

**CLINICAL TRIAL PROTOCOL**

Document Number:		<b>c03714648-02</b>
<b>EudraCT No.:</b>	2015-004412-38	
<b>BI Trial No.:</b>	1160.248	
<b>BI Investigational Product:</b>	Pradaxa®, dabigatran etexilate	
<b>Title:</b>	RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period	
<b>Brief Title:</b>	A clinical trial comparing efficacy and safety of dabigatran etexilate with warfarin in patients with cerebral venous and dural sinus thrombosis (RE-SPECT CVT)	
<b>Clinical Phase:</b>	III	
<b>Trial Clinical Monitor:</b>	Phone: Fax:	
<b>Coordinating Investigator:</b>	Phone: Fax:	
<b>Status:</b>	Final	
<b>Version and Date:</b>	<b>Version: 2.0</b>	<b>Date: 10 February 2017</b>
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## **CLINICAL TRIAL PROTOCOL SYNOPSIS**

<b>Name of company:</b>	<b>Boehringer Ingelheim</b>		
<b>Name of finished product:</b>	Pradaxa®		
<b>Name of active ingredient:</b>	Dabigatran etexilate		
<b>Protocol date:</b> 07 July 2016	<b>Trial number:</b> 1160.248		<b>Revision date:</b> 10 February 2017
<b>Title of trial:</b>	RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period		
<b>Principal Investigator &lt; for single-centre trial or &gt; Coordinating Investigator&lt; for multi-centre trial if applicable &gt;:</b>			
<b>Trial site(s):</b>	Multi-centre trial		
<b>Clinical phase:</b>	III		
<b>Objective(s):</b>	This is an exploratory trial to investigate the efficacy and safety of dabigatran etexilate versus dose-adjusted warfarin in patients with cerebral venous and dural sinus thrombosis (CVT).		
<b>Methodology:</b>	This is a phase III randomised, open label, exploratory trial with two parallel groups over 24 weeks, with blinded endpoint adjudication (PROBE design, i.e. prospective, randomised, open-label, blinded endpoint).		
<b>No. of patients:</b>			
<b>total entered:</b>	120 planned		
<b>each treatment:</b>	60 planned in each treatment arm		
<b>Diagnosis :</b>	CVT diagnosed using one or more of the following techniques:		

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<b>Name of active ingredient:</b>	Dabigatran etexilate		
<b>Protocol date:</b> 07 July 2016	<b>Trial number:</b> 1160.248		<b>Revision date:</b> 10 February 2017
	<ul style="list-style-type: none"> <li>• Magnetic Resonance Imaging (MRI)+MR venography (preferred) and/or</li> <li>• Computed tomography (CT)+CT venography and/or</li> <li>• MRI or CT in combination with catheter angiography (DSA)</li> </ul>		
<b>Main criteria for inclusion:</b>	<ul style="list-style-type: none"> <li>• Patients aged <math>\geq</math> 18 years and <math>&lt;</math> 79 years with confirmed diagnosis of CVT, with or without intracranial haemorrhage (ICH), excluding patients whose CVT is associated with central nervous system infection or is due to head trauma</li> <li>• Patient has achieved clinical stability after having received standard acute CVT treatment as required, including anticoagulation therapy for 5-15 days which has been administered until randomisation; anticoagulation must include full-dose low molecular weight heparin (LMWH) or unfractionated heparin (UFH) and may be followed by oral vitamin K antagonist (VKA) treatment.</li> <li>• Eligible for treatment with an oral anticoagulant for CVT</li> <li>• Exclusion criteria include conditions associated with increased risk of bleeding, severe renal impairment, active liver disease and current or recent malignancies</li> </ul>		
<b>Test product(s):</b>	Dabigatran etexilate		
<b>dose:</b>	150 mg b.i.d.		
<b>mode of administration:</b>	p.o		
<b>Comparator products:</b>	Warfarin		
<b>dose:</b>	1, 3 and 5 mg (dose adjusted to INR 2.0 – 3.0)		
<b>mode of administration:</b>	p.o.		

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Name of company:	Boehringer Ingelheim		
Name of finished product:	Pradaxa®		
Name of active ingredient:	Dabigatran etexilate		
Protocol date: 07 July 2016	Trial number: 1160.248		Revision date: 10 February 2017
Duration of treatment:	24 weeks		
Endpoints:	<p>Primary endpoint (based on adjudicated data):</p> <ul style="list-style-type: none"> <li>Composite endpoint: number of patients with major bleeding according to ISTH (International Society on Thrombosis and Haemostasis) criteria and venous thrombotic event (VTE) (recurring CVT; deep vein thrombosis (DVT) of any limb, pulmonary embolism (PE), splanchnic vein thrombosis) after up to 24 weeks</li> </ul> <p>Secondary efficacy endpoints (based on adjudicated data):</p> <ul style="list-style-type: none"> <li>Number of patients with recurring CVT; DVT of any limb, PE or splanchnic vein thrombosis after up to 24 weeks</li> <li>Cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses after up to 24 weeks</li> </ul> <p>Secondary safety endpoints (based on adjudicated data):</p> <ul style="list-style-type: none"> <li>Number of patients with major bleeding according to ISTH criteria after up to 24 weeks</li> <li>Composite endpoint of number of patients with new ICH or worsening of the haemorrhagic component of a previous lesion after up to 24 weeks</li> <li>Number of patients with clinically relevant non-major bleeding events (CRNMBE) after up to 24 weeks</li> <li>Number of patients with major bleeding according to ISTH criteria or CRNMBE after up to 24 weeks</li> <li>Number of patients with any bleeding event after up to 24 weeks (not based on adjudicated data)</li> </ul>		
Safety criteria:	In addition to the above mentioned safety endpoints the following safety parameters are assessed: laboratory parameters and adverse events.		

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<b>Name of active ingredient:</b>		Dabigatran etexilate	
<b>Protocol date:</b> 07 July 2016	<b>Trial number:</b> 1160.248		<b>Revision date:</b> 10 February 2017
<b>Statistical methods:</b>	The study is an exploratory trial and not intended for registration. No formal hypothesis will be tested. All analyses are descriptive in nature and confidence intervals and p-values from statistical models are used for exploratory purposes only		

## FLOW CHART

Trial Periods	Screening Period	Randomised Treatment Period				Follow-up period	Extended follow-up for early discontinuations
Visit	1 <sup>1</sup>	2 <sup>2</sup>	3	4	5 End of treatment <sup>3</sup>	6 <sup>3</sup>	7 <sup>4</sup>
Study Day	-1	Day 1	Day 29	Day 85	Day 169	Day 7 after Visit 5	Day 176
Time window for visits	Up to -15 days	none	±7 days	±7 days	±7 days	+7 days	+7 days
Informed consent <sup>1,5</sup>	X						
Demographics	X						
Medical history	X						
CVT risk score	X						
Physical examination	X	X				X	
NIHSS <sup>6</sup>	X						
Vital signs	X	X	X	X	X		
Weight and height <sup>7</sup>	X		X	X	X		
Safety laboratory tests	X		X	X	X		
Pregnancy test <sup>8</sup>	X		X	X	X		
12 lead-ECG		X					
Assessment of venous occlusion / recanalisation by imaging		X <sup>9</sup>				X <sup>10</sup>	
Assessment of intracranial haemorrhage by CT or MRI <sup>11</sup>	X <sup>9</sup>				X		
Review of in-/exclusion criteria	X	X					
Randomisation		X					
Dispense trial drugs		X	X	X			
First administration of trial medication		X					
INR / warfarin dose adjustment <sup>12</sup>		X		X			
Adverse events	X	X	X	X	X	X	X
Assessment of bleeding	X	X	X	X	X	X	X
Collection of data of new venous thrombotic events (CVT, DVT, PE, splanchnic vein thrombosis) <sup>11</sup>		X <sup>13</sup>	X	X	X	X	X
Compliance check			X	X	X		
Termination of trial medication					X		
Concomitant therapy	X	X	X	X	X	X	
Collection of post-study anti-coagulation information							X
Completion of patient participation <sup>15</sup>						X	X

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- 1) Signing of informed consent and subsequent screening should be done after the diagnosis of CVT has been established, treatment with parenteral anticoagulation has started and the patient is considered to be stable. A fictitious Day number (Day -1) has been assigned to the Screening Visit (Visit 1). See Footnote 2 and Sections [6.1](#), [6.2.1](#) and [6.2.2](#) on the performance of Visit 1 and Visit 2, including instructions on the use of existing pre-trial data (from moment of diagnosis of CVT) for the purpose of this trial.
- 2) Day of Randomisation. May be performed on the same day as Visit 1. In that case Visit 2 procedures that are performed as part of Visit 1 do not need to be repeated.
- 3) End of Treatment (EOT) and follow-up procedures (Visits 5 and 6) are performed for all patients at the time of discontinuation of trial medication. This includes patients who discontinue trial medication prior to Day 169 (the Day number does not apply in that case). See also footnotes 4 and 15.
- 4) Extended follow-up applies only to patients who discontinue trial medication early (see Section [3.3.4](#)).
- 5) Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's (Boehringer Ingelheim's) instructions.
- 6) National Institutes of Health Stroke Scale (NIHSS) is a tool used to evaluate impairment after a stroke. See Section [5.6.2](#). This neurological assessment is to be completed for the qualifying CVT.
- 7) Height is measured at screening only.
- 8) Pregnancy tests required for all women of childbearing potential. See Section [3.3.2](#) for definition of women of childbearing potential. A urine test is acceptable, unless local regulations demand a serum test to be performed. If a pregnancy test is not routinely performed in female CVT patients, the test at the Screening visit should be performed after informed consent has been obtained.  
In addition to the tests performed at the visits, women of child bearing potential will be supplied with pregnancy tests and instructed to perform pregnancy testing every 4 weeks when visits are more than 4 weeks apart.
- 9) At screening imaging should not be performed specifically for the trial. The imaging that was done for diagnosis of the cerebral venous or dural sinus thrombosis (CVT) will be used and should be submitted for review by the trial's Adjudication Committee (AC). It is expected that CVT is diagnosed and venous occlusion assessed by any of the following techniques: MRI+MR venography, CT+CT venography or MRI or CT in combination with catheter angiography (DSA).
- 10) At EOT the assessment of recanalisation must be done by MRI+MR venography. A separate MRI protocol will be provided as part of the ISF and should be followed for the EOT imaging. The EOT images should be submitted for review by the Adjudication Committee.
- 11) Throughout the trial, whenever routine imaging is performed due to worsening of the patient's condition, a suspected new intracranial haemorrhage or a new venous thrombotic event (VTE), those images are to be made available to the trial's AC for independent blinded review.  
EOT assessment of intracranial haemorrhage is to be done by MRI (see also Footnote 10).
- 12) Assessment of International Normalised Ratio (INR) for:
  - Patients who are on a vitamin K antagonist (VKA) prior to randomisation. At least one measurement prior to start of trial treatment in order to determine when to stop initial parenteral therapy and when to start trial treatment (see Section [4.1.4](#)); further measurements until start of trial treatment as outlined in Section 4.1.4;
  - Patients randomised to warfarin. Daily measurements from just prior to start of treatment until concomitant heparin treatment is stopped. At least two-weekly INR measurements for the first three months and monthly subsequently.
- 13) At Visit 2 information on any new venous thrombotic events since signing of consent is collected.
  
- 15) Completion of patient participation
  - Patients who complete the full treatment period of 169 days complete their participation at the follow-up visit (Visit 6);
  - Patients who discontinue trial medication early (see Section 3.3.4): after the follow-up visit they should be followed , for major bleeding events, VTE events and any other adverse events until Day 176 (25 weeks) after randomisation. They complete participation at that moment.

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## ABBREVIATIONS

AC	Adjudication Committee
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA/ASA	American Heart Association/American Stroke Association
ALT (SGPT)	Alanine aminotransferase
APCC	Activated prothrombin complex concentrates
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BP	Blood Pressure
CCDS	Company Core Data Sheet
CI	Confidence Interval
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form
CRNMBE	Clinically Relevant Non-Major Bleeding Event
CT	Computed Tomography
cTn	Cardiac troponin
CTP	Clinical Trial Protocol
CVT	Cerebral venous and dural sinus thrombosis
DEDP	Drug exposure during pregnancy
DMC	Data Monitoring Committee
DSA	Digital Subtraction Angiography
dTT	Diluted thrombin time
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
ECT	Ecarin clotting time
EFNS	European Federation of Neurological Societies
EOT	End of treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HI	Haemorrhagic infarction
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	Intracranial haemorrhage
IEC	Independent Ethics Committee
INR	International normalised ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

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ISF	Investigator Site File
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to treat
i.v.	intravenous
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
LPDD	Last Patient Drug Discontinuation
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
NIHSS	National Institutes of Health Stroke Scale
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamics
PE	Pulmonary Embolism
P-gp	P-glycoprotein
PH	Parenchymatous haematoma
PK	Pharmacokinetics
p.o.	per os (oral)
PPS	Per Protocol Set
PROBE	Prospective, Randomised, Open label, Blinded Endpoint
q.d.	quaque die (once a day)
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SC	Steering Committee
s.c.	subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SNRI	Serotonin norepinephrine re-uptake inhibitor
SOP	Standard Operating Procedure
SPAF	Stroke prevention in atrial fibrillation
SSRI	Selective serotonin re-uptake inhibitor
TCM	Trial Clinical Monitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
TT	Thrombin clotting time
TTR	Time in therapeutic range
UFH	Unfractionated heparin
ULN	Upper limit of normal
VKA	Vitamin K antagonist(s)
VTE	Venous thromboembolic event / venous thrombotic event
WBC	White blood cell
WOCBP	Women of childbearing potential

## **1. INTRODUCTION**

### **1.1 MEDICAL BACKGROUND**

According to the American Heart Association/American Stroke Association (AHA/ASA) Scientific Statement on Diagnosis and Management of Cerebral Venous Thrombosis, published 2011 [[R15-5005](#)], cerebral venous and dural sinus thrombosis (CVT) is a thrombosis of the dural sinus and/or cerebral veins considered to be an uncommon form of stroke. It is estimated that approximately 5 persons per million experience it annually and that it may account for 0.5% to 1% of all strokes. Even large medical centres only admit 5-10 cases in a given year [[R15-5879](#)]. At the same time, CVT can be life-threatening and can have a sustained negative impact on a patient's health status. Approximately 5 percent of patients die in the acute phase of the disorder [[R15-5857](#), [R15-5861](#)]. In addition, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) [[R15-4849](#)] found that acute CVT was associated with a 15 percent overall death or dependency rate at the end of follow-up, which varied from 3 to 78 months.

