be assessed by modified Rankin Scale (mRS) at the onset of stroke and at 3 months after recurrent stroke, if this time frame falls anytime within the study participation. (see Appendix 10.4 for definition). Has been changed to: Severity of recurrent stroke will be assessed by modified Rankin Scale (mRS) at the onset of stroke and at 3 months after recurrent stroke, if this time frame falls anytime within the study participation. **Disabling stroke is defined as a stroke with mRS ≥4 at 3 months** (see Appendix 10.**3** for definition **of mRS**).
Rationale for change		Additional definition not previously included in error. Appendices re-numbered due to removal of clinical evaluation of liver injury - for rationale refer

Number of global amendment		1
		to update made to section 5.2.2.2 Definitions of AEs.
Section to be changed		5.2.2.2 Definitions of AEs
Description of change		Protocol-specified Adverse Events of Special Interest (AESI) The following are considered as Protocol-specified Adverse Events of Special Interest: • Hepatic injury defined by an elevation of AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appendix 10.1 of this CTP and the Drug Induced Liver Injury (DILI) checklist provided in the eCRF and the ISF. Protocol-specified AESIs are to be reported by the Investigator to the Sponsor in an expedited manner (within 24 hours of awareness) similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria. For details please see Section 5.2.2.3. Has been changed to: Protocol-specified Adverse Events of Special Interest (AESI) **No AESIs are defined for this trial.**
Rationale for change		DILI monitoring is no longer considered necessary for dabigatran etexilate at this advanced stage of development for the following reasons: • During the clinical development of the product, extensive DILI monitoring had been conducted. Extensive data available from clinical trials conducted so far in different indications with close to 30,000 patients exposed to dabigatran in clinical trials has not evidenced risk of hepatoxicity (U98-3208). In fact, data of liver enzymes from the pivotal trials during and post-

Number of global amendment		1
		treatment did not indicate that administration of dabigatran etexilate is associated with hepatotoxicity. Independent of the indication, there does not appear to be any dose response effect in the frequency of occurrence of liver enzyme (ALT/AST) elevations with dabigatran etexilate . Also, a recently published systematic review and meta-analysis concluded that the NOACs (dabigatran etexilate, rivaroxaban, apixaban, darexaban, edoxaban) were not associated with an increased risk of DILI (P14-02938). • Post-marketing experience from over 4 million patient-years over a period of more than 6 years has not evidenced signs of hepatotoxicity. The evaluation of BI cumulative data collected since market introduction has not evidenced any risk of severe liver injury/hepatotoxicity associated with the use of dabigatran etexilate. • Removal of DILI monitoring is not contradicting FDA requirements for assessing the potential for a drug to cause severe liver injury, which in general applies to premarketing clinical evaluation (FDA Guidance for Industry: "Drug-Induced Liver Injury) and this assessment has already been extensively done for dabigatran. • Additionally, a DMC will be regularly monitoring and evaluating the safety of the patients included in the study and will be able to make recommendations based on the available data.
Section to be changed		5.2.2.3 Adverse event and serious adverse event reporting
Description of change		The Investigator must report the following events via fax immediately (within 24 hours or the next business day, whichever is shorter) to the sponsor: SAEs, AESIs and non-serious AEs relevant to the SAE or AESI. Has been changed to: The Investigator must report the following events

Number of global amendment		1
		via fax immediately (within 24 hours or the next business day, whichever is shorter) to the sponsor: SAEs and non-serious AEs relevant to the SAE.
Rationale for change		Removal of AESI. For rationale refer to update made to section 5.2.2.2 Definitions of AEs.
Section to be changed		5.2.3 Assessment of safety laboratory parameters
Description of change		Blood samples will be taken at the screening visit for those parameters required to verify eligibility and will be analysed by a local laboratory Has been changed to Blood samples will be taken at the screening visit for those parameters required to verify eligibility **(haemoglobin, platelets, ALT and / or AST, AP and creatinine (the latter to calculate CrCl according to the Cockcroft-Gault formula))** and will be analysed by a local laboratory. **If standard of carelaboratory blood results are available, taken within 7 days prior to screening, these can be used to verify eligibility.**
Rationale for change		To provide clarification of laboratory parameters needed to verify eligibility and to minimise blood samples that need to be taken from patient. The use of standard of care local laboratory results taken within 7 days prior to screening is considered acceptable.
Section to be changed		5.2.3 Assessment of safety laboratory parameters
Description of change		**Pregnancy Testing** ……Urine pregnancy tests will be provided by the central laboratory. Has been changed to: **Pregnancy Testing** …….. Urine pregnancy tests will be provided.
Rationale for change		It is not possible for the central laboratory to provide urine pregnancy testing kits for home testing in all countries therefore these tests will be sourced locally in all countries except the USA.
Section to be changed		5.2.3 Assessment of safety laboratory parameters

