Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c03118416-03**
BI Study Number:	1160.188
BI Investigational Product(s):	Not applicable.
Title:	Cha**R**act**E**rization of patients following a**C**ute venous thr**O**mboembolism (**VTE**) and assessment of safety and effectiveness of dabigatran etexilate (DE) in the t**R**eatment and secondar**Y** prevention of acute deep vein thrombosis (**DVT**) and pulmonary embolism (**PE**) in comparison to vitamin K antagonist (VKA) in routine clinical practice - **RE-COVERY DVT/PE**
Brief lay title	RE-COVERY DVT/PE: global study on treatment and secondary prevention of acute venous thromboembolism
Protocol version identifier:	3.0
Date of last version of protocol:	16 Nov 2016
PASS:	Yes
EU PAS register number:	EUPAS11368
Active substance:	Dabigatran etexilate
Medicinal product:	Dabigatran etexilate
Product reference:	Not applicable
Procedure number:	Not applicable
Joint PASS:	No
Research question and objectives:	There are two primary objectives in this study: • To characterize the DVT / PE patient population including the initial acute event phase. All patients with a DVT and/or PE will be enrolled for cross-sectional characterization of the VTE patient population and descriptions of current treatment

	patterns, and stratified by geographical location. • To analyze the safety and effectiveness of dabigatran etexilate regimens in the treatment of DVT and PE over 1 year of follow-up in comparison to a VKA regimen. Additional further exploratory objectives are: • To evaluate geographical variations in health care resource utilization and patient satisfaction with their treatment in routine clinical practice. • To conduct stratified analysis for the safety and effectiveness of dabigatran etexilate according to dose. The following research questions will be investigated: • With the approval of dabigatran etexilate and other non-vitamin K oral anticoagulant (NOACs), what treatments are being administered for acute VTE in routine clinical practice in the different regions of the world? • When presenting with an acute VTE event, what factors influence the choice of treatment for the event? • What is the safety and effectiveness of dabigatran etexilate versus VKA under conditions of routine clinical practice? • What health care resources are utilized in patients who are treated with dabigatran etexilate or VKA for an acute VTE under conditions of routine clinical practice? • For patients who are treated with either dabigatran etexilate or VKA, what is patients' satisfaction with their treatment under conditions of routine clinical practice?
Country(-ies) of study:	Global study including countries from North and South America, Europe, Middle East and Asia.
Author:	Phone: Fax:
Marketing authorization holder(s):	
MAH contact person:	

EU-QPPV:	Phone:
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	01 Sep 2017

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2. LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse event of special interest
AF	Atrial fibrillation
b.i.d.	bis in die (two times a day)
CA	competent authority
CBC	Complete blood count
CCS	Canadian cardiovascular society
CI	Confidence Interval
CRA	Clinical Research Associate
CRNMB	Clinically relevant non major bleeding
DE	Dabigatran etexilate
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
GCP	Good Clinical Practice
GEP	Good epidemiology practices
GPP	Good pharmacoepidemiology practices
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ISF	Investigator Site File
LMWH	Low molecular weight heparin
MAH	Marketing authorization holder
Mg	Milligram
NCB	Net clinical benefit
NOAC	Non-vitamin K anticoagulant
NSTEMI	Non-ST elevation myocardial infarction
PACT-Q2	Perception of anticoagulant treatment questionnaire 2
PE	Pulmonary embolism
SAE	Serious Adverse Event
SEAP	Statistical and epidemiological analysis plan
STEMI	ST elevation myocardial infarction
Tn	Cardiac troponin
TTR	Time in therapeutic range
UA	Unstable angina
UFH	Unfractionated heparin
V-Q	ventilation/perfusion (scan)
VKA	Vitamin K antagonist
vs	Versus
VTE	Venous thromboembolism

3. RESPONSIBLE PARTIES

Therapeutic Area – Cardiovascular Medicine		
of Global Epidemiology Team Cardiovascular		
Team Member Medical Affairs		
Team Member Epidemiology		
Trial Clinical Monitor (TCM)		
Trial Statistician		
Steering Committee		

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Dabigatran etexilate			
Name of active ingredient: Dabigatran etexilate			
Protocol date: 28 May 2015	**Study number:** 1160.188	**Version/Revision:** 3.0	**Version/Revision date:** 01 Sep 2017
Title of study:	Cha**R**act**E**rization of patients following a**C**ute venous thr**O**mboembolism (**VTE**) and assessment of safety and effectiveness of dabigatran etexilate (DE) in the t**R**eatment and secondar**Y** prevention of acute deep vein thrombosis (**DVT**) and pulmonary embolism (**PE**) in comparison to vitamin K antagonist (VKA) in routine clinical practice - **RE-COVERY DVT/PE**		
Rationale and background:	The collection of clinical practice data is important for studying large patient numbers that include a broad spectrum of co-morbidities and co-medication use with the use of a new drug. Observational studies can provide complementary data, including safety data and health care resource utilization. This can expand the knowledge previously collected from randomized clinical trials, which generally have stricter entry criteria and structured monitoring schemes. With the recent approval of NOACs for the treatment and prevention of recurrent VTE, the use of older, traditional treatments, such as VKA, may change and it is therefore important to understand how patients with different characteristics are treated in routine clinical practice. In addition, there may be geographical differences in treatment patterns based on a number of factors including patient co-morbidities and co-medication use or cost and access to newer therapies. Dabigatran etexilate safety and efficacy with the 150 mg b.i.d. dose has been demonstrated in large randomized clinical trials for several indications (e.g., VTE, stroke prevention in atrial fibrillation (AF)). However, the safety and effectiveness of 110 mg b.i.d. dabigatran etexilate compared