Although the pathophysiology of CVT is not yet completely understood, there are at least two different mechanisms that may contribute to the clinical features of CVT [[R15-5879](#)]:

- Thrombosis of cerebral veins or dural sinus leading to cerebral parenchymal lesions or dysfunction
- Occlusion of dural sinus resulting in decreased cerebrospinal fluid absorption and elevated intracranial pressure

Risk factors for CVT are diverse (e.g. coagulopathies, pregnancy, oral contraception, puerperium, head injury, etc.). It is noteworthy that 75% of all patients suffering CVT are female. The mean age of patients in ISCVT was 39 years [[R15-4849](#)] and only a few CVT patients (less than 10%) are older than 65 years of age.

CVT have a highly variable clinical presentation [[R15-5858](#)] and many of the symptoms are non-specific, making it difficult to diagnose. The onset of symptoms can be acute, sub-acute, or chronic. Symptoms and signs can be grouped in three major syndromes:

- Isolated intracranial hypertension syndrome (headache with or without vomiting in close to 90% of patients, papilledema, and visual problems) [[R15-5851](#)]
- Focal syndrome (focal deficits, seizures, or both)
- Encephalopathy (multifocal signs, mental status changes, stupor, or coma) [[R15-5878](#)]

In patients with CVT, 30-40% present with intracerebral haemorrhage [[R15-5859](#), [R15-5863](#)]. The haemorrhage in CVT is believed to be caused by venous outflow blockage and very high intradural and intravenous pressure, leading to both rupture of venules and to haemorrhagic transformation of venous infarctions. This difference in aetiology compared to arterial haemorrhagic stroke is why anticoagulation is not contraindicated in this setting.

Clinical trial results support this approach, as reflected in the AHA/ASA guidelines [[R15-5005](#)].

Magnetic resonance imaging (MRI) in combination with magnetic resonance (MR) venography is the most sensitive examination technique for demonstrating the thrombus and the occluded dural sinus or vein (absence of flow and intraluminal venous thrombus). Computed tomography (CT) venography is a useful alternative to MR venography. Although a head CT scan alone is normal in up to 30 percent of CVT cases and most of the findings with CVT are nonspecific; the overall accuracy of head CT combined with CT venography is 90 to 100 percent. Cerebral intra-arterial angiography is recommended when the diagnosis of CVT is uncertain, such as in the rare suspected cases of isolated cortical vein thrombosis, or when the clinical suspicion for CVT is high but CT venography or MR venography are inconclusive [[R15-5005](#)]. Regarding relevant lab values, an elevated plasma D-dimer level supports the diagnosis of CVT, but a normal D-dimer does not exclude CVT in patients with suggestive symptoms *and predisposing factors* [[R15-5005](#)]. In contrast, a recent meta-analysis concluded that *in low-risk patients* with isolated headache the absence of increased D-dimer levels does have a high predictive value for excluding CVT. In these patients D-dimer is as sensitive for diagnosing CVT as it is in Pulmonary Embolism (PE) and deep venous thrombosis (DVT) [[R15-6315](#)].

Initial therapy, as recommended by the AHA/ASA Scientific Statement, is intravenous (i.v.) heparin or subcutaneous (s.c.) low molecular weight heparin (LMWH). Upon stabilisation, the patient is switched to oral anticoagulation, until now, vitamin K antagonists (VKA). The duration of the oral anticoagulant therapy depends upon the suspected cause of the CVT. In patients with transient causes, 3-6 months; in patients with other factors, 6-12 months; in patients with recurrent CVT or venous thrombotic event (VTE) after CVT or first CVT in presence of severe thrombophilia, permanent anticoagulation is considered.

The immediate goals of antithrombotic treatment are:

- To recanalise the occluded sinus/vein
- To prevent the propagation of the thrombus to the bridging cerebral veins
- To treat, if applicable, an underlying prothrombotic state, in order to prevent venous thrombosis in other parts of the body, particularly PE [[R15-5864](#)], and to prevent the recurrence of CVT

Where available, endovascular treatment is another option, but its use is typically restricted to patients with a poor prognosis who have not responded to anticoagulation with heparin or LMWH [[R15-5865](#)]. Available data suggest that cerebral vein and sinus recanalisation occurs in 40 to 90 percent of patients after CVT, mostly within the first four months [[R15-5239](#)].

Randomised controlled studies with non-VKA oral anticoagulants have not been conducted in patients with CVT to date. Therefore information on their use in this indication is limited to publications of individual case studies and case series. The largest case series of patients with CVT administered dabigatran etexilate included 15 patients and there were no recurrent events detected over 6 months [[P15-10422](#)]. In order to evaluate their efficacy and safety in the treatment of CVT, clinical trials with non-VKA oral anticoagulants are needed.

## **1.2 DRUG PROFILE**

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

In vivo and ex vivo animal studies have demonstrated anti-aggregatory efficacy and anticoagulant activity of dabigatran after both i.v. and oral administration in various animal models of arterial and venous thrombosis.

Dabigatran etexilate was well tolerated in more than 47 Phase I studies at all doses evaluated (up to 400 mg three times a day) with no evidence of major bleeding. These studies have established the pharmacokinetics (PK), pharmacodynamics (PD) and tolerability of dabigatran etexilate, and included testing selected populations (Japanese, elderly, those with renal and hepatic impairment), testing for food-drug and drug-drug interactions and for QT prolongation.

The PK profile is characterized by peak plasma concentrations of dabigatran etexilate that occur approximately two hours after oral administration of the prodrug and a half-life depending on renal function (see Table 4.2.1.3: 1 for prolongation of half-life with decline in renal function). Dabigatran maximum plasma concentrations and area under curve increase in a dose proportional manner. Pharmacokinetic steady state is reached in three days with twice daily (b.i.d.) dosing; PD (anticoagulant) activity is closely correlated with dabigatran plasma concentrations. Dabigatran is eliminated primarily by the kidneys with urinary excretion accounting for approximately 80% of the dose administered intravenously. The absolute bioavailability of the current capsule formulation of dabigatran etexilate is approximately 6.5%.

Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and had no effects in vitro on human cytochrome P450 enzymes. Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein (P-gp). In Phase I drug-drug interaction studies with other P-gp substrates, no significant influence of dabigatran etexilate on the PK of atorvastatin, diclofenac or digoxin was found, and the exposure of dabigatran was not significantly altered by these drugs. There was, however, an effect on dabigatran etexilate bioavailability after co-administration with some P-gp inhibitors or inducers. The concomitant use with P-gp inducers (e.g. rifampicin) reduces exposure to dabigatran and should be avoided. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole (contraindicated), dronedarone (not recommended), ticagrelor and clarithromycin) results in increased dabigatran plasma concentrations which increases bleeding risk.

The concomitant use of dabigatran etexilate with treatments that act on haemostasis or coagulation including VKA can markedly increase the risk of bleeding. Antiplatelet agents (acetylsalicylic acid (ASA) or clopidogrel) are also known to increase bleeding; in the phase III RE-LY study in patients with atrial fibrillation bleeding risk was

about twice as high in patients receiving additional ASA or clopidogrel both in patients treated with dabigatran etexilate and warfarin [[P13-00071](#)].

The concomitant use of dabigatran etexilate with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (UFH) (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, LMWH, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, non-VKA-anticoagulants, prasugrel, VKA, and the P-gp inhibitors itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

In addition, bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRI) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs).

The PK and PD of dabigatran in subjects with normal renal function in comparison to patients with varying degrees of renal impairment have been studied in an open, group-comparison design trial of 36 subjects. In otherwise healthy volunteers with mild (creatinine clearance (CrCl)  $\geq 50$  and  $< 80$  mL/min), moderate (CrCl  $\geq 30$  and  $< 50$  mL/min), and severe (CrCl  $< 30$  mL/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  $> 80$  mL/min). This is in accordance with the fact that dabigatran is mainly renally excreted. Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCl  $< 30$  mL/min), and patients who develop acute renal failure should discontinue dabigatran etexilate. Factors such as decreased renal function (CrCl 30-50 mL/min) and age  $\geq 75$  years are associated with increased dabigatran plasma levels. The presence of one, or more than one factor may increase the risk of bleeding.

Dabigatran etexilate is currently authorised for marketing in over 100 countries worldwide. There are 4 authorised indications for dabigatran etexilate:

- Prevention of venous thromboembolic events (VTEs) in patients who have undergone major orthopaedic surgery
- Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation
- Treatment of acute DVT and/or PE and prevention of related death
- Prevention of recurrent DVT and/or PE and related death

Results of pivotal clinical trials for the authorised indications:

- In the studies in which primary prevention of DVT after major orthopaedic surgery was investigated (total knee replacement RE-MODEL, total hip replacement RE-NOVATE and RE-NOVATE II) dabigatran etexilate was non-inferior to enoxaparin 40 mg daily. In one study on elective total knee surgery (RE-MOBILIZE), non-inferiority as compared to enoxaparin was not established.
- The study on stroke prevention in atrial fibrillation (SPAF) (RE-LY) demonstrated superior efficacy of dabigatran etexilate 150 mg b.i.d. over warfarin (international normalised ratio (INR) 2-3) regarding prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Dabigatran etexilate 110 mg b.i.d. was

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non-inferior to warfarin. Intracranial bleeding and total bleeding were reduced with both doses. Vascular mortality was reduced with dabigatran etexilate 150 mg b.i.d. Overall, lower plasma concentrations were associated with a higher risk of ischemic stroke, whereas the risk of major bleeding increased with higher plasma concentrations [[P13-12662](#)].

- In treatment of acute DVT and PE, RE-COVER and RE-COVER II demonstrated that 150 mg b.i.d. was non-inferior to treatment with warfarin with respect to efficacy, and any bleeding was significantly lower in patients receiving dabigatran etexilate 150 mg b.i.d.
- In the clinical trials investigating prevention of recurrent DVT and/or PE, RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg b.i.d. was non-inferior to warfarin ( $p=0.0135$  for non-inferiority). Bleeding events (major bleeding events (MBEs)/clinically relevant non-major bleeding events (CRNMBEs); any bleeding) were significantly lower in patients receiving dabigatran etexilate compared to those receiving warfarin.

For a more detailed description of the dabigatran etexilate drug profile please refer to the current Investigator's Brochure (IB) [\[REDACTED\]](#), which will be included in the Investigator Site File (ISF).

## **2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT**

### **2.1 RATIONALE FOR PERFORMING THE TRIAL**

As in other conditions where anticoagulation is required, warfarin has many challenges and risks associated with its use. These include among others numerous drug-drug interactions, drug-food interactions, risk of bleeding and the need of regular INR monitoring.

Thus, an alternative method of anticoagulation which can be taken orally, has fewer interactions and no regular monitoring requirement would be beneficial for the post-acute care of CVT patients. Dabigatran etexilate has a marketing authorisation for treatment of DVT and PE in many countries. The aetiology of CVT can be considered sufficiently similar to other VTE [[P10-00396](#), [R15-5862](#)] to consider treatment with the same dose of dabigatran etexilate as an alternative to standard treatment with VKA. Therefore, the selected dose of 150 mg b.i.d. is expected to be as efficacious as warfarin without the burden/disadvantages associated with that drug. It can be expected that the overall bleeding risk under dabigatran etexilate will be similar to that of warfarin or potentially better.

There is currently limited but promising clinical data on the use of dabigatran in this indication. Since the incidence of CVT is very low and the occurrence of clinical endpoints is infrequent, a large confirmatory phase III trial including clinical endpoints in this indication is not feasible. Although considered a phase III trial, this trial is not designed to show statistically significant differences in clinical endpoints and is not conducted for registration purposes. The trial is designed as an exploratory trial that could provide numerical reassurance regarding net clinical benefit of dabigatran etexilate compared to warfarin. A largely comparable percentage of clinical endpoints (VTE + MBEs according to International Society on Thrombosis and Haemostasis (ISTH) definition) for both treatment arms would provide clinicians with important new information.

### **2.2 TRIAL OBJECTIVES**

This is an exploratory trial to investigate the efficacy and safety of dabigatran etexilate versus dose-adjusted warfarin in patients with CVT after initial acute treatment.

The primary objective is to compare the net clinical benefit of the treatment arms, as measured by the composite of VTE (recurring CVT; DVT of any limb, PE, or splanchnic vein thrombosis) + major bleeding according to ISTH criteria after up to 24 weeks.

Secondary objectives include a comparison of additional efficacy and safety parameters.

## **2.3 BENEFIT - RISK ASSESSMENT**

At the time this protocol was prepared, the safety and efficacy of dabigatran etexilate had been evaluated in more than 27,000 patients in over 47 Phase I studies, nine completed Phase II studies, and 11 completed Phase III studies within multiple populations including:

- Venous thromboembolism (i.e. DVT and/or PE) prevention in patients who have undergone major orthopaedic surgery
- prevention of stroke and systemic embolism in patients with non-valvular AF
- acute treatment and secondary prevention of VTE (DVT and PE)

The most commonly reported adverse reactions of dabigatran etexilate are bleedings events. Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Standard management for bleeding (such as transfusion of blood products, etc.) needs to be applied as described in Section [4.2.1](#) and in Figure [4.2.1.1: 1](#). A specific reversal agent (idarucizumab) for dabigatran 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 from commercial supply if it becomes locally approved. See Section [4.2.1.1](#) (Major Bleeds) for more information regarding the specific reversal agent for dabigatran.

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

Major advantages of treatment with dabigatran etexilate lie in the greater convenience for the patient. Dabigatran etexilate does not require regular monitoring of the anticoagulant effect, and it has no food interactions, and few clinically relevant drug-drug interactions compared to VKA.

In addition, dabigatran etexilate has been shown to be associated with significantly less intracranial haemorrhage (ICH) compared to warfarin (relative risk reduction of 60-70%), which is seen irrespective of age and dosing .