Number of global amendment		1
Description of change		**Renal Function Measurements** CrCl will be calculated using the Cockcroft-Gault formula, as follows: • For creatinine in μMol/L: $\frac{(140\text{-age [years]}) \times \text{weight [kg]} \times 1.23\ (\times 0.85 \text{ if female})}{\text{serum creatinine [μMol/L]}}$ Has been changed to **Renal Function Measurements** CrCl will be calculated using the Cockcroft-Gault formula, as follows: • For creatinine in μMol/L: $\frac{(140\text{-age [years]}) \times \text{weight [kg]} \times 1.23\ (\times 0.85 \text{ if female})}{\text{serum creatinine [μMol/L]}}$
Rationale for change		Correction to formatting
Section to be changed		5.2.5.1 Full Physical Examination
Description of change		5.2.5.1 Full Physical Examination A complete physical examination will be performed by the Investigator according to the flowchart. Has been updated to: 5.2.5.1 Physical Examination A **cardiovascular focused** physical examination will be performed by **medical qualified personnel** according to the flowchart.
Rationale for change		To operationally simplify the study procedures and focus the physical examination to the relevant organ system.
Section to be changed		6.1 Visit Schedule
Description of change		The study will consist of three sequential periods, Screening/Baseline Period of up to 3 days, a Treatment Period of up to approximately 30 months and a Follow up Period of four weeks.

Number of global amendment		1
		Has been updated to: The study will consist of three sequential periods, Screening/Baseline Period of up to **5** days, a Treatment Period of up to approximately 30 months and a Follow up Period of four weeks.
Rationale for change		To facilitate patient recruitment and to operationally simplify where possible.
Section to be changed		6.2.2 Treatment period(s)
Description of change		Randomisation can occur immediately after successful screening and up to 72 hours post PCI. The first dose of trial medication will be taken between 6 hours after sheath removal and up to 72 hours post PCI (end of intervention), with haemostasis assured. Has been changed to: Randomisation can occur immediately after successful screening and up to **120** hours post PCI **however, randomisation within 72 hours is preferable**. The first dose of trial medication will be taken between 6 hours after sheath removal and **preferably within** 72 hours post PCI (end of intervention **i.e. when the last catheter used for PCI is removed**), with haemostasis assured, **however, randomisation up to 120 hours post PCI is allowed.**
Rationale for change		To facilitate patient recruitment and to operationally simplify where possible.
Section to be changed		6.2.2 Treatment period(s)
Description of change		All patients who discontinue treatment 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 ECGs will be performed and the collection of AEs, OEs (including completion of the bleeding questionnaire) and use of concomitant medication will be made. Has been changed to:

Number of global amendment		1
		All patients who discontinue treatment 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 **(as indicated in the Flow Chart)** ECGs will be performed and the collection of AEs, OEs (including completion of the bleeding questionnaire) and use of concomitant medication will be made.
Rationale for change		To provide guidance on the tests and assessments to be conducted for patients that discontinue study medication but are to be followed up to end of study.
Section to be changed		7.3.4 Interim analyses
Description of change		The DMC may choose to recommend capping the 110mg DE-DAT arm at the interim analysis stage if DTE or MBE event rates are different in patients who are ≥80 years old. Has been changed to: The DMC may choose to recommend capping the 110mg DE-DAT arm at the interim analysis stage if the DTE or MBE event rates **were to differ significantly from the trial assumptions and/or the anticipated event rates**.
Rationale for change		To reflect the responsibilities of the DMC and not limit their remit
Section to be changed		Section 9 References
Description of change		1) Reference P14-02938 added 2) References P13-12832, R11-2774, R13-4131, R13-4137, R13-4177, R13-5264 removed. 3) Reference R05-0344 updated to: Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, Definition of major bleeding in clinical **investigations of antihemostatic medicinal products in non-surgical patients. J**

Number of global amendment		1
		Thromb Haemost 3, 692 - 694 (2005) 4) Reference R15-0010 added
Rationale for change		1) Addition of new reference as result of AESI / DILI removal 2) Removal of references included in error that are not referenced within the protocol 3) Correction 4) Updated publication added
Section to be changed		Section 10 Appendices
Description of change		Appendix 10.1 Clinical Evaluation of Liver Injury has been removed and subsequent appendices have been re-numbered.
Rationale for change		See rationale specified in section 5.2.2.2 Definitions of AEs
Section to be changed		Section 10.1.1 (Formerly Section 10.2.1)
Description of change		Section heading re named from: When to start dabigatran etexilate following treatment by parenteral anticoagulants to: When to start dabigatran etexilate following treatment by **other** anticoagulants And the following text has been added: **Vitamin K antagonists** **Patients already on VKA, should start dabigatran etexilate once the INR is <2.0. If the INR is ≥2.0, study medication can be dispensed but the patient will be instructed not to start it until notified. Follow-up INR testing will be performed in 1-2 day intervals until INR falls below 2.0, at which time the patient will be instructed to start taking the study medication.** **Novel Oral Antiocagulants** **Patients taking apixaban, edoxaban or**

Number of global amendment		1
		rivaroxaban, dabigatran etexilate can be initiated at the time the next dose of the novel oral anticoagulant would have been due. As there is no clinical experience for switching from other novel oral anticoagulants to dabigatran etexilate, the decision must be taken based on clinical considerations and recommendations [P13-06400].
Rationale for change		Guidance updated to cover switch from oral anticoagulant aswell as parenteral anticoagulant.
Section to be changed		Section 10.1.2 (Formerly Section 10.2.2)
Description of change		Section heading re named from When to start warfarin following treatment by parenteral anticoagulants or VKAs to: When to start warfarin following treatment by **other** anticoagulants or VKAs And the following text has been added: **Novel Oral Anticoagulants** **An overlapping therapy with both novel oral anticoagulant and warfarin should not be performed for patients randomised to warfarin. It is recommended to use bridging therapy with a parenteral anticoagulant instead while initiating warfarin.** **The novel oral anticoagulant should be discontinued and the parenteral anticoagulant should be started at the time of the next scheduled dose of the novel oral anticoagulant (in line with the respective novel oral anticoagulant label).**
Rationale for change		Guidance updated to cover switch from novel oral anticoagulant aswell as parenteral anticoagulant.

Number of global amendment		2
Date of CTP revision		05 April 2016
EudraCT number		2013-003201-26
BI Trial number		1160.186
BI Investigational Product(s)		Pradaxa®, dabigatran etexilate
Title of protocol		A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting (**RE-DUAL PCI**)
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		Clinical Trial Protocol Synopsis Objectives
Description of change		The study aims to show non-inferiority of both doses of DE-DAT when compared to Warfarin-TAT in efficacy and safety. Efficacy will be determined by comparing a composite event rate of death, MI, stroke and systemic embolism (SE). Safety will be determined by comparing the rates of clinically relevant bleeding, assessed using the modified International Society of Thrombosis and

Number of global amendment		2
		Haemostasis (ISTH) major classification. Has been changed to: The study aims to show non-inferiority of **each dose** of DE-DAT when compared to Warfarin-TAT in **terms of** safety. **Safety is** determined by bleeding **events**, assessed using the modified International Society of Thrombosis and Haemostasis (ISTH) classification **of Major Bleeding and Clinically Relevant Non-Major Bleeding Events (CRNMBE).**
Rationale for change		The study has been progressing behind schedule due to many reasons (e.g. patients previously treated with NOACs not willing to be randomised to warfarin, patients with co-morbidities not qualifying for the study). Although, a recent protocol amendment 1 (dated 16-Sep-2015) included some measures to facilitate recruitment (e.g. expanding the time-window for study drug administration, simplifying laboratory requirements for selection of patients), these changes alone are not considered to be sufficient to achieve the original required number of patients (8,520) in the planned timeline. Thus, the study design needed to be revised and will now focus on safety. It will be powered to test the non-inferiority of each of the dabigatran etexilate doses (110mg and 150 mg bid) in a dual antithrombotic regimen versus warfarin in a triple antithrombotic regimen in respect to bleeding events (time to first ISTH major bleeding or clinically relevant non-major bleeding event). Efficacy parameters (e.g. all death, myocardial infarction, stroke/systemic embolism), including the original co-primary endpoints (DTE), will now be evaluated as secondary endpoints. The adoption of a safety primary endpoint is similar to other contemporary clinical trials in the same setting.
Section to be changed		Clinical Trial Protocol Synopsis total entered and each treatment
Description of change		Total entered: 8520

Number of global amendment		2
		Has been changed to: **2502** Each treatment: 2840 Has been changed to: **834**
Rationale for change		See rationale for first change, sample size calculations now based on revised study design focusing on safety.
Section to be changed		Clinical Trial Protocol Synopsis Criteria for Efficacy
Description of change		The dual primary endpoints are a composite endpoint of efficacy and a safety endpoint: 1. Time to death or first thrombotic event (all death, MI, stroke/SE) 2. Time to first major bleed (ISTH major) Has been changed to: The primary **endpoint for this trial is a safety endpoint, please see below.** **The secondary efficacy** endpoints **(all time to first event)** are**:** • **A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG** • **A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)** • **Individual outcome events:** o **All death (Cardiovascular death, Non-cardiovascular death, Undetermined),** o **MI** o **Stroke**

Number of global amendment		2
		○ **SE** ○ **Stent Thrombosis** • **Composite endpoint of death + MI + stroke** • **Unplanned revascularisation by PCI/CABG**
Rationale for change		Efficacy parameters (e.g. all death, myocardial infarction, stroke/systemic embolism), including the original co-primary composite endpoint (DTE), will now be evaluated as secondary endpoints. A composite endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG has been included comparable to the composite efficacy secondary endpoint included in the WOEST study.
Section to be changed		Clinical Trial Protocol Synopsis Criteria for Safety
Description of change		See criteria for efficacy Has been changed to: **The primary endpoint for this trial is time to first ISTH Major or Clinically Relevant Non-Major Bleeding Event.**
Rationale for change		The study design has been revised to focus on safety.
Section to be changed		Clinical Trial Protocol Synopsis Statistical methods
Description of change		The following text has been added: **To control the Type I error rate at a one-sided 0.025 level, a hierarchical procedure for multiple testing will be used to test the safety hypotheses. Additional testing for safety and efficacy endpoints will also be included in this hierarchical procedure.**
Rationale for change		To clarify that a hierarchical approach will replace the original Benjamini-Hochberg procedure as the Type I error rate control method.
Section to be changed		1.1 Medical Background
Description of change		The present recommendation of the European and