In the CVT indication, the recommended warfarin dosing is identical to the warfarin dosing recommended for the SPAF indication and the acute treatment/secondary prevention of DVT/PE indications in which dabigatran etexilate was tested against warfarin. The recommended dosing of dabigatran etexilate for these indications (300 mg total daily dose) has therefore been chosen as the best equivalent for the CVT indication (see Section [4.1.3](#)).

Apart from the general considerations above, patient safety will be protected by recommendations provided in this clinical trial protocol. Patients may only be enrolled after stabilisation of the acute phase of the CVT. Patients participating in this clinical trial will be monitored throughout the course of the study for recovery from CVT and for any adverse effects of the trial medication.

Further safeguards that will be implemented to protect patient safety include:

- For both trial medications, the protocol includes guidance on handling haemorrhages which may occur in either treatment arm.
- In patients in the comparator arm (standard VKA treatment) plasma INR will be monitored and should be maintained between 2 and 3 to optimize efficacy and minimize risk of haemorrhage with VKA.
- Concerning the dabigatran etexilate treatment arm, similar efficacy to VKA is expected based on the mode of action of the drug and previous clinical trial experience in other indications.
- Medications which interact with dabigatran etexilate or warfarin are forbidden during the trial.
- Patients will undergo CrCl measurements at screening and patients with CrCl <30mL/min (at screening) will be excluded from participation to reduce the risk of bleeding when randomised to dabigatran etexilate; see Section [3.3.3](#) exclusion criteria.
- If a patient randomised to dabigatran etexilate experiences severe renal impairment (CrCl <30mL/min) during the study, study drug will be withheld or stopped (see Section [3.3.4.1](#) and Section [5.3.3](#)).
- Patients with a large volume of ICH will be excluded from this trial, by excluding patients that are planned for surgical treatment for CVT (e.g. decompressive surgery, ear-nose-throat surgery)
- Based on the findings on the nonclinical studies with dabigatran etexilate conducted to date and the available information for warfarin, and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or foetus to the investigational drug, WOCBP must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.
- Female patients are required to immediately contact the investigator if they experience signs and/or symptoms suggesting a potential pregnancy, or know that they are pregnant.
- A Data Monitoring Committee (DMC) will be established to monitor safety data of the study throughout the trial, and will recommend to the Sponsor (BI) whether to continue, modify or terminate the study (refer to Section [3.1.1](#) for details).

It is expected that this study will provide data that support the assumption that the net clinical benefit (composite of recurrent CVT/VTE and major ISTH bleeding) of dabigatran etexilate in CVT is similar to warfarin, with an overall lower risk of haemorrhage.

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Thus, 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 phase III randomised, open label, exploratory trial with two parallel groups, with blinded endpoint adjudication (PROBE design, i.e. prospective, randomised, open-label, blinded endpoint).

Patients may be enrolled into the trial (i.e. sign informed consent) once they have a confirmed diagnosis of CVT and have received any required treatment for the acute phase of the illness as recommended by the AHA/ASA [R15-5005] and the European Federation of Neurological Societies (EFNS) [P10-11802]. This should include any treatment required for causal pathology or secondary symptoms, such as intracranial hypertension and must also include standard treatment with initial parenteral anticoagulation (UFH or LMWH) according to local treatment practice. Patients may have started oral anticoagulation with a VKA. After a short screening period patients should be randomised 5 to 15 days after start of UFH / LMWH (see Section 4.1.4 for details).

Patients will be randomised in a 1:1 ratio to receive either dabigatran etexilate (150 mg b.i.d.) or warfarin (dose adjusted to maintain an INR between 2.0 and 3.0).

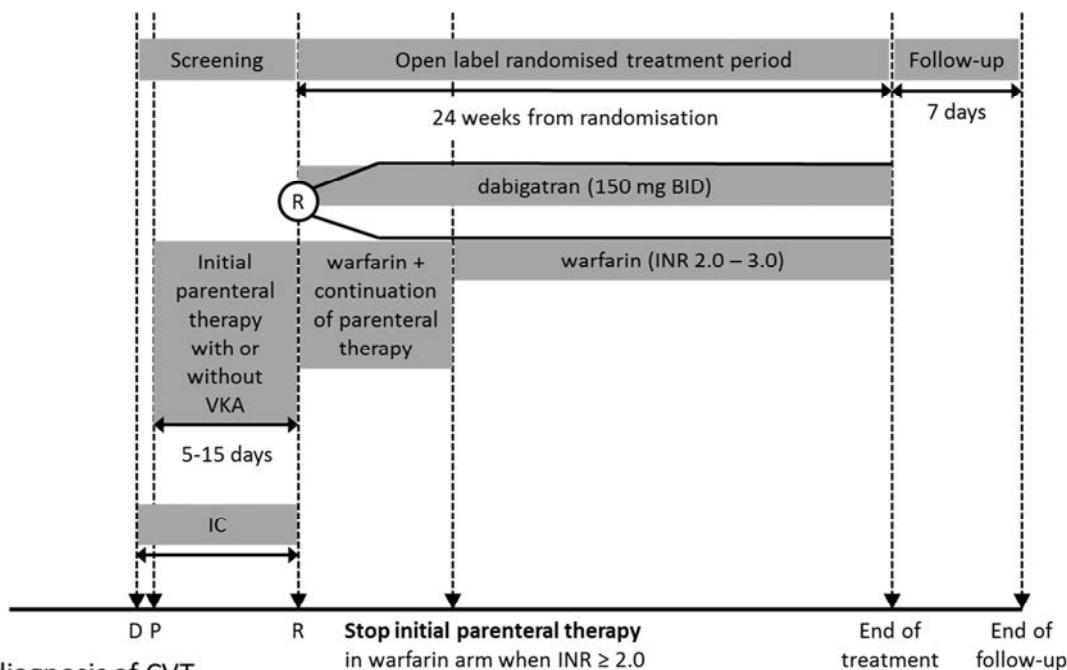


Figure 3.1: 1 Study Design

### **3.1.1      Administrative structure of the trial**

A Coordinating Investigator will be nominated and will be responsible to coordinate investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the Trial Master File (TMF).

A Steering Committee (SC) consisting of external (non-BI) experts and BI representatives has been established to support the Coordinating Investigator who will be the chair of the SC. The composition of the SC will be documented in the TMF. The tasks and responsibilities will be agreed in a SC-charter, which will be filed in the TMF.

A DMC, independent of the sponsor (BI) and of the SC, will be established to assess the progress of the clinical trial (including safety and efficacy assessment at specified intervals) and to recommend to the SC/sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

An endpoint Adjudication Committee (AC), independent of the study sites and the SC, will be established for blinded adjudication of the following:

- VTEs
- MBE and CRNMBE
- Composite endpoint of new ICH or worsening of the haemorrhagic component of a previous lesion
- Cerebral venous recanalisation

The tasks and responsibilities of the AC will be specified in a charter.

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors, Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical evaluation, including programming, will be done according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of relevant responsible persons and relevant local contact information can be found in the ISF.

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

Since VKAs are the standard of care for CVT, a controlled trial versus one such drug, warfarin, is considered appropriate. Dabigatran etexilate has been proven to be at least non-inferior in efficacy vs. warfarin in several trials of other indications, with fewer bleeding events as compared to warfarin, specifically less ICH .

Double-blind, double-dummy trials in anticoagulation have limitations due to potential unavoidable deviations from routine clinical procedures [[R08-4453](#)]. This exploratory trial will use the PROBE design (Prospective Randomised Open-label with Blinded Endpoint assessment). The PROBE approach has been used in several trials of anticoagulation comparing against VKA, e.g. in patients with atrial fibrillation.

In accordance with the applicable BI-SOP the trial database will be handled in a blinded way as appropriate until database lock; see also Section [4.1.5.1](#).

An independent DMC will ensure patient safety in case of a highly relevant difference in the efficacy or safety between the trial treatments. The trial duration is in line with current CVT treatment guidelines from AHA/ASA [[R15-5005](#)] and EFNS [[P10-11802](#)] and with the duration of anticoagulation trials conducted in DVT/PE.

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

- 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.
- Blinded AC:  
The events that make up the primary endpoint and the most relevant secondary endpoints will be adjudicated by blinded adjudication experts independent of the study sites and the SC. Blinding of all event documentation will be performed by trained specialists. The committee will report to the SC and the DMC.
- Review of Data for Clinical Events:  
Any Adverse Event (AE) indicative for a focal neurological deficit, such as limb weakness, loss of vision or sensory disturbance will trigger a request for more information from the centre for event adjudication if potentially consistent with a trial endpoint. Any decrease in haemoglobin of >2g/dL and any new VTE will be similarly investigated.

- **Data Handling:**

Patients will be randomly allocated to the treatment arms via Interactive Response Technology (IRT). Wherever feasible, data review and data handling will be undertaken without knowledge of patient treatment allocation. By treatment data tabulations will not be reviewed during the course of the trial.

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

### **3.3 SELECTION OF TRIAL POPULATION**

This study will randomise approximately 120 patients at approximately 50 trial sites. This means that each site should randomise 2-3 patients.

Trial sites are anticipated to mainly be stroke units or neurology wards.

Enrolment will be competitive and will be terminated when the required number of patients have been included into the trial, regardless of enrolment at individual centres. If enrolment is delayed, additional study centres may be recruited.

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

If a patient is deemed ineligible for a reason which later resolves and all eligibility criteria can be met (e.g. requirement to take specific restricted medication), patients can be re-screened up to one time provided they can still be randomised within 5 to 15 days after start of initial parenteral therapy. Patients cannot be re-screened if any of the following exclusions were met during the initial screening: # 2, 3, 4, 7, 11, 12 and 13.

#### **3.3.1 Main diagnosis for trial entry**

Patients with CVT who are eligible to receive treatment with oral anticoagulation and who meet all other eligibility criteria can enter the trial. CVT should be diagnosed per local practice, using the following techniques:

- MRI+MR venography (preferred) and/or
- CT+CT venography and/or
- MRI or CT in combination with catheter angiography (DSA)

Please refer to Section [8.3.1](#) (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

#### **3.3.2 Inclusion criteria**

1. Written informed consent in accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines and local legislation and/or regulations.

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2. Male or female patients. WOCBP<sup>1</sup> must be ready and able to use highly effective methods of birth control per International Conference on Harmonization M3(R2) [R09-1400] that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided Section [4.2.2.4](#) and in the patient information.
3. Age  $\geq$  18 years and  $< 79$  years at Visit 1.
4. Confirmed diagnosis of CVT<sup>2</sup>, with or without ICH.
5. Patient has achieved clinical stability after having received standard acute CVT treatment as required, including anticoagulation therapy for 5-15 days which has been administered until randomisation; anticoagulation must include full-dose LMWH or UFH and may be followed by oral VKA treatment.
6. Eligible for treatment with an oral anticoagulant for their CVT, based on Investigator judgment. Based on risk assessment and clinical condition, patient should be a candidate for at least 24 weeks of oral anticoagulation.
7. Availability of the imaging that was used to diagnose the CVT for the purpose of external review.

### 3.3.3 Exclusion criteria

1. Inability to swallow medications.
2. CVT associated with central nervous system infection.
3. CVT due to head trauma.
4. Planned for surgical treatment for CVT (e.g. decompressive surgery, ear-nose-throat surgery).
5. Conditions associated with increased risk of bleeding<sup>3</sup> such as:
  - Major<sup>3</sup> surgery in the month prior to Visit 1
  - Planned major<sup>3</sup> surgery or intervention in the next 6 months
  - History of intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired per Investigator judgment (e.g. by surgery)
  - Gastrointestinal haemorrhage within the past six months (prior to Visit 1) unless the cause has been permanently eliminated or repaired per Investigator judgment (e.g. by surgery), or endoscopically documented gastroduodenal ulcer disease in the previous 30 days prior to Visit 1

<sup>1</sup> WOCBP are defined as:

Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

Women not of childbearing potential are defined as:

Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

<sup>2</sup> Diagnosis of CVT will need to be confirmed by means of any (combination) of the following techniques: MRI+MR venography, CT+CT venography and/or MRI or CT in combination with catheter angiography (DSA).

<sup>3</sup> Definition of "increased bleeding risk" and "major" is per Investigator judgment.

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- Haemorrhagic disorder or bleeding diathesis, e.g. history of thrombocytopenia or platelet count <100,000/ml at screening, von Willebrand disease, haemophilia A or B or other hereditary bleeding disorder, history of prolonged bleeding after surgery/intervention
- Fibrinolytic agents within 48 hours of starting trial medication
- Uncontrolled hypertension (Systolic Blood Pressure (BP) >180mmHg and/or Diastolic BP >100 mmHg)
- Any history of intracranial aneurysm (unless it was permanently resolved with either clipping or coiling at least one year prior to the study entry)

6. Life-threatening or major bleeding (per ISTH criteria, see Section [5.3.5.2](#)) other than ICH due to the index CVT, during the 6 months prior to randomisation or while on anticoagulants during the acute phase of CVT.
7. History of symptomatic non-traumatic ICH with risk of recurrence according to Investigator judgment (including haemorrhagic stroke within 6 months prior to screening, but other than ICH during the acute phase of CVT).
8. Severe renal impairment defined as CrCl (calculated by Cockcroft-Gault equation) <30mL/min at screening, or if the Investigator expects CrCl is likely to drop below 30mL/min during the course of the study.
9. Patients who require taking any of the drugs listed as restricted in Section [4.2.2.1](#) while on active treatment with study drug.
10. Patients receiving treatment with warfarin, dabigatran etexilate or other antithrombotic regimen (i.e. anticoagulants or anti-platelet medication) for an indication other than CVT and requiring continuation of that treatment for the original diagnosis without change in the regimen.
11. Patients with prosthetic heart valves.
12. Known hypersensitivity to dabigatran etexilate or warfarin or to any of the excipients of either product.
13. Any current or recent malignancy ( $\leq$  6 months prior to Visit 1) unless the malignancy was a basal cell carcinoma that was completely removed.
14. Concomitant disease that increases the risk of an adverse reaction to study interventions or with life expectancy < 6 months (for any reason) as per Investigator's judgment.
15. Pre-menopausal women (last menstruation  $\leq$  1 year prior to Visit 1) who are pregnant, nursing, or who plan to become pregnant while in the trial.
16. Patients who have participated in another trial with an investigational drug or device within the past 14 days preceding Visit 1 or who currently are participating in another trial<sup>1</sup>. Patients who are still experiencing a clinical effect from an investigational drug or device.
17. Patients considered unreliable by the Investigator concerning the requirements for follow-up during the study or at the end of the study.
18. Any condition the Investigator believes would not allow safe participation in the study.
19. Active liver disease, as indicated by at least one of the following:
  - Prior and persistent Alanine aminotransferase (ALT (SGPT)) or Aspartate transaminase (AST (SGOT)) or Alkaline Phosphatase  $>3$  x upper limit of normal (ULN)

<sup>1</sup> Patients participating in a purely observational study will not be excluded.

and/or

- Known Active hepatitis C (as evidenced by positive hepatitis C virus ribonucleic acid assay by sensitive polymerase chain reaction (PCR) based assay, such as Roche Monitor or Bayer TMA assay)  
and/or
- Known Active hepatitis B (HBs antigen positive or anti HBc IgM positive)<sup>1</sup>  
and/or
- Known Active hepatitis A

20. Previous randomisation in this trial.

Note to the eligibility criteria: Pre-randomisation interventional treatment (i.v. r-tPA or urokinase and/or stenting) is neither required nor excluded provided that the start of trial medication is at least 48 hours after the application of any fibrinolytic agent.

### **3.3.4 Removal of patients from therapy or assessments**

#### **3.3.4.1 Removal of individual patients**

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

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

Regardless of whether or not study drug continues to be taken, patients will continue to participate in regularly scheduled follow-up visits and assessments until 25 weeks after randomisation, unless they withdraw their consent to do so. Patients not actively taking study drug are strongly encouraged to continue trial participation,

and report events that comprise the primary endpoint at minimum.

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

If study drug is permanently stopped, patients should attend two follow-up visits. Refer to Section 6.2.3 for further details.

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

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<sup>1</sup> Patients having received recent hepatitis B vaccination and thus testing positive for these antibodies will not be excluded.

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- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient becomes pregnant.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication (see Section [4.2.2](#)).
- Patients randomised to receive dabigatran who are found to have a CrCl <30mL/min during the course of the trial should have trial medication temporarily discontinued (see Section [5.3.3](#) for calculation of CrCl). Labs can be repeated before stopping trial medication if Investigator wishes to confirm initial lab result. The patient will be permanently discontinued from trial medication, unless CrCl recovers to  $\geq 30$ mL/min within seven days.  
A patient should also be permanently discontinued from trial medication if CrCl drops <30mL/min on two different occasions during the trial. During period of interruption, a patient can be treated per standard of care according to Investigator's discretion.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Guidelines for transitioning to non-study antithrombotic medications are provided in Appendix [10.2](#).

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the [Flow Chart](#) and Section [6.2.3](#).

For all patients the reason for withdrawal (e.g. AEs) must be recorded in the Case Report Form (CRF). These data will be included in the trial database and reported.

If a trial patient becomes pregnant, the trial medication will be discontinued permanently. All end of treatment (EOT) procedures should be performed and the patient should be followed in the trial as outlined in the Flow Chart and below for patients who discontinue trial medication early.

In addition the patient will be followed up until birth or otherwise termination of the pregnancy. See also Section [5.3.7](#).

The data of the patient until last patient last visit (for the total trial) will be collected and reported in the clinical trial report. Any events thereafter will be reported in the BI drug safety database only.

Patients who discontinue trial treatment before completing 24 weeks of treatment will be followed-up for the collection of further data on \_\_\_\_\_, MBEs, VTEs, any other AEs and post-study anti-coagulation therapy (until 25 weeks after the date of randomisation), unless they withdraw their consent for any further participation. Data will be collected during a contact at 25 weeks after randomisation and from existing medical records. Every effort should be made to obtain this information. Patients who discontinue trial medication and who do not agree to be contacted themselves should be asked if they agree to another person being contacted to obtain this information. Contact details of that person should then be obtained.

### 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. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial
4. Advice of the independent DMC, decision by an independent ethics committee (IEC)/institutional review board (IRB) or Competent Authority

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

## **4. TREATMENTS**

### **4.1 TREATMENTS TO BE ADMINISTERED**

The trial medication will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

#### **4.1.1 Identity of BI investigational product and comparator product**

The investigational product dabigatran etexilate and the comparator warfarin will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. For details see Table 4.1.1: 1 and Table 4.1.1: 2.

Table 4.1.1: 1                    Dabigatran etexilate (Investigational drug)

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

The main excipients of the dabigatran capsule include tartaric acid, acacia, hypromellose, dimeticone, talc, and hydroxylpropyl cellulose, 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
Unit strength	1 mg; 3 mg; 5 mg
Posology	As needed to maintain a target INR of 2.0- 3.0
Route of administration:	p.o.

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

Patients will in general take warfarin once daily (q.d.). The individual doses will be titrated as needed, without splitting of any tablet, to maintain a target INR of 2.0 - 3.0. INR controls in patients randomised to receive warfarin will be performed as described in Section [4.1.4](#) and the [Flow Chart](#).

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

#### **4.1.2      Method of assigning patients to treatment groups**

During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via IRT. Note that the medication number is different from the patient number (the latter is assigned at trial entry). Site personnel will enter the medication number in the CRF.

To facilitate the use of the IRT system, all necessary instructions for using the system will be described in a user guide/manual, a copy of which will be available in the ISF.

#### **4.1.3      Selection of doses in the trial**

Many experts with specific knowledge regarding CVT are of the opinion that CVT should be regarded as a thrombosis at a specific site and is more similar than dissimilar to DVT / PE [[P10-00396](#)], [[R15-5862](#)]. It was therefore decided to use the approved dosage of dabigatran for treatment of acute DVT/PE, i.e. 150 mg b.i.d. This dose was also used in a 15-patient case series [[P15-10422](#)] published on dabigatran use in CVT which resulted in favourable efficacy and safety outcomes for all patients.

The comparator warfarin will be administered according to an accepted standard regimen recommended for treatment of CVT (titration to maintain an INR of 2.0-3.0) [[P10-11802](#)], [[R15-5005](#)].

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.

#### **4.1.4      Drug assignment and administration of doses for each patient**

Each patient will be randomised at Visit 2 to receive either dabigatran etexilate 150 mg b.i.d. or warfarin. Randomisation should take place within the timeframe provided below as soon as the patient is stable and is considered eligible to receive oral anticoagulation therapy:

- Ideally patients are randomised 5 days (120 hours) after start of UFH / LMWH;
- Randomisation should not take place before 5 days of initial treatment with UFH or LMWH have been given;
- Randomisation should occur no later than 15 days after start of initial UFH / LMWH.

If there is no need for wash-out (see below), the first dose of trial medication will be taken at the study centre. Patients who need a wash-out period will take the first dose after completion of that wash-out. This may be done at home as instructed by their investigator.

### Patient randomised to receive dabigatran etexilate

Patients randomised to dabigatran etexilate will start the trial medication on the day of randomisation if they are not on oral anticoagulation (VKA) or if the INR is  $<2.0$ . If a patient is still receiving parenteral therapy, the first dose (capsule) of dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of the initial parenteral therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. i.v. UFH).

If the patient is on oral anticoagulation with a VKA for their CVT and the INR is  $\geq 2.0$ , trial medication can be dispensed but the patient will be instructed not to start it until notified.

The initial parenteral anticoagulation and VKA will be discontinued. Follow-up INRs will be performed in 1-3 day intervals until it falls below 2.0, at which time the patient will be instructed by telephone to start taking the trial medication.

Actual date and time of administration of the first dose of trial medication and in case of interruptions are to be recorded in the CRF.

Patients will take their dabigatran etexilate dose as scheduled for a period of 24 weeks.

Dabigatran etexilate capsules should be taken in the morning and in the evening (one at each time point), at approximately 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 instruct the patient to take the medication together with food and/or should consider adding a proton pump-inhibitor 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 who decides to discontinue trial medication should be considered for a switch to an appropriate (non-study) anticoagulant according to local practice. For patients receiving dabigatran etexilate, continuation of trial medication 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

Patients randomised to warfarin will start the trial medication on the day of randomisation. If they are on oral anticoagulation (VKA) at the moment of randomisation, it needs to be confirmed that INR is  $<3.0$  before trial medication is started. If the INR is  $\geq 3.0$ , warfarin must not be started until the INR is in the therapeutic range. Actual date and time of administration of the first dose of warfarin are to be recorded in the CRF.

Initial parenteral anticoagulation should be continued together with study warfarin if INR is  $<2.0$ . Initial parenteral therapy should be discontinued as soon as INR is  $\geq 2.0$  (one measurement). Randomisation should occur no later than 15 days after start of UFH /

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LMWH. For patients randomised to receive warfarin, UFH / LMWH may continue beyond day 15 until the requirement of INR  $\geq 2.0$  has been met.

INR monitoring should continue and warfarin doses adjusted to maintain an INR between 2.0 and 3.0.

Warfarin tablets are to be taken with water, preferably at the same time each day.

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 adjustments will be done according to usual clinical practice, taking into account that tablets may not be split (i.e. only whole tablets to be taken by the patient). The Investigator will be responsible for reporting INR results and the dose of warfarin prescribed.

For patients randomised to warfarin, the INR measurements should be performed as necessary for dose adjustment and maintenance until the EOT visit in order to obtain the target INR as soon as possible and to avoid over- or under-dosing. INR measurements should be performed daily from the start of treatment until concomitant heparin treatment is stopped (if applicable), at least once every two weeks for the first three months thereafter and monthly subsequently. More frequent INR measurements will be done as necessary at the discretion of each Investigator or anticoagulation clinic.

To aid investigators, a validated nomogram will be provided 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.

Patients with protein C deficiency are at risk of developing skin necrosis when starting warfarin treatment. Therefore, for patients with known protein C deficiency, therapy should be introduced slowly without a loading dose of warfarin even if heparin is given. Patients with protein S deficiency may also be at risk and it is advisable to also introduce warfarin therapy slowly in such patients.

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 measurements are performed when other medications are initiated, discontinued or taken irregularly and/or in case of 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](#)), however all available INR values should be entered into the CRF. It is critical to obtain the best possible level of INR control.

### **Heparin and LMWH**

In accordance with current treatment guidelines (AHA/ASA scientific statement on diagnosis and management of CVT [[R15-5005](#)] and EFNS guideline [[P10-11802](#)]), patients must be treated with parenteral anticoagulation during the acute stage of illness until they are medically stable and can be switched to oral anticoagulation. Patients must be randomised

into this trial within 5-15 days after start of parenteral anticoagulation. This parenteral treatment will not be provided as part of the clinical trial supplies, unless required by local laws or regulations.

#### **4.1.4.1 Completion of trial treatment**

Regular trial treatment will be completed with the last dose of trial medication being taken on the evening before or the morning of the EOT visit. Decisions regarding the continuation of anticoagulation agents after the completion of the treatment period (EOT) should be based on the recommendations and guidelines of the AHA/ASA [[R15-5005](#)] and the EFNS [[P10-11802](#)] or alternative local treatment practice.

For recommendations on how to switch from trial treatment to other anticoagulants see Appendix [10.2](#).

#### **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. Trial medication will be identified by a medication code number. This code number will be entered into the CRF. Despite the trial being open label, the activities conducted by the trial team will be performed in a blinded manner as much as possible until database lock. Specifically, medical and quality review and review of protocol violations will be performed without knowledge of or reference to the treatment that the patient was assigned to, or any other unblinding information.

For further justification of the PROBE design chosen for this study see Section [3.2](#).

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

##### **4.1.5.2 Unblinding and breaking the code**

Not applicable.

#### **4.1.6 Packaging, labelling, and re-supply**

Dabigatran etexilate will be provided in bottles. Each bottle will contain 60 capsules of 150 mg dabigatran etexilate. The number of bottles provided to the patient will vary depending on the time between visits.

Patients on warfarin will receive the required combination of 1 mg, 3 mg and 5 mg tablets in blister strips placed into wallet cards according to their actual needs as defined by the measured INR value. Each warfarin wallet will contain 70 tablets. The number of wallets provided to the patient will vary depending on the time between visits.

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

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

#### **4.1.7 Storage conditions**

Patients randomised to dabigatran should be instructed to keep medication bottles tightly closed. It is not allowed to use medication from more than one dabigatran etexilate bottle at the same time.

Patients should be instructed not to remove tablets/capsules from original package material until immediately prior to time of intake.

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.

#### **4.1.8 Drug accountability**

The Investigator and/or Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- 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,
- Availability of the proof of a medical license for the principal Investigator, if applicable.

Trial medication may only be dispensed to trial patients fulfilling the inclusion and none of the exclusion criteria by authorised study personnel as documented in the ISF.

The Investigator and/or 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 warehouse/drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse/drug distribution centre will maintain records of the disposal. Account must be given for any discrepancies.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or appointed contract research organisation, 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.

## **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.

Certain concomitant therapies (e.g. fibrinolitics, 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.

### **4.2.1 Rescue medication, emergency procedures, and additional treatment(s)**

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 trial medication should be temporarily stopped and the source of bleeding investigated and treated. This will generally involve coagulation testing (e.g. activated partial thromboplastin time (aPTT), thrombin clotting time (TT), ecarin clotting time (ECT)), platelet count, and possibly transfusion, diagnostic procedures and/or surgical haemostasis. Renal function should be assessed.

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.

For situations of life-threatening or uncontrolled bleeding when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent (idarucizumab) may be available from commercial supply depending on the status of national authorization.

Idarucizumab is indicated for use in selected patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is urgently needed (i.e., for emergency surgery/urgent procedures or if there is life-threatening or uncontrolled bleeding). Idarucizumab is a humanized monoclonal antibody fragment that immediately neutralizes the anticoagulant effect of dabigatran as evidenced by reduced unbound dabigatran concentrations and normalized coagulation tests. Preliminary Phase 3 results from the RE-VERSE-AD trial (Pollack et al. 2015, [P15-06362](#)) demonstrated a median maximum reversal of 100%, a median time to bleeding cessation of 11.4 hours, and normal intraoperative haemostasis in 92% of patients requiring an urgent procedure. Current evidence suggests that idarucizumab functions as a safe, effective, and specific “off-switch” to dabigatran-based anticoagulation in selected cases of life-threatening or uncontrolled bleeding or when in need for emergency surgery.

Idarucizumab should be used according the locally approved labelling information.

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 trial(s).