Number of global amendment		2
		North American Consensus of using triple therapy for patients with recent MI and/or PCI and concurrent AF is established because of OAC being indicated for AF patients with stroke risk factors and DAT being indicated after ACS or PCI [P10-07397, P11-09369]. Has been changed to: Recommendation of the European and North American Consensus of using triple therapy for patients with recent MI and/or PCI and concurrent AF is established because of OAC being indicated for AF patients with stroke risk factors and DAT being indicated after ACS or PCI [P10-07397, P11-09369]. **The WOEST results have been reflected in some of the recent guidelines for NVAF patients undergoing PCI with stenting [P14-05384, P14-12794, P16-02545] which recommend to consider the use of DAT in certain patients.**
Rationale for change		Updated to include reference to recently issued guidelines and publications
Section to be changed		2.2 Trial Objectives
Description of change		The study aims to show non-inferiority of both doses of DE-DAT when compared to Warfarin-TAT in efficacy and safety. Efficacy will be determined by comparing a composite event rate of death, MI, stroke and SE. Safety will be determined by comparing the rates of clinically relevant bleeding, assessed using the modified International Society of Thrombosis and Haemostasis (ISTH) major classification. Has been changed to: The study aims to show non-inferiority of **each dose** of DE-DAT when compared to Warfarin-TAT in **terms of** safety. Safety will be determined by comparing the rates of bleeding **events**, assessed using the modified International Society of Thrombosis and Haemostasis (ISTH) classification **of Major Bleeding and CRNMBE**.
Rationale for change		See rationale for first change, objective aligned with new study design focusing on safety.

Number of global amendment		2
Section to be changed		2.3 Benefit - Risk Assessment
Description of change		Therefore, a thorough exploration of a less-is-more approach is crucial as no firm knowledge exists on the effectiveness of adding 2 instead of 1 antiplatelet agent on top of OAC. …… A dual antithrombotic regimen is particularly appealing due to the potential benefit in terms of reduced risk of intracranial bleeding as well as due to the potential benefit of a reduced risk of major bleeding events in a post-PCI setting while maintaining the required level of efficacy for preventing the major ischaemic thrombotic events post-procedure (death, stroke, MI). Has been changed to: **The WOEST results have nevertheless been reflected in some of the recent guidelines for NVAF patients undergoing PCI with stenting [P14-05384, P14-12794, P16-02545] which recommend to consider the use of DAT in certain patients. However, data from clinical trials concerning the possibility of implementing DAT regimens with dabigatran etexilate and other new NOACs in this setting are needed.** ……. A dual antithrombotic regimen **with a NOAC** is particularly appealing due to the potential benefit in terms of reduced risk of intracranial bleeding as well as due to the potential benefit of a reduced risk of major bleeding events in a post-PCI setting.
Rationale for change		See rationale for first change. Text aligned with the change in study design.
Section to be changed		3.1 Overall Trial Design And Plan
Description of change		This trial is designed to test two combined efficacy-safety hypotheses in NVAF patients that have undergone a successful PCI (elective or due to ACS)

Number of global amendment		2
		with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure. ……. The trial is event driven and is designed to continue until 723 deaths or thromboembolic events (in total) occur. Has been changed to: This trial is designed to test **the** safety in NVAF patients that have undergone a successful PCI (elective or due to ACS) with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure. ….. The trial is event driven and is designed to continue until **approximately 500 patients with at least one MBE or CRNMBE** (in total) occur.
Rationale for change		The study design has been revised to focus on safety, for more details refer to rationale for first change
Section to be changed		3.2 Discussion Of Trial Design, Including The Choice Of Control Group(S)
Description of change		The following text has been added: **The WOEST results have been reflected in some of the recent guidelines for NVAF patients undergoing PCI with stenting [P14-05384, P14-12794, P16-02545] which recommend to consider the use of DAT in certain patients. However, data from clinical trials concerning the possibility of implementing DAT regimens with dabigatran etexilate and other new NOACs in this setting are needed.**
Rationale for change		Updated to include reference to recent guidelines and publications

Number of global amendment		2
Section to be changed		3.3 Selection Of Trial Population
Description of change		In order to test the two combined efficacy-safety hypotheses in NVAF patients that have undergone a successful PCI, at least 2840 patients per treatment group are estimated to be required (see Section 7.6). Approximately 700 trial centres worldwide will participate in the trial. Has been changed to: In order to test the two combined efficacy-safety hypotheses in NVAF patients that have undergone a successful PCI, at least **834** patients per treatment group are estimated to be required (see Section 7.6). Approximately **550** trial centres worldwide will participate in the trial.
Rationale for change		See rationale for first change, sample size calculations now based on revised study design focusing on safety.
Section to be changed		4.1.1 Identity Of BI Investigational Product And Comparator Products
Description of change		For easy identification warfarin tablet strengths will have a different colour bottle label. Has changed to: For easy identification warfarin tablet strengths will have a different colour label.
Rationale for change		Reference to packaging removed to take into account the plan for the new warfarin packaging.
Section to be changed		4.1.6 Packaging, Labelling, And Re-Supply
Description of change		Patients on warfarin will receive the required combination of 1mg, 3mg and 5mg tablets in bottles according to their actual needs as defined by the measured INR value. Each warfarin bottle will contain 66 tablets. Warfarin bottles should be checked at each visit to ensure the patient has sufficient supplies and that expiry dates will not be compromised prior to the next clinic visit.