It is at the discretion of the Investigator whether trial medication should be re-administered after the bleeding has resolved and haemostasis has been achieved. 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 bleeding events on dabigatran etexilate is presented in Figure [4.2.1.1; 1](#).

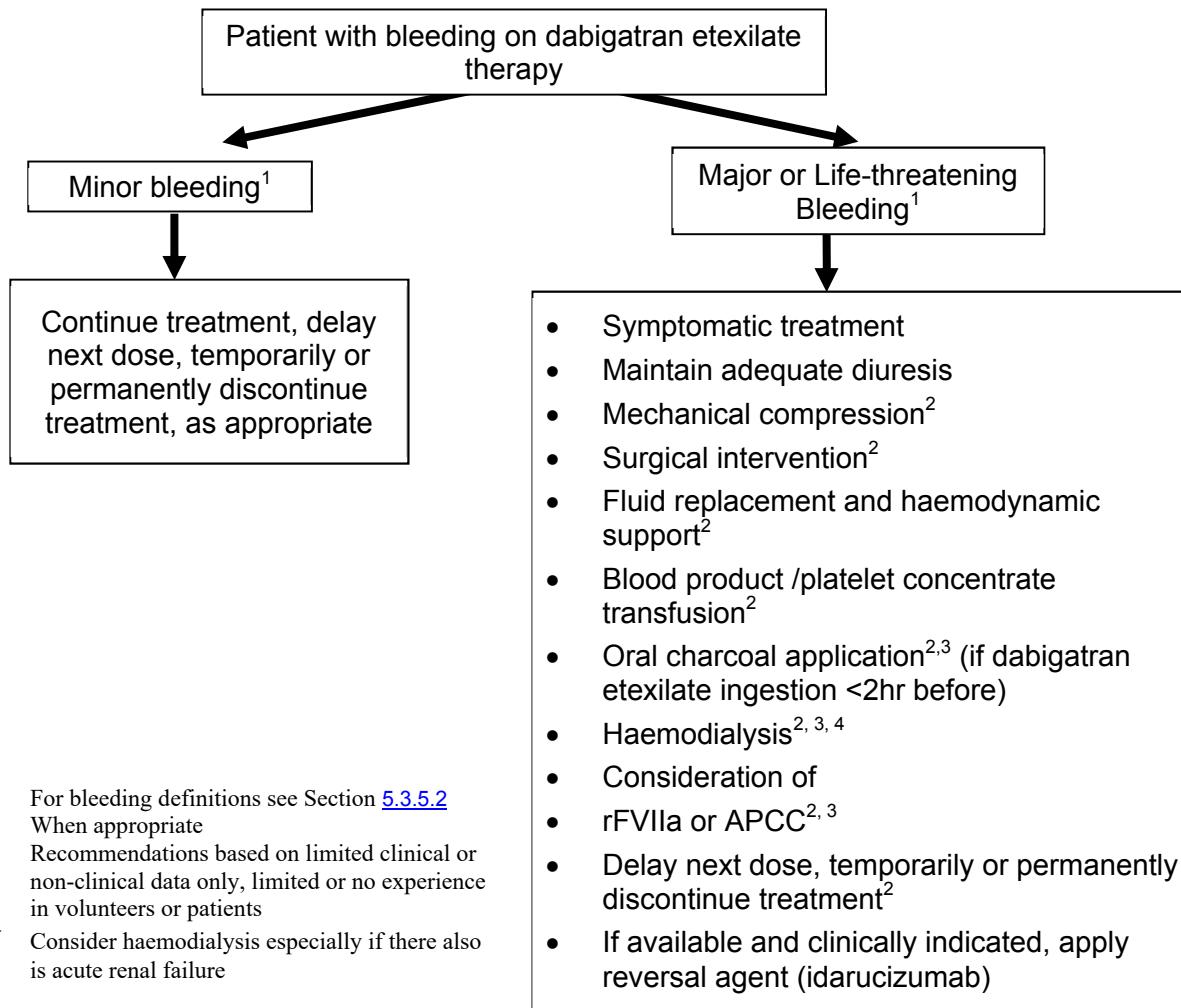


Figure 4.2.1.1: 1 Management of bleeding on dabigatran etexilate therapy [[P10-03790](#)]

### 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, trial medication may be continued, interrupted temporarily or permanently discontinued, at the discretion of the Investigator. It is not a requirement, however, that trial medication 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, trial 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 trial medication.

In an emergency event, a measure of anticoagulation may become necessary to manage the situation. A physician may consider using the TT or diluted thrombin time (dTT) (where available), aPTT or ECT. For an adequate interpretation of the results the time of last intake of dabigatran etexilate needs to be known. For further details on results of coagulation times expected with dabigatran etexilate, see Section on elective surgery below.

If the condition is considered life threatening and surgery cannot be postponed, consider measures to reduce anticoagulation as described under major bleeds. See Section [4.2.1.1](#). In case of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effect is required the specific reversal agent (idarucizumab) to dabigatran may be available in the context of a clinical trial, or from commercial supply depending on status of national authorization.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

###### Preoperative phase, Elective Surgery:

Physicians may consider the following information regarding dabigatran etexilate when patients need to undergo surgery or elective procedures. Provided that the patient has normal renal function, the onset of effect of dabigatran etexilate 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 at 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 [5.3.3](#)). Patients with a CrCl <30mL/min during the course of this study should not be receiving trial 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 etexilate 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 trial medication in relation to the timing of major surgery

<b>Renal function (CrCl, mL/min)<sup>1</sup></b>	<b>Estimated half- life if on dabigatran etexilate</b>	<b>Stop study dabigatran etexilate before surgery</b>	
		<b>High Risk of bleeding<sup>2</sup></b>	<b>Standard Risk</b>
≥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

<sup>1</sup> CrCl can be estimated using serum creatinine by the Cockcroft-Gault formula (see Section 5.3.3). Patients who develop CrCl <30mL/min during the course of the trial should have trial medication stopped (see Section 3.3.4.1).

<sup>2</sup> 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.

The clinician should consider delaying surgery 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 TT or dTT (dTT only in countries where this assay is approved). 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 150 mg b.i.d., the median peak aPTT is approximately 63 sec . 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 1.5 times the upper limit of normal . Twelve hours after the last dose, the median aPTT is approx. 1.3 times upper limit of normal (median trough aPTT prolongation for patients receiving 150 mg b.i.d. in RE-LY: 51.9 sec), with less than 10% of patients exceeding 2 times upper limit of normal (90th percentile trough aPTT prolongation for patients receiving 150 mg b.i.d. in RE-LY: 76.4 sec)

ECT shows a linear correlation with the plasma concentrations of direct thrombin inhibitors, including dabigatran. Median ECT ratios over baseline (median baseline: 30.3 sec) of approx. 2.1 at trough (median trough ECT prolongation for patients receiving 150 mg b.i.d. in RE-LY: 62.9 sec) and 3.0 at peak (median peak ECT prolongation for patients receiving 150 mg b.i.d. in RE-LY: 92.9 sec) have been observed after intake of dabigatran etexilate 150 mg b.i.d . Twelve hours after the last dose, less than 10% exceed a ratio of 3.5 from baseline (90th percentile of trough ECT for patients receiving 150 mg b.i.d. as observed

in RE-LY: 103 s) Coagulation times should always be interpreted in relation to the timing of last drug intake of trial 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 s.c. UFH or s.c. 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. See Section [3.3.4.1](#) for how to handle patients receiving dabigatran etexilate and for whom CrCl drops to <30 mL/min during the course of the study.

**Warfarin Treated Group**

**Preoperative Phase**

Bridging therapy with a parenteral anticoagulant should be considered depending on the length of trial medication 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) heparin or s.c. LMWH and simultaneously with study warfarin until the INR is  $\geq 2.0$ . Parenteral bridging therapy should be stopped when target INR is achieved (see Appendix 10.1 for guidance).

**4.2.1.4 Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture**

**Dabigatran etexilate 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 trial medication after complete haemostasis is achieved, but at minimum an interval of one hour should elapse for all patients. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

**4.2.1.5 Stroke of non-CVT origin**

Patients with documented or suspected stroke of non-CVT origin should be managed according to usual clinical practice. It is anticipated that in most cases trial medication will be

withheld until a CT or MRI scan has been obtained and diagnosis has been made. For recommendations regarding a new CVT or worsening of symptoms of the index CVT, refer to Section [4.2.1.6](#).

### **Ischaemic stroke**

For ischaemic stroke usual clinical practice may be followed, which may include administration of ASA and/or clopidogrel, or ASA/dipyridamole (the latter in lieu of clopidogrel). The decision whether or not to continue administration of the trial medication is at the discretion of the local Investigator, also taking into account the possible presence of bleeding [[P13-06400](#)].

Fibrinolitics may be considered for ischaemic stroke, if the patient presents with a TT, dTT, ECT, or (if TT, dTT or ECT are not available) an aPTT lab result not exceeding the upper limit of normal (ULN) according to the local reference range for patients receiving dabigatran etexilate, or if the INR is  $\leq 1.7$  in patients receiving warfarin.

### **Haemorrhagic stroke**

For haemorrhagic stroke (not directly related to CVT) 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 trial treatment following a stroke**

#### **Dabigatran Etexilate Treated Group**

The decision for restarting dabigatran etexilate following a stroke is at the discretion of the Investigator. For the timing of restarting anticoagulation after stroke event clinical recommendations should be consulted [[P12-02400](#)]. The following recommendations on when to restart dabigatran etexilate are provided for guidance only: In general, dabigatran etexilate can be restarted after a TIA as soon as imaging has excluded a cerebral haemorrhage. For mild, moderate and severe stroke, expert recommendations [[P12-02400](#)] suggest restarting dabigatran etexilate 3-5 days, 5-7 days, and 2 weeks after stroke onset, respectively.

#### **Warfarin Treated Group**

The decision for restarting study warfarin following a stroke and its exact timing is at the discretion of the Investigator.

#### **4.2.1.6 Venous thrombotic event (VTE)**

#### **CVT**

A new event of CVT occurring during the trial treatment period, as well as worsening symptoms such as an ischaemic stroke as a result of the index CVT, should be treated according to current AHA/ASA and EFNS guidelines [[R15-5005](#); [P10-11802](#)]. Trial treatment should be interrupted while the patient is being treated with other antithrombotic therapy or with other medication that is restricted per Section [4.2.2.1](#). The decision for restarting trial treatment is at the discretion of the Investigator.

### **DVT, PE or splanchnic vein thrombosis**

An event of DVT, PE or splanchnic vein thrombosis occurring during the trial treatment period should be treated according to local clinical practice. Trial treatment should be interrupted if the patient is being treated with other anticoagulation therapy or with other medication that is restricted per Section [4.2.2.1](#). The decision for restarting trial treatment is at the discretion of the Investigator.

#### 4.2.1.7      Renal failure

See Section [3.3.4.1](#) for instructions in case CrCl drops to below 30mL/min in a patient randomised to receive dabigatran etexilate.

#### 4.2.1.8      Other Medical Intervention

### **Other Minor Procedures:**

#### **Dabigatran Etexilate Treated Group**

In the case of other elective procedures or minor surgery, dabigatran etexilate can be continued until 24 hours before the procedure. For the timing of treatment interruption before the procedure see also Table [4.2.1.3: 1](#).

#### **Warfarin Treated Group**

For patients randomised to Warfarin, refer to Section [4.2.1.3](#).

### **Reintroduction following medical intervention**

#### **Dabigatran Etexilate Treated Group**

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](#).

#### **Warfarin Treated Group**

For patients randomised to Warfarin, refer to Section 4.2.1.3.

#### 4.2.1.9      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 150 mg 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](#).

If an overdose is associated with bleeding, see the advice given in Section [4.2.1.1](#), and [4.2.1.2](#).

## **4.2.2      Restrictions**

### **4.2.2.1      Restrictions regarding concomitant treatment**

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

- Fibrinolytic agents (see Section [4.2.1.5](#) for exceptions)
- GPIIb/IIIa antagonists (e.g. abciximab, tirofiban)
- Rivaroxaban, apixaban and edoxaban, or other oral anticoagulants (e.g. VKAs)
- Treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus and dronedarone, and rifampicin, carbamazepine, phenytoin and St. John's Wort
- Any type of dual antiplatelet therapy

#### **Patients suffering from seizures**

- Patients with CVT often have seizures, requiring anticonvulsive treatment. Due to (a potential for) interactions with dabigatran etexilate and warfarin, phenytoin and carbamazepine should not be used in those cases. It is possible to use levetiracetam instead, if available.

### **4.2.2.2      Precautions regarding concomitant treatment**

#### **General precautions**

ASA, dipyridamole, clopidogrel, ticagrelor, prasugrel, corticosteroids, or non-steroidal anti-inflammatory drugs (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 ASA-containing over-the-counter medications on a regular basis. In case of the need for pain relief, the use of acetaminophen, diclofenac or ibuprofen instead of ASA should be considered where appropriate. The use of these medications should be limited to the absolute minimum possible time period.

Co-administration of oral anti-platelet (including ASA) and NSAID therapies increase the risk of bleeding .

For any drug potentially increasing the risk of bleeding the factor age needs to be considered as the effect may be more pronounced in elderly patients ( $\geq 75$  years). If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in haemoglobin is suggested . 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.

### **Dabigatran Etexilate Treated Group**

The Investigator is alerted to the use of concomitant administration of moderate to strong P-gp inhibitors in patients receiving dabigatran etexilate (e.g. such as amiodarone, verapamil, quinidine, nelfinavir, ritonavir, saquinavir and tipranavir+ritonavir or lopinavir+ritonavir) or P-gp inducers 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 or thromboembolic 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.

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

If dabigatran etexilate is given at least two hours before verapamil particularly in 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. As with verapamil separation of administration (dabigatran etexilate given at least two hours before any P-gp inhibitor) will mitigate any potential risk of drug interaction.

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, LMWHs, fondaparinux, desirudin, ticlopidine, dextran, sulfapyrazone, prasugrel, direct thrombin inhibitors, VKAs.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors or selective serotonin norepinephrine re-uptake inhibitors

### **Warfarin Treated Group**

Patients randomised to receive warfarin must be aware of the potential risk of over- or under dosing with changes of co-medications (e.g. use of antibiotics), including over the counter medicines, herbal remedies or vitamin preparations.

For more specific advice on potential interactions with warfarin and on how to handle those, please refer to the summary of product characteristics that will be provided in the ISF.

#### **4.2.2.3      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 warfarin 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 concomitant diseases (e.g. diarrhoea).

#### **4.2.2.4      Restrictions regarding women of childbearing potential**

WOCBP must be ready and able to use highly effective methods of birth control per International Conference on Harmonization M3(R2) [[R09-1400](#)] that result in a low failure rate of less than 1% per year when used consistently and correctly. This includes:

- Placement of intrauterine device (IUD) or intrauterine system (IUS; e.g. Mirena (IUS with low dose progesterone))
- Bilateral tubal occlusion
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Complete sexual abstinence

Periodic abstinence, e.g. calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not considered acceptable methods of contraception based on the above criterion of low failure rate of less than 1% per year.

Highly effective methods of contraception should be applied from signing of informed consent until the follow-up visit (Visit 6).

#### WOCBP are defined as:

Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

#### Women not of childbearing potential are defined as:

Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

Please also refer to the inclusion and exclusion criteria for this study (see Sections [3.3.2](#) and [3.3.3](#))

In the case of male patients participating in the trial, since there is no documented evidence to suggest a risk to sperm quality (for either dabigatran etexilate or warfarin), no special consideration is required.

#### **4.3 TREATMENT COMPLIANCE**

Principles regarding the evaluability of non-compliant patients will be outlined in the Trial Statistical Analysis Plan (TSAP). Decisions about evaluability of patients will be made at the Blinded<sup>1</sup> Report Planning Meeting and at the latest prior to database lock.

##### **Patient randomised to receive 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.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}^2}$$

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 be re-informed about the purpose and conduct of the trial. Non-compliance should be discussed with BI.

##### **Patient randomised to receive 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.

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) 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 (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.

<sup>1</sup> Despite the trial being open label, medical and quality review will be performed without reference to the trial treatment that the patient receives.

<sup>2</sup> The number of tablets which should have been taken should take into account any temporary interruptions in trial medication

## **5. VARIABLES AND THEIR ASSESSMENT**

### **5.1 TRIAL ENDPOINTS**

#### **5.1.1 Primary Endpoint(s)**

The primary endpoint for this trial is the composite of the number of patients with major bleeding according to ISTH criteria and VTE (recurring CVT; DVT of any limb, PE, splanchnic vein thrombosis) after up to 24 weeks. All components are adjudicated in a blinded manner by an AC.

#### **5.1.2 Secondary Endpoint(s)**

All secondary endpoints will be based on adjudicated data (except for any bleeding event).

The secondary efficacy endpoints are:

- Number of patients with recurring CVT; DVT of any limb, PE or splanchnic vein thrombosis after up to 24 weeks
- Cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses after up to 24 weeks

The secondary safety endpoints are:

- Number of patients with major bleeding according to ISTH criteria after up to 24 weeks
- Composite endpoint of number of patients with new ICH or worsening of the haemorrhagic component of a previous lesion after up to 24 weeks
- Number of patients with CRNMBe after up to 24 weeks
- Number of patients with major bleeding according to ISTH criteria or CRNMBe after up to 24 weeks
- Number of patients with any bleeding event after up to 24 weeks

#### **5.1.4 Classification of endpoints for trial disclosure purposes**

This trial and its results will be publicly disclosed. Disclosure of trial endpoints should include information as to whether or not the endpoint pertains to a known safety issue. For that purpose the primary endpoint (major bleeding according to ISTH criteria and VTE) and all secondary safety endpoints (major bleeding according to ISTH criteria, composite endpoint of new ICH or worsening of the haemorrhagic component of a previous lesion, CRNMBe, the composite of major bleeding according to ISTH criteria or CRNMBe, and the endpoint of any bleeding events) are considered to pertain to a known safety issue. The other endpoints are not.

### **5.2 ASSESSMENT OF EFFICACY**

#### **5.2.1 Venous thrombotic events**

VTE should meet the following criteria:

##### CVT

New neurological signs / symptoms or worsening of previous signs / symptoms with new CVT on neuroimaging.

New CVT must be confirmed by the AC by review of appropriate imaging as mentioned in Section [3.3.1](#) for the qualifying CVT.

##### DVT (of any limb)

DVT is generally documented by one of the following:

- Abnormal compression ultrasonography
- An intraluminal filling defect on venography
- At autopsy

Any suspected DVT must be confirmed by the AC by review of images and/or reports of venous compression ultrasonography or of venography.

##### Splanchnic vein thrombosis

The presence of endoluminal material or absence of flow in the extrahepatic portal veins or mesenteric veins as shown by duplex-Doppler ultrasound, or contrast-enhanced CT scan or MRI.

Any suspected splanchnic vein thrombosis must be confirmed by the AC by review of images and/or reports of above mentioned imaging techniques.

##### PE

Pulmonary embolism is generally documented by one of the following:

- An intraluminal filling defect in segmental or more proximal branches on spiral CT scan

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

Any suspected PE must be confirmed by the AC by review of images and/or reports of any of the above in order to be considered a PE.

These events will be assessed based on clinical information and supporting imaging. No specific imaging will be required to be performed, but events will only be considered as confirmed if images as indicated above (from routine medical practice) that support the diagnosis are available.

Note: the endpoint of new VTE does NOT include retinal thrombosis



## **5.2.6 Cerebral venous recanalisation**

Cerebral venous recanalisation will be assessed by imaging and will be adjudicated by the AC. Due to the specific skills that are required to assess recanalisation, an investigator assessment of this endpoint will not be requested.

Recanalisation as a secondary efficacy endpoint will be assessed as described below, analogues to the calculations made by Miranda et al [[R16-2716](#)].

1. At baseline and at the end of treatment, occlusion of cerebral veins and sinuses will be scored as follows:

1 = full occlusion

0 = no occlusion or partial occlusion

2. This score will be applied to each of the veins and sinuses using the below conventions:

- Superior sagittal sinus, straight sinus, cavernous sinus, left jugular vein, right jugular vein will each be scored individually (i.e. each will be scored as either 0 or 1)

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- Right lateral transverse and sigmoid sinus will be scored together (i.e. 0 points if neither is fully occluded; 1 point if at least one of them is fully occluded)
- Left lateral transverse and sigmoid sinus will be scored together (i.e. 0 points if neither is fully occluded; 1 point if at least one of them is fully occluded)
- Superior petrous sinus and inferior petrous sinus will be scored together (i.e. 0 points if neither is fully occluded; 1 point if at least one of them is fully occluded)
- Deep venous system will be scored as system, irrespective of the number of occluded veins (i.e. 0 points if none is fully occluded; 1 point if at least one is fully occluded)
- Superficial cortical veins will be scored as system, irrespective of the number of occluded veins (i.e. 0 points if none is fully occluded; 1 point if at least one is fully occluded)
- Cerebellar veins will be scored as system, irrespective of the number of occluded veins (i.e. 0 points if none is fully occluded; 1 point if at least one is fully occluded)

3. For each individual patient a total score will be calculated at baseline and at the end of treatment.
4. A recanalisation score will subsequently be calculated for each patient as the difference between the baseline total score and the end of treatment total score.

Patients who died during the trial before an EOT scan is made and patients for whom for other reasons no EOT scan is available or analyzable will not be included in the analysis of recanalisation (this applies to change in number of occluded cerebral veins and sinuses)

Diagnosis of CVT and assessment of venous occlusion is expected to be performed by any of the following techniques or a combination of them:

- MRI + MR venography
- CT + CT venography
- MRI or CT in combination with angiography (DSA)

Patients are diagnosed prior to trial entry. The imaging that was performed for diagnosis of CVT (as part of the clinical routine) will be used as baseline assessment.

At EOT the assessment of recanalisation must be done by MRI+MR venography. These techniques are expected to provide a better view of any remaining venous occlusion than CT would. Furthermore, for WOCBP it is desirable to refrain from CT scans in the non-acute setting due to radiation exposure of CT scans.

A separate MRI protocol will be provided as part of the ISF and should be followed for the EOT imaging.

All scans (both baseline and EOT) will be sent in for central review by the AC. Review criteria will be outlined in the AC charter governing the adjudication process. Details on how to provide the images will be provided in the ISF. Central review will focus on assessment of endpoints (grade of cerebral venous recanalisation / recurrence of CVT).

## 5.3 ASSESSMENT OF SAFETY

### 5.3.1 Physical examination

A complete physical examination will be performed by the Investigator at the visits indicated in the Flow Chart. Documentation of the physical examination and any findings must be part of the source documents available at the site.

### 5.3.2 Vital Signs, body weight and height

Systolic and diastolic BP and Pulse Rate should be performed at the visits indicated in the Flow Chart. The testing should be performed after resting for at least five minutes. For each patient, all BP recordings should be made using the same type of instrument (i.e. manual BP recording vs. automatic digital vital signs monitor) on the same arm if possible. Weight should be measured at the visits indicated in the Flow Chart in order to calculate CrCl according to Cockcroft-Gault (see Section 5.3.3). Height should be measured at the screening visit.

### 5.3.3 Safety laboratory parameters

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

Blood samples for safety testing will be analysed at the local laboratory and results will be recorded in the CRF. Testing should be done at visits as specified in the Flow Chart. The tests to be performed are listed in Table 5.3.3: 1.

If medically indicated, laboratory parameters may be retested or followed-up on as unscheduled tests.

Table 5.3.3: 1 Safety laboratory parameters

<u>Chemistry</u>	<u>Haematology</u>
ALT (SGPT)	Erythrocytes
AST (SGOT)	Haemoglobin
Alkaline Phosphatase	Haematocrit
Bilirubin total, fractionated if increased	Platelet Count
GGT	WBC count
Creatinine	
CrCl**	

\*\* According to Cockcroft-Gault formula

## Pregnancy Testing

A pregnancy test will be performed locally on all women of child bearing potential at the visits as specified in the [Flow Chart](#). A urine test is acceptable, unless local regulations

demand a serum test to be performed.

In addition, women of child bearing potential will be supplied with pregnancy tests and will be instructed to perform pregnancy testing every 4 weeks when visits are more than 4 weeks apart.

### **Renal Function Measurements**

Renal function must be measured before enrolling a patient in the trial, and at visits as indicated in the [Flow Chart](#) (safety laboratory tests). CrCl will be calculated using the Cockcroft-Gault formula, as follows:

- For creatinine in  $\mu\text{Mol/L}$ :

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

- For creatinine in  $\text{mg/dL}$ :

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

### **5.3.4      Electrocardiogram**

12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be performed using the site's own devices at the visits indicated in the Flow Chart. The ECGs must be evaluated by the Investigator or a designee immediately, for investigation or treatment if necessary.

### **5.3.5      Other safety parameters (safety endpoints)**

#### **5.3.5.1      Composite endpoint of new haemorrhagic brain lesion or worsening of the haemorrhagic component of a previous lesion**

The neuroimaging which established the diagnosis of CVT will be used as baseline value. The safety endpoint "new haemorrhagic brain lesion or worsening of the haemorrhagic component of a previous lesion" will be assessed by comparing repeated neuroimaging that is routinely performed if the patient has a neurological worsening during the trial, or at the EOT visit, to the baseline image. The comparing of images and the categorisation of the lesions (see below) will be done by the AC.

A separate MRI protocol will be provided as part of the ISF and should be followed for the EOT imaging.

In order to assess any worsening of previous lesions, haemorrhagic brain lesions at baseline and during treatment / at EOT will be categorised as indicated in Table [5.3.5.1: 1](#) below, according the definitions as recommended by Von Kummer et al [[P15-09432](#)]:

Table 5.3.5.1: 1      Categorisation of haemorrhagic brain lesions

<b>Class</b>	<b>Type</b>	<b>Description</b>
1		Haemorrhagic transformation of infarcted brain tissue
1a	HI-1*	Scattered small petechiae, no mass effect
1b	HI-2	Confluent petechiae, no mass effect
1c	PH-1*	Haematoma within infarcted tissue, occupying <30%, no substantive mass effect
2		Intracerebral haemorrhage within and beyond infarcted brain tissue
	PH-2	Haematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3		Intracerebral haemorrhage outside the infarcted brain tissue or intracranial-extracerebral haemorrhage
3a		Parenchymal haematoma remote from infarcted brain tissue
3b		Intraventricular haemorrhage
3c		Subarachnoid haemorrhage
3d		Subdural haemorrhage

\* HI: haemorrhagic infarction; PH: parenchymatous haematoma

Any new haemorrhagic brain lesion will be categorised as Class 3 (Intracerebral haemorrhage outside the infarcted brain tissue or intracranial-extracerebral haemorrhage).

If there is more than one haemorrhagic lesion present on imaging, the category of the most severe lesion is assigned.

### 5.3.5.2      Bleeding

All bleeding events that occur after signing of informed consent will be collected. Depending on the specific endpoint, events that occur after randomisation to trial medication or events that occur after first intake of trial medication will be part of the analysis of the bleeding events. See Section [7.3](#) for more details.

Patients should be carefully assessed for signs and symptoms of bleeding. Bleeding will be classified as major or minor. Major bleeds will be further sub-classified as fatal 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. MBEs and CRNMBEs will be reviewed by the AC.

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<sup>1</sup>, 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) within 24 hours, or leading to transfusion of two or more units of blood or packed cells<sup>2</sup>

and/or

- Fatal bleed

**Definition of a life-threatening bleed**

For the purpose of exclusion criterion 5, life-threatening bleeds are defined as follows:

- Symptomatic intracranial bleed

and/or

- reduction in haemoglobin of at least 5g/dL

and/or

- transfusion of at least four units of blood or packed cells, associated with hypotension requiring the use of i.v. inotropic agents

and/or

- necessitates surgical intervention.

**Definition of intracranial haemorrhage (ICH)**

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 AC determines as the primary cause of death or contributing directly to death.

<sup>1</sup> A seizure associated with a new intracranial bleed will be considered a symptomatic bleeding in a critical organ.

<sup>2</sup> Bleeding should be overt and the haemoglobin drop should be considered to be due to and temporally related to the bleeding event.

### **Definition of a CRNMBE**

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

- A hospital admission (i.e. overnight stay in the hospital) for bleeding  
or
- A physician guided medical or surgical treatment for bleeding  
or
- A physician guided change, interruption<sup>1</sup> or discontinuation of trial medication

### **Any bleed**

This is the sum of all major and non-major bleeds.