Number of global amendment		2
		Has been changed to: Patients on warfarin will receive the required combination of 1mg, 3mg and 5mg tablets in bottles **or blister packs** according to their actual needs as defined by the measured INR value. Each warfarin bottle will contain 66 tablets. **Each blister pack will contain 70 tablets.** Warfarin **supplies** should be checked at each visit to ensure the patient has sufficient **quantity** and that expiry dates will not be compromised prior to the next clinic visit.
Rationale for change		Updated to also reflect the new warfarin packaging that is planned.
Section to be changed		4.1.7 Storage conditions
Description of change		All unused medication including bottles and outer boxes (empty or filled) must be either returned to the Sponsor, or, following written authorisation from the Sponsor, may be destroyed at site. Has been changed to: All unused medication including bottles, **blisters** and outer boxes (empty or filled) must be either returned to the Sponsor, or, following written authorisation from the Sponsor, may be destroyed at site.
Rationale for change		Updated to also reflect the new warfarin packaging that is planned.
Section to be changed		Figure 4.2.1.1: 1 Management of bleeding on dabigatran therapy
Description of change		The following text has been added: **Administration of reversal agent[4]** **[4] see Section 4.2.1.7 Overdose, for more information regarding the specific reversal agent for dabigatran**
Rationale for change		To add the reversal agent for dabigatran into the guidance on management of bleeding on dabigatran therapy.
Section to be changed		4.2.1.7 Overdose Specific reversal agent to dabigatran

Number of global amendment		2
Description of change		A specific reversal agent (idarucizumab) has been developed and is currently being reviewed for registration in various countries. Has been changed to: A specific reversal agent (idarucizumab) has been developed and is currently **available in many countries and** being reviewed for registration in various **other** countries.
Rationale for change		Updated to reflect current approval status of idarucizumab
Section to be changed		5.1.1 Endpoints of efficacy
Description of change		The dual primary endpoints for this trial are a composite endpoint of efficacy and a safety endpoint: 1. Time to death or first thrombotic event (DTE) (all death, MI, stroke/SE) 2. Time to first ISTH Major Bleeding Event (MBE) The secondary endpoints of efficacy are (all time to event endpoints): 1. Individual outcome events: o All death ▪ Cardiovascular death ▪ Non-cardiovascular death ▪ Undetermined o MI o Stroke o SE o Stent thrombosis 2. Composite endpoint of death + MI + stroke 3. Repeated revascularisation by PCI/CABG Has been changed to: The primary **endpoint** for this trial **is** a safety endpoint. **See section 5.2.1. There are no primary efficacy endpoints.** The secondary **efficacy** endpoints (all time to **first**

Number of global amendment		2
		event) **are**: **1. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG** **2. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)** 3. Individual outcome events: o All death o Cardiovascular death o Non-cardiovascular death o Undetermined o MI o Stroke o SE o Stent thrombosis 4. Composite endpoint of death + MI + stroke 5.**Unplanned** revascularisation by PCI/CABG
Rationale for change		Efficacy parameters including combined endpoints (e.g. all death, myocardial infarction, stroke/systemic embolism) will now be evaluated as secondary endpoints.
Section to be changed		5.1.2.6 Repeated revascularisation by PCI/CABG
Description of change		Repeated revascularisation due to objectively documented recurrent ischaemia, stent thrombosis or ACS. These cases will not undergo adjudication. Has been changed to: Repeated revascularisation due to objectively documented recurrent ischaemia, stent thrombosis or ACS. **Unplanned revascularisation is any repeated revascularisation not planned prior to informed consent.** These cases will not undergo adjudication.
Rationale for change		To add clarity that unplanned revascularisation is any repeated revascularisation not planned prior to informed consent
Section to be changed		5.2.1 Endpoints of safety
Description of change		The dual primary endpoints for this trial are a composite endpoint of efficacy and a safety

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		endpoint (see Section 5.1.1). Other safety endpoints are: 1.Clinically relevant bleeding measured using the following definitions: • Bleeding Academic Research Consortium (BARC) ≥3 • TIMI group - Major and Minor 2.Minor and total bleeding (ISTH, BARC and TIMI) 3.Intracranial haemorrhage Has been changed to: The primary **endpoint** for this trial **is time to first ISTH MBE or CRNMBE. For definition of CRNMBE see section 5.2.2.1.** Other safety endpoints are: **1.Major bleeding (ISTH)** **2.CRNMBE (for definition see section 5.2.2.1)** 3.Clinically relevant bleeding measured using the following definitions: • Bleeding Academic Research Consortium (BARC) ≥3 • TIMI group - Major and Minor 4.Minor and total bleeding (ISTH, BARC and TIMI) 5.Intracranial haemorrhage
Rationale for change		The study design has been revised to focus on safety, for more details refer to rationale for first change
Section to be changed		5.4 Appropriateness Of Measurements
Description of change		The primary endpoints for this study are combined efficacy and safety endpoints 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]). Has been changed to: The primary **endpoint** for this study **is a** safety **endpoint** using the ISTH definition f**or major**

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		bleeding and CRNMBEs which **are** similar **endpoints** to **those** used in **other contemporary clinical trials** in the same setting **(ClinicalTrials.gov: NCT01830543 and NCT02415400).**
Rationale for change		Updated to reflect new study design
Section to be changed		7.1 Statistical Design - Model
Description of change		This study is designed to test two combined efficacy-safety hypotheses in NVAF patients that have undergone a successful PCI (elective or due to ACS) with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure. The two primary outcomes (one composite efficacy outcome and one safety outcome) are stated in Section 5.1.1. 1. Efficacy: combined thrombotic events or death (DTE: all death + MI + stroke/SE). 2. Safety: ISTH Major Bleeding Events (MBE) Has been changed to: This study is designed to test **a** safety **hypothesis** in NVAF patients that have undergone a successful PCI (elective or due to ACS) with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure. **The primary outcome is stated in Section 5.2.1.** 1. **ISTH MBE and CRNMBE**
Rationale for change		The study design has been revised to focus on safety, for more details refer to rationale for first change
Section to be changed		7.2 Null And Alternative Hypotheses

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Description of change		Two combined efficacy-safety hypotheses (110mg Dabigatran Etexilate (DE-DAT) vs. warfarin-TAT and 150mg DE-DAT vs. warfarin-TAT) will be tested: 1.110mg DE-DAT is non-inferior to warfarin-TAT over the duration of the trial with respect to DTE AND non-inferior[1] with respect to MBE over the duration of the trial 2.150mg DE-DAT is non-inferior to warfarin-TAT over the duration of the trial with respect to DTE AND non-inferior[1] with respect to MBE over the duration of the trial. The study will be considered a success if either combined hypothesis above is accepted. To control the Type I error rate at a one-sided 0.025 level, the Benjamini-Hochberg [P05-11198] procedure for multiple testing will be used to test the above hypotheses. Specifically, the study will be considered a statistical success under the following scenarios: • Scenario A o Hypothesis 1 is proven if the non-inferiority of 110mg DE-DAT to warfarin-TAT in DTE AND the non-inferiority[2] of 110mg DE-DAT to warfarin-TAT in MBE are both met at a one-sided 0.025 level of significance. AND o Hypothesis 2 is proven if the non-inferiority of 150mg DE-DAT to warfarin-TAT in DTE AND the non-inferiority1 of 150mg DE-DAT to warfarin-TAT in MBE are both met at a one-sided 0.025 level of

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		significance • Scenario B o Hypothesis 1 is proven if the non-inferiority of 110mg DE-DAT to warfarin-TAT in DTE <u>AND</u> the non-inferiority[1] of 110mg DE-DAT to warfarin-TAT in MBE are both met at a one-sided 0.0125 level of significance. <u>OR</u> o Hypothesis 2 is proven if the non-inferiority of 150mg DE-DAT to warfarin-TAT in DTE AND the non-inferiority1 of 150mg DE-DAT to warfarin-TAT in MBE are both met at a one-sided 0.0125 level of significance The Non-Inferiority (NI) margin used for DTE and MBE will be 1.38 (on the relative HR scale). See Section 7.6 for a clinical justification of this margin. The upper bound of the CI of the HR of DE-DAT vs. warfarin-TAT (one-sided 97.5% or one-sided 98.75%) will be compared to this NI margin for the NI testing. [1] Superiority will be tested if non-inferiority has been demonstrated first Has been changed to: Two safety hypotheses (110mg Dabigatran Etexilate (DE-DAT) vs. warfarin-TAT and 150mg DE-DAT vs. warfarin-TAT) will be tested: 1. 110mg DE-DAT is non-inferior to warfarin-TAT with respect to MBE/**CRNMBE** over the duration of the trial 2. 150mg DE-DAT is non-inferior to warfarin-TAT **with respect to MBE/CRNMBE** over the duration of the trial. To control the Type I error rate at a one-sided 0.025

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		level, **a hierarchical** procedure for multiple testing will be used to test the above hypotheses. **Additional testing for safety and efficacy endpoints will also be included in this hierarchical procedure. The following hierarchical procedure will be applied:** **Step 1 – Non-inferiority of 110mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance** **Step 2 – Non-inferiority of 150mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance** **Step 3 – Non inferiority of 150mg DE-DAT and 110mg DE-DAT combined to warfarin-TAT in DTE and unplanned revascularisation by PCI/CABG is met at the one-sided 0.025 level of significance** **Step 4 –Superiority of 110mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance** **Step 5 – Non inferiority of 150mg DE-DAT and 110mg DE-DAT combined to warfarin-TAT in DTE is met at the one-sided 0.025 level of significance** **Step 6 – Superiority of 150mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance** **If any of the steps above fail to meet statistical significance, the testing procedure will stop at that step and subsequent tests will not be performed.** The Non-Inferiority (NI) margin used for MBE/**CRNMBE** will be 1.38 (on the relative HR scale). See Section 7.6 for a clinical justification of this margin. The upper bound of the **Wald confidence interval (CI)** of the HR of DE-DAT vs. warfarin-TAT (one-sided 97.5%) will be compared to this NI margin for the NI testing.