## **5.3.6 Assessment of adverse events**

### **5.3.6.1 Definitions of AEs**

#### **Adverse event (AE)**

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

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

#### **Adverse reaction**

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

#### **Serious adverse event (SAE)**

An SAE is defined as any AE which:

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

<sup>1</sup> Interruption of trial medication (more than omitting one dose) due to the bleeding event.

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

Any suspected transmission via a medicinal product of an infectious agent is considered a serious adverse reaction.

### **AEs considered “Always Serious”**

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

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

The latest list of “Always Serious AEs” can be found in the RDC system. These events should always be reported as SAEs as described in Section [5.3.7](#).

### **Adverse events of special interest (AESIs)**

No AESIs have been defined for this trial.

### **Intensity of AEs**

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

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

### **Causal relationship of AEs**

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

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial medication treatment continues or remains unchanged.

### **5.3.7 Adverse event collection and reporting**

#### **AE Collection**

The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate CRF by the Investigator:

- From signing the informed consent onwards through the follow-up period (which includes the Residual Effect Period (REP)), until individual patient's end of trial (for patients who discontinue trial medication early, this includes the extended follow-up period):
  - All AEs (serious and non-serious)
- After the individual patient's end of trial:
  - The Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs which the Investigator may become aware of

The AE reporting requirements are displayed in Figure [5.3.7: 1](#).

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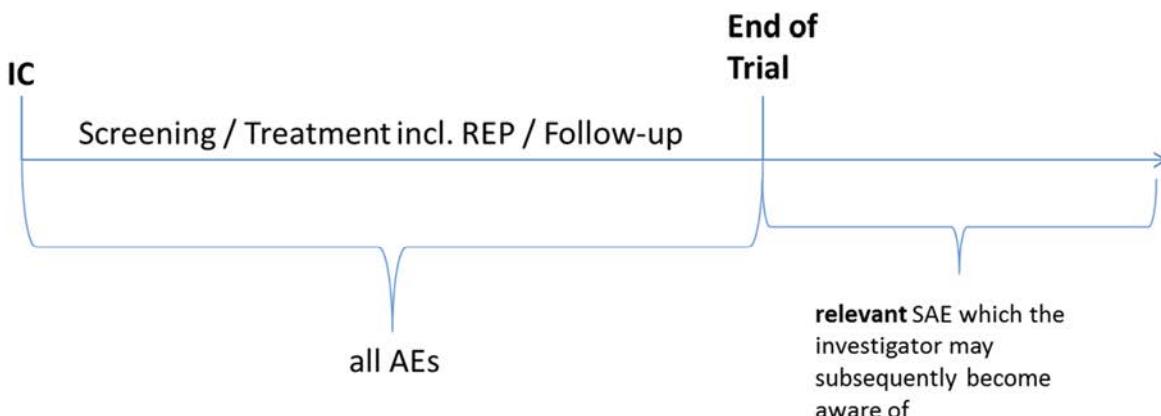


Figure 5.3.7: 1AE reporting requirements

The REP is defined as 6 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment (see Section [7.3.4](#)). Events which occurred after the REP will be considered as post treatment events.

#### AE reporting to sponsor and timelines

The Investigator must report SAEs, and non-serious AEs which are relevant for the reported SAE, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

#### Information required

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

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

**Pregnancy**

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the DEDP must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

**5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS**

**5.4.1 Assessment of Pharmacokinetics**

Not applicable

**5.4.2 Methods of sample collection**

Not applicable

**5.4.3 Analytical determinations**

Not applicable

**5.4.4 Pharmacokinetic – Pharmacodynamic Relationship**

Not applicable

## **5.6 OTHER ASSESSMENTS**

### **5.6.1 CVT risk score**

The CVT risk score is assessed for each patient at baseline for characterisation of the patient population. The score is applied as described by Ferro et al [[R15-5237](#)].

<b>Prognostic variable</b>	<b>Risk points</b>
Malignancy	2
Coma	2
Thrombosis of the deep venous system	2
Mental status disturbance	1
Male gender	1
ICH	1

The scores for the individual variables are summed up to arrive at the CVT risk score.

The following definitions apply:

#### **Coma**

Persistent disturbance of consciousness, patient being non-alert and non-arousable, with a Glasgow Coma Scale score measured at admission of < 9 points.

#### **Mental status disturbance**

Includes executive deficits (frontal lobe syndromes), delirium and personality or other acute behavioural changes, but not disturbances of the instrumental cognitive domains, such as aphasia, apraxia, agnosia, amnesia or visuospatial disturbances, present from onset of symptoms to the day of the diagnosis.

#### **Intracranial haemorrhage**

Any ICH, including haemorrhagic transformation of a venous infarct, detected on the admission neuroimaging (CT or MR).

#### **Thrombosis of the deep venous system**

Thrombosis of any of the veins of the deep cerebral venous system (Rosenthal's basal vein, inferior longitudinal sinus, thalamo-striate vein), isolated or in combination with thrombosis of other veins or sinus.

#### **Malignancy**

Any malignant tumour in any location of the body or any haematological malignancy (leukaemia or lymphoma), diagnosed before CVT or during hospitalisation for acute CVT.

### **5.6.2 National Institutes of Health Stroke Scale**

The National Institutes of Health Stroke Scale (NIHSS) will be recorded, if it had been collected at the time of qualifying (index) CVT. In patients, where NIHSS has not been done at the time of index CVT, it will be performed at study entry (at Visit 1). It is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, and for each item a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0 [[R13-4008](#), [R13-4023](#), [P13-10973](#)].

Score	Stroke Severity
0	No Stroke Symptoms
1-4	Minor Stroke
5-15	Moderate Stroke
16-20	Moderate to Severe Stroke
21-42	Severe Stroke

The NIHSS is located in [Appendix 10.3](#).

### **5.7 APPROPRIATENESS OF MEASUREMENTS**

All used methods are standard and generally recognized.

## **6. INVESTIGATIONAL PLAN**

### **6.1 VISIT SCHEDULE**

Informed consent of all study patients (or their legally acceptable representative) will be obtained in compliance with the International Conference on Harmonization and GCP guidelines and the principles stipulated in the Declaration of Helsinki prior to any study related procedure.

The study will consist of three sequential periods, a Screening Period of up to 15 days, a Treatment Period of 24 weeks and a Follow-up Period of one week. If a patient discontinues trial medication prior to completing 24 weeks of treatment, he/she will be followed up until 25 weeks after randomisation. Their trial participation will then end.

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

There is no requirement for clinic visits to take place at a specific time of day.

Visits 1 and 2 may take place on the same day (see also Flow Chart and Section [6.2.2](#)). In that case Visit 2 procedures that are performed as part of Visit 1 do not need to be repeated.

It is anticipated that most patients are still hospitalised for their CVT at the time of randomisation. Investigators should ensure that all required procedures of trial visits are performed at the scheduled time points, even if the patient is still hospitalised. The allowed visit windows (see Flow Chart) can be used in order to avoid having patients return to the trial centre for a trial visit within a few days from hospital discharge.

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

The procedures to be conducted at each visit are provided in the Flow Chart and further described in Section [6.2](#).

## **6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS**

### **6.2.1 Screening period**

#### Screening Period

Patients may be enrolled into the trial (i.e. sign informed consent) once they have a confirmed diagnosis of CVT and have received any required treatment for the acute phase of the illness as recommended by the AHA/ASA [[R15-5005](#)] and EFNS [[P10-11802](#)]. See Sections [3.1](#) and [4.1.4](#). Written informed consent must be obtained prior to any study specific procedures.

It is anticipated that the majority of Screening procedures (see [Flow Chart](#)) will already have been performed as part of the routine care during hospitalisation and diagnosis. Trial related data from these procedures will be used for the trial and the procedures should not be repeated for the purpose of the trial. Any trial procedures that were not performed as part of routine care yet, should only be performed after informed consent has been obtained.

Brain images (i.e. CT, CT venography, MRI, MRI venography, or other) related to the qualifying CVT and any imaging performed during the trial (both those required by the Flow Chart as well as those performed as part of medical care) plus their corresponding reports must be provided to sponsor's designee where possible.

#### Baseline Conditions

The individual components of the CVT risk score and of the NIHSS will also serve as documentation of baseline conditions. In addition conditions relevant to the current CVT and symptoms of CVT not captured by the two scores mentioned above will be collected.

#### Medical History:

Data on any history of thromboembolic events and haemorrhagic events, including detailed history of the qualifying CVT, data on cardiovascular disease, known coagulopathies, other risk factors for VTE (including CVT) and any other relevant medical and surgical history will be collected.

### **6.2.2 Treatment period(s)**

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

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

At the start of Visit 2, it should be ensured that all Visit 1 procedures have been successfully completed. Visit 2 procedures are outlined in the Flow Chart. Restricted medications as outlined in Section [4.2.2](#) will be stopped if applicable.

Randomisation should occur as soon as the patient is stable and patient eligibility is confirmed, at 5 days (120 hours) and up to a maximum of 15 days (360 hours) after start of initial parenteral therapy (LMWH or UFH) (see Sections [3.1](#) and [4.1.4](#)).

Trial medication will be dispensed and should be initiated as outlined in Section [4.1.4](#).

In short, patients randomised to receive warfarin will start trial medication on the day of randomisation. They must continue to receive LMWH / UFH until the patient's INR  $\geq 2.0$  (one measurement). At that moment LMWH / UFH will be discontinued. If they are on oral anticoagulation (VKA) at the moment of randomisation, it needs to be confirmed that INR is  $< 3.0$  before trial medication is started. If the INR is  $\geq 3.0$ , warfarin must not be started until the INR is  $< 3.0$ .

Patients randomised to receive dabigatran etexilate will also start trial medication on the day of randomisation if they are not on oral anticoagulation (VKA) or if the INR is  $< 2.0$ . The first dose (capsule) of dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of the initial parenteral therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. i.v. UFH).

If the patient is on oral anticoagulation with a VKA for their CVT and the INR is  $\geq 2.0$ , trial medication can be dispensed but the patient will be instructed not to start it until notified. No further parenteral anticoagulation or VKA should be given. Follow-up INRs will be performed in 1-3 day intervals until it falls below 2.0, at which time the patient will be instructed by telephone to start taking the trial medication.

Patients will take trial medication until 24 weeks after randomisation.

AEs and SAEs, including specified endpoints, will be collected as described in Section [5.1](#), Section [5.2](#) and Section [5.3](#).

Treatment visits will take place as indicated in the [Flow Chart](#).

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

### **6.2.3 Follow Up Period and Trial Completion**

For any patient who discontinues trial medication (both patients who complete the full 24-week treatment period as well as patients who discontinue early) the EOT (Visit 5) procedures as specified in the Flow Chart should be performed at that moment.

All patients should be followed for another 7 days after the EOT visit and a Follow-up Visit be performed 7 to 14 days after the EOT visit. If the patient needs to continue with dabigatran etexilate trial medication for bridging to VKA (see Appendix [10.2](#)), the follow-up visit should be performed 7 days after the last trial medication intake. In that case used and unused trial medication should be collected at that visit.

Patients who discontinue trial medication early (see Section [3.3.4](#)) should be followed (after the follow-up visit) for MBEs, VTE and any other AEs until Day 176

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(25 weeks) after randomisation, unless they withdraw their informed consent completely. In addition, data on post-study anti-coagulation therapy will be collected. Those patients complete trial participation at that contact moment (Day 176).

This follow-up may be done in any way that is acceptable to the patient, i.e. it does not need to consist of clinic visits. The minimum requirement is a contact at 25 weeks after randomisation. It is anticipated that the majority of data (such as data on bleeding events and VTE, if any) will be collected from existing medical records. Patients should be made aware of this. See [Flow Chart](#) and Section [3.3.4](#) for further details.

After discontinuation of trial medication, further treatment is up to the discretion of the treating physician, in accordance with relevant treatment guidelines. For recommendations on how to switch from dabigatran etexilate to other anticoagulants see Appendix [10.2](#).

## **7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE**

### **7.1 STATISTICAL DESIGN - MODEL**

This study is a PROBE (Prospective, Randomised, Open label, Blinded Endpoint), multicentre, international, parallel group study with an active control and equal treatment allocation. This phase III study is planned to investigate the efficacy and safety of dabigatran etexilate versus dose-adjusted warfarin in patients with CVT over a 24-week period. The primary endpoint is a composite of the number of patients with new VTE (CVT, DVT, PE, splanchnic vein thrombosis) or major bleeding according to ISTH criteria after up to 24 weeks.

The study is an exploratory trial and not intended for registration. No formal statistical hypothesis will be tested. All analyses are descriptive in nature and confidence intervals and p-values from statistical models are used for exploratory purposes only.

### **7.2 NULL AND ALTERNATIVE HYPOTHESES**

This trial is conducted as an exploratory trial; no hypotheses testing will be performed.

### **7.3 PLANNED ANALYSES**

The following analysis sets will be defined for this trial:

- **Screened Set (SCR):**  
All patients who sign informed consent and complete at least some screening procedures.
- **Treated set:**  
The set includes patients who receive at least one dose of study medication and will be analysed according to the treatment they have received.
- **Full analysis set (FAS):**  
All patients randomised will be analysed in the treatment group to which they are randomised regardless of whether they took study medication. The start date of the observation period for this analysis set is the date of randomisation. This follows the intent-to-treat (ITT) principle.
- **Per protocol set (PPS):**  
This is a subset of the Treated set, restricted to patients without important protocol violations. Important protocol violations will be defined in the TSAP. If the number of patients excluded from PPS is small, (e.g. <10% of the Treated set), then analyses on this set may not be conducted.

The efficacy analysis based on FAS will follow the ITT principle. Patients will be allocated to the randomised treatment groups regardless of actual medication taken.

Two observation periods are defined:

- Full observation period: from date of randomisation until the end of the trial, including all observed time on and off trial medication until the last known alive date (or date of death).
- On-treatment: from date of first intake of trial medication until discontinuation of trial medication + 6 days.

### 7.3.1 Primary endpoint analyses

The primary analysis will be based on the FAS and will use the full observation period for each patient. Patients will be analysed according to the treatment as randomised to follow the ITT principle.

The primary endpoint is defined as the number of patients with composite of VTE or major bleeding according to ISTH criteria after up to 24 weeks.

The number and frequency of patients by treatment as well as by subgroup will be displayed along with the 95% confidence intervals. No difference between the treatments dabigatran etexilate versus warfarin will be tested. Hazard ratios (HR) and 95% CI will be displayed, only if data is sufficient to do so.

The primary endpoint will also be analysed by subgroup, i.e. by stratification factor (see Section [7.6](#)). The following subgroups are of interest:

- Patients with or without ICH at baseline as assessed by the investigator. It is estimated that 30-40% of patients would present with intracerebral haemorrhage (which is a subtype of ICH) at baseline.

Further specification of analyses and further subgroups may be defined in the TSAP.

### 7.3.2 Secondary endpoint analyses

Secondary analyses will be based on the FAS for the following endpoints: number of patients with CVT, DVT, PE, splanchnic vein thrombosis and the endpoint on cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses after up to 24 weeks.

The following analyses will be based on the treated set: number of patients with major bleeding according to ISTH, number of patients with clinically relevant non-major bleeding, as well as the composite of the two mentioned above, number of patients with any bleeding, number of patients with composite endpoint of new ICH or worsening of the haemorrhagic component of a previous lesion.

The analyses for the secondary endpoints as described in Section [5.1.2](#) will be mainly based on frequency counts and percentages along with 95% confidence intervals.

Means and standard deviations will be displayed by treatment arm for the endpoint on cerebral venous recanalisation as measured by the change in number of occluded cerebral

veins and sinuses after up to 24 weeks. Means and standard deviations will be displayed by stratification factor of presence or absence of ICH at baseline. Patients with missing or not analysable MRI scans at EOT would need to be excluded from this analysis.

The composite endpoint of new ICH or worsening of the haemorrhagic component of a previous lesion will be categorized as described in Section [5.3.5.1](#). This ordinal endpoint will be analysed with Cochrane-Mantel-Haenszel test.

Further specification of analyses can be found in the TSAP.

#### **7.3.4 Safety analyses**

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding dictionary available at database lock. Standard BI summary tables and listings will be produced. All AEs with an onset between start of trial medication and end of the REP, a period of 6 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 6 days. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

### **7.3.5 Pharmacokinetic analyses**

Not applicable.

## **7.4 INTERIM ANALYSES**

No interim analysis is planned but the conduct of the trial will be monitored by a DMC (see Section [3.1.1](#)). Formal efficacy or safety stopping rules, if any, will be defined in the DMC charter. The DMC will review the trial data at pre-defined intervals. The number of patients in each treatment group is small and only a limited number of outcome events is expected to occur. It is therefore not expected that DMC review will result in statistically significant differences between the treatment groups. In order for the trial to provide relevant data, the full sample size and follow-up period are likely to be necessary. Only under exceptional circumstances, in case of highly relevant difference in the efficacy or safety between the trial treatments, should the DMC consider early termination of the trial.

## **7.5 HANDLING OF MISSING DATA**

For the primary and secondary endpoints no general imputations are planned. In case of early discontinuation of patients with no follow-up and no events, those will be handled as imputed no event.

In case of no available or no analysable MRI scans at EOT, those patients will be graded as 0 for a sensitivity analysis for grading of recanalisation.

## **7.6 RANDOMISATION**

Patients will be randomised in blocks to open-label treatment with stratification by presence or absence of ICH at baseline. Presence of ICH prior to randomisation will be assessed by the investigator from the scans made at the moment of diagnosis. Approximately equal numbers of patients will be randomised to each treatment group. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves 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 Clinical Trial Report. Access to the codes will be controlled and documented.

## **7.7 DETERMINATION OF SAMPLE SIZE**

It is planned to randomise 60 patients per arm, resulting in 120 patients randomised in total. Assuming a drop-out rate of 10%, this should result in 108 evaluable patients (54 per treatment arm).

Due to the rare nature of the disease (CVT incidence of around 2 per 100.000 per year), and with limited availability of patients in this indication, the planned sample size in this trial is not based on any statistical considerations. No hypotheses will be tested or confirmed.

Data about recurrence rates for CVT patients are limited; Martinelli et al. [[R15-5570](#)] report a 5% recurrence rate after discontinuation of anticoagulation within the first year. We assume a 2-3% event rate for the composite primary endpoint with 6 months of treatment.

The trial is designed as exploratory; a comparable frequency for the primary endpoint between dabigatran and warfarin would provide clinicians with important new information.

## **8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY**

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for GCP, relevant BI SOPs, the EU regulation 536/2014 and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of International Conference on Harmonization GCP.

The BI transparency and publication policy can be found on the following web page: [trials.boehringer-ingelheim.com](http://trials.boehringer-ingelheim.com). 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 rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF where required.

### **8.1 TRIAL 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 International Conference on Harmonization / 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.

Due to the nature of the disease under study, it is anticipated that patients may be enrolled who cannot personally consent to trial participation. In such cases consent should be obtained from a legally acceptable representative, if acceptable per the regulatory and legal requirements of the participating country. A document will be provided in the ISF to specify the procedures to be followed for those patients, or to clarify that consent by a legally acceptable representative is not accepted at the specific trial site or in the country.

## **8.2 DATA QUALITY ASSURANCE**

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

## **8.3 RECORDS**

Electronic CRFs for individual patients will be provided by the sponsor.  
For drug accountability, refer to Section [4.1.8](#).

### **8.3.1 Source documents**

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). For this trial source documents are expected to include:

- Originals or copies of imaging diagnostics
- ECG results (original or copies of printouts)
- Medical chart including all documentation about the hospital admission for and diagnosis of the qualifying CVT
- All proceedings / medical notes from the moment of diagnosis of CVT until the completion of the patient participation in the trial
- Documentation of the results of local laboratory tests, including INR results
- Notes of telephone contact with patients,

It is anticipated that the majority of screening procedures will already have been performed as part of the routine procedures for hospitalisation and diagnosis before enrolment of the patient into the trial. These data (that will be generated before informed consent will have been obtained) will be used for the trial. The original hospital records for these data will be the source documents.

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

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must put every effort into retrieving previous medical records prior to randomisation of the patient. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- NIHSS
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Documentation of all INR measurements both from prior to start of trial medication (patients on a VKA prior to randomisation) and during the 24-week treatment period (patients randomised to receive warfarin) (e.g. sponsor-provided INR logs; this may be a (paper or electronic) copy of original data in case INR management is done by another facility)
- Termination of trial medication (last date of intake and the reason for termination in case of premature discontinuation)
- Completion of Patient's Participation in the trial (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

For adjudication purposes, supporting documentation and imaging (as needed and available) must be provided.

### **8.3.2 Direct access to source data and documents**

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by

assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section [8.3.1](#). The sponsor will also monitor compliance with the protocol and International Conference on Harmonization GCP.

### **8.3.3 Storage period of records**

#### Trial site(s)

The trial site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

#### Sponsor

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

## **8.4 EXPEDITED REPORTING OF ADVERSE EVENTS**

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

## **8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY**

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

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

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

## **8.6 TRIAL MILESTONES**

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

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"). The "**Last Patient Drug Discontinuation**" (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

**Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

**Temporary halt of the trial** is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

**Suspension of the trial** is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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## **10. APPENDICES**

### **10.1 TRIAL MEDICATION START AND BRIDGING RULES**

#### **10.1.1 When to start dabigatran etexilate following treatment by other anticoagulants**

##### **Heparins**

UFH or LMWH (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: initiate dabigatran etexilate at the time the UFH is stopped
- LMWH: initiate dabigatran etexilate 0-2 hours prior to the time that the next dose of the LMWH would be due.

##### **Vitamin K antagonists**

Patients already on VKA, should start dabigatran etexilate once the INR is  $<2.0$ . If the INR is  $\geq 2.0$ , 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.

#### **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.

#### **10.1.3 Bridging Therapy (e.g. for temporary interruptions of trial medication due to interventions)**

The use of bridging therapy depends on the thromboembolic 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.

## **10.2 SWITCHING FROM TRIAL TREATMENT AT EOT**

Any patient that decides to discontinue trial medication should be considered for a switch to an appropriate (non-study) anticoagulant according to local practice. For patients receiving dabigatran etexilate in the trial, continuation of trial medication for 2-3 days to assist bridging may be appropriate in case patients are switched to a VKA.

Decisions regarding the continuation of the systemic anticoagulation agents after the completion of the treatment period (EOT) should be based on the recommendations and guidelines of the AHA/ASA [[R15-5005](#)] and EFNS [[P10-11802](#)] or alternative local treatment practice.

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, if any.

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

### **OPTION 1: STARTING VKA PRIOR TO DABIGATRAN ETEXILATE DISCONTINUATION**

Start VKA at the EOT Visit and continue on dabigatran etexilate for 2-3 days after the EOT Visit<sup>1</sup>.

- In patients with CrCl >50mL/min who discontinue dabigatran etexilate but still require anticoagulation, dabigatran etexilate should be continued for three days together with VKA.
- For patients with moderate renal dysfunction (CrCl  $\geq$ 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 VKA naïve patients before starting VKA. There is no special need to measure the INR before starting a VKA. If the INR is checked on the day of the EOT visit, Investigators should recognise that the presence of dabigatran etexilate 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**

A 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.

<sup>1</sup> The date of final intake of dabigatran etexilate must be documented in the CRF.

The decision to use bridging therapy is at the discretion of the investigator.

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.

**10.3 NATIONAL INSTITUTES OF HEALTH STROKE SCALE**

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

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

## **11. DESCRIPTION OF GLOBAL AMENDMENT(S)**

### **11.1 GLOBAL AMENDMENT 1**

<b>Number of global amendment</b>	1
<b>Date of CTP revision</b>	10 February 2017
<b>EudraCT number</b>	2015-004412-38
<b>BI Trial number</b>	1160.248
<b>BI Investigational Product(s)</b>	Pradaxa®, dabigatran etexilate
<b>Title of protocol</b>	RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>	X
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>	
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>	
<b>Section to be changed</b>	Clinical Trial Protocol Synopsis 3.3 SELECTION OF TRIAL POPULATION 7.7 DETERMINATION OF SAMPLE SIZE
<b>Description of change</b>	No. of patients was changed from total 180 planned to total 120 planned and from 90 to 60 planned in each treatment arm The anticipated drop-out rate was changed from 15-20% to 10%, resulting in 108 evaluable patients (54 per treatment arm)
<b>Rationale for change</b>	Due to the exploratory nature of the trial the total number of required patients is difficult to determine. During trial preparation it became clear that the trial may be conducted with fewer patients than originally assumed. Since it would be

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		considered unethical to put more patients at risk than is required, the number was reduced. The drop-out rate was updated based on experience of the trial's Steering Committee members
<b>Section to be changed</b>		Flow Chart, footnote 8 5.3.3 Safety laboratory parameters
<b>Description of change</b>		Text about pregnancy testing was changed to clarify that all WOCBP should perform a pregnancy test every 4 weeks (instead of only women randomised to warfarin)
<b>Rationale for change</b>		Request from authorities and simplification of instructions for trial sites
<b>Section to be changed</b>		3.3.2 Inclusion criteria 4.2.2.4 Restrictions regarding women of childbearing potential
<b>Description of change</b>		Addition of a list of acceptable contraception methods to section 4.2.2.4 and Inclusion criterion 2 was updated to include a reference to that list; Removal of tubal ligation from the list of procedures to render a woman not of childbearing potential; Addition of text (section 4.2.2.4) to specify that WOCBP should use effective methods of birth control from the moment of signing informed consent for the trial until completion of the follow-up visit (Visit 6)
<b>Rationale for change</b>		Request from the authorities and adaptation to recently updated recommendations from the European Union Heads of Medicines Agency related to contraception and pregnancy testing in clinical trials (CTFG, 2014)
<b>Section to be changed</b>		2.2 TRIAL OBJECTIVES
<b>Description of change</b>		Clarification that the primary objective does not require 24 weeks of treatment
<b>Rationale for change</b>		To be consistent with the description of the trial's endpoints: the primary endpoint will be assessed up to 24 weeks after randomisation irrespective of whether or not treatment was taken for 24 weeks.
<b>Section to be changed</b>		3.1.1 Administrative structure of the trial 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)
<b>Description of change</b>		Change in set-up of the adjudication committee
<b>Rationale for change</b>		For this exploratory trial the adjudication committee (AC) for central assessment of endpoints will be set-up by the sponsor, hiring

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	external experts. By not using a third party vendor for AC coordination, the AC may not be considered completely independent of the sponsor by all stakeholders, although all decisions made by AC members will not be influenced by the sponsor. Therefore the description of the AC is changed.
<b>Section to be changed</b>	4.1.4 Drug assignment and administration of doses for each patient
<b>Description of change</b>	Addition of caution statement about treatment with warfarin in patients with known protein C or protein S deficiency
<b>Rationale for change</b>	Request from authorities
<b>Section to be changed</b>	5.2.1 Venous thrombotic events
<b>Description of change</b>	The requirements for confirmation of DVT, PE and splanchnic vein thrombosis were changed to require images and/or reports (instead of both) to be provided to the AC
<b>Rationale for change</b>	In order to be in line with what was done in prior trials with the same IMP, and in order to limit the source data transfer to the necessary elements required for adjudication
<b>Section to be changed</b>	7.3 PLANNED ANALYSES
<b>Description of change</b>	An additional patient population, Screened Set (SCR), was defined, i.e. All patients who sign informed consent and complete at least some screening procedures.
<b>Rationale for change</b>	This patients set will be used for display of disposition tables etc.
<b>Section to be changed</b>	8.3.1 Source documents
<b>Description of change</b>	Deletion of the list of documents and images that will be made available for adjudication purposes
<b>Rationale for change</b>	This will be defined in the adjudication charter instead of the trial protocol



## APPROVAL / SIGNATURE PAGE

**Document Number:** c03714648

**Technical Version Number:** 2.0

**Document Name:** clinical-trial-protocol

**Title:** RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period

### Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		14 Feb 2017 10:12 CET
Author-Statistician		14 Feb 2017 10:45 CET
Approval-Team Member Medicine		14 Feb 2017 17:06 CET
Approval-Therapeutic Area		14 Feb 2017 19:14 CET
Verification-Paper Signature Completion		15 Feb 2017 10:58 CET

(Continued) Signatures (obtained electronically)

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>