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Rationale for change		To clarify that a hierarchical approach will replace the original Benjamini-Hochberg procedure as the Type I error rate control method.
Section to be changed		7.3.1 Primary Analyses
Description of change		The dual primary endpoints (both measured from date of randomisation to end of observation period) are: • Time to first DTE (composite efficacy outcome) • Time to first MBE (safety outcome) as determined by the IAC. They will be analysed using the stratified Cox proportional hazards regression model including factors for age (<80 or ≥80 years old) and treatment arm (110mg DE-DAT vs warfarin-TAT and 150mg DE-DAT vs warfarin-TAT) …. Patients who discontinue study medication will be followed until the end of the trial for vital status (DTE and MBE). Patients who are lost to follow-up for vital status will be censored for the primary endpoints at the time of their last known vital status. …….. The robustness of the primary analyses will be assessed by an on-treatment analysis. This on-treatment analysis will only count events that occur while a patient is taking study medication (including the REP of 6 days – see Section 5.2.2.2). Has been changed to The primary **endpoint** (measured from date of randomisation to end of observation period) **is**: • Time to first MBE/**CRNMBE** as determined by the IAC. **It** will be analysed using the stratified Cox proportional hazards regression

Number of global amendment		2
		model including factors for age (<80 or ≥80 years old) and treatment arm (110mg DE-DAT vs warfarin-TAT and 150mg DE-DAT vs warfarin-TAT). …….. Patients who discontinue study medication will be followed until the end of the trial. Patients who are lost to follow-up for vital status will be censored for the primary **endpoint** at the time of their last known vital status. …….. The robustness of the primary **analysis** will be assessed by an on-treatment analysis. This on-treatment analysis will only count events that occur while a patient is taking study medication (including the REP of 6 days – see Section 5.2.2.2). It will also analyse patients by the actual treatment that was being taken while the event occurred.
Rationale for change		The study design has been revised to focus on safety, for more details refer to rationale for first change. Patients will be followed up per section 6.2.2.2 of the protocol
Section to be changed		7.3.2 Secondary analyses

Description of change		Secondary efficacy endpoints (all time to first event, measured from date of randomisation to end of observation period) are:
		
		• All death
		  o Cardiovascular death
		  o Non-cardiovascular death
		  o Undetermined
		• MI
		• Stroke
		• SE
		• Stent thrombosis
		• Composite of death + MI + stroke
		• Repeated revascularisation by PCI /CABG
		
		Time to first event endpoints will be analysed using the same methods as for the primary endpoints. No

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		multiplicity adjustments are planned for secondary endpoints. Nominal one-sided p-values will be reported for descriptive purposes.
		
		All secondary analyses will be performed on the FAS. The robustness of these analyses will be assessed by on-treatment analyses (see Section 7.3.1).
		
		The other endpoint of TIA (see Section 5.3.1) will be analysed using the same approaches as above.
		
		Has been changed to:
		
		Secondary efficacy endpoints (all time to first event, measured from date of randomisation to end of observation period) are:
		
		• **A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI /CABG**
		• **A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)**
		• All death
		  o Cardiovascular death
		  o Non-cardiovascular death
		  o Undetermined
		• MI
		• Stroke
		• SE
		• Stent thrombosis
		• Composite of death + MI + stroke
		• **Unplanned** revascularisation by PCI /CABG
		
		Time to first event endpoints will be analysed using the same methods as for the primary **endpoint**. No multiplicity adjustments are planned for secondary endpoints **(apart from those mentioned in the hierarchy, see Section 7.2)**. Nominal one-sided p-values will be reported for descriptive purposes.
		
		All secondary analyses will be performed on the FAS. The robustness of these analyses will be assessed by on-treatment analyses (see Section

Number of global amendment		2
		7.3.1). TIA (**further endpoint**, see Section 5.3.1) will be analysed using the same approaches as above.
Rationale for change		All efficacy parameters (e.g. all death, myocardial infarction, stroke/systemic embolism), including the original co-primary endpoint (DTE), will now be evaluated as secondary endpoints.
Section to be changed		7.3.3. Safety Analyses
Description of change		These endpoints will be analysed using the same methods as the primary endpoints. No multiplicity adjustments are planned for safety endpoints (apart from those mentioned in the hierarchy, see Section 7.2). Has been changed to: These endpoints will be analysed using the same methods as the primary endpoints. No multiplicity adjustments are planned for safety endpoints **(apart from those mentioned in the hierarchy, see Section 7.2)**.
Rationale for change		To clarify that a hierarchical approach will replace the original Benjamini-Hochberg procedure as the Type I error rate control method.
Section to be changed		7.3.4 Interim analyses
Description of change		Has been updated to say: No interim analysis is planned, but blinded sample size re-calculations may be performed. The conduct of the trial will be monitored by a DMC. The DMC will hold regular meetings to monitor imbalance in endpoints, with the focus on MBE/CRNMBE. The DMC's objectives and working practices are documented in the DMC charter. The DMC may recommend terminating the study at any time for DE-DAT safety concerns. Further details will be included in the DMC charter. The DMC will have unblinded safety reviews every

Number of global amendment		2
		2 months.
Rationale for change		Removal of unblinded interim analyses due to study design changes. The DMC will continue with the tasks specified in the DMC charter.
Section to be changed		7.6 Determination Of Sample Size
Description of change		Has been updated to say: This is an event-driven trial where it is assumed that the first patient recruited into the study will be followed up for a maximum of approximately 30 months and the last patient recruited into the trial will be followed up for a minimum of 6 months. It is assumed that patient accrual will be approximately uniform over the 24 month recruiting period. **The proportion of patients with at least one MBE/CRNMBE at one year is estimated to be 14% based on current blinded trial data.** A relative NI margin for the **original co-primary endpoint (DTE)** was chosen in analogy to recent SPAF trials with primary endpoints of stroke/SE, where 1.38 was used by the FDA for ximelagatran, apixaban, rivaroxaban and dabigatran to preserve at least 50% of the relative reduction (on the log scale) in the risk associated with warfarin in six previous (historical), randomised, controlled trials. See publication by Jackson K, Gersh BJ, Stockbridge N, et al. [R08-2662]. **The same NI margin has been applied to MBE/CRNMBE** as it was considered the most clinically relevant available reference in the absence of any other type of data. The overall sample size is driven by the non-inferiority comparison of **MBE/CRNMBE** between 110mg DE-DAT or 150mg DE-DAT and warfarin-TAT. With alpha=**0.025** (one-sided) and **14% of** patients with at least **one event at one year, 334 patients with at least one MBE/CRNMBE** in each pair of treatment groups (i.e. **167** patients with **MBE/CRNMBE** per treatment group) are required to achieve **83.6%** power for this endpoint, yielding a final sample size estimated at **834** patients in each treatment group (i.e. 2502 randomised patients in

Number of global amendment		2
		total). **Therefore** approximately **500** patients with at least one **MBE/CRNMBE** are required in total across the three treatment groups. As described in Section 7.3.1, for the comparison of 150mg DE-DAT vs warfarin-TAT, patients from the EU/ROW who are ≥80 years old will be excluded from the warfarin-TAT arm (as patients who are ≥80 years old from the EU/ROW are not randomised to 150mg DE-DAT). The actual number of patients entered may increase or decrease based upon actual event rates. As this is an event-driven trial, the trial can conclude earlier, if an adequate number of events are reported sooner or later, if more events are needed. Because the last patient entered must be followed up for a minimum of 6 months and to avoid accruing too many events, recruitment will need to be stopped before the required number of events are observed. **Blinded** event rates will be monitored closely by **BI** (and the Executive Steering Committee) to predict the time at which recruitment should be stopped. Sites will be notified when recruitment ends.
Rationale for change		See rationale for first change, sample size calculations now based on revised study design focussing on safety.
Section to be changed		9.1 Published References
Description of change		**The following references have been added:** **P14-05384 January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society: developed in collaboration with the Society of Thoracic Surgeons. J Am Coll Cardiol, 64(21):2246-2280 (2014)** **P14-12794 Lip GYH, Windecker S, Huber K, Kirchhof P, Marin F, Berg JM ten, Haeusler KG,**

Number of global amendment		2
		Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J, 35(45):3155-79 (2014) **P16-02545 Windecker S, et al, 2014ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS): developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 35, 2541 - 2619 (2014)**
Rationale for change		Recently released publications added
Section to be changed		9.2 Unpublished References
Description of change		The following reference has been added: **U11-1642-01 [redacted]. Amendment to Pradaxa ® CCDS after approval of dabigatran etexilate for SPAF in US and EU Amendment to Pradaxa ® CCDS concerning the use of fibrinolytic agents for acute ischemic stroke and the simultaneous use of ticagrelor (plus ASA), selective serotonin re-uptake inhibitors or dronedarone (Multaq®). 23 September 2011**
Rationale for change		Previous omission.
Section to be changed		10.1.3 Bridging Therapy (e.g. for temporary interruptions of study drug due to interventions)

Number of global amendment		2
Description of change		For recommendations how to switch back to study drug (dabigatran etexilate or warfarin) see Sections 10.2.1 and 10.2.2. Has been changed to: For recommendations how to switch back to study drug (dabigatran etexilate or warfarin) see Sections 10.**1**.1 and 10.**1**.2.
Rationale for change		Correction in sections referenced

Number of global amendment		3
Date of CTP revision		21 July 2016
EudraCT number		2013-003201-26
BI Trial number		1160.186
BI Investigational Product(s)		Pradaxa®, dabigatran etexilate
Title of protocol		A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting (**RE-DUAL PCI**)
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		5.1.2.6 Repeated revascularisation by PCI/CABG
Description of change		These cases will not undergo adjudication. Has been changed to: These cases will undergo adjudication for confirmation of whether the event was unplanned, the type of procedure, the indication and if it is a target lesion revascularisation.
Rationale for change		The DMC have requested that repeated revascularisations are adjudicated by the IAC.

APPROVAL / SIGNATURE PAGE

Document Number: c02214385 **Technical Version Number:9.0**

Document Name: 1160-0186-clinical-trial-protocol-version-04

Title: A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary…

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	01 Aug 2016 09:24 CEST
Author-Trial Statistician		01 Aug 2016 10:32 CEST
Author-Trial Clinical Monitor		01 Aug 2016 11:39 CEST
Approval-Pharmacovigilance		01 Aug 2016 14:26 CEST
Approval-Team Member Medicine		01 Aug 2016 16:07 CEST
Verification-Paper Signature Completion		02 Aug 2016 12:11 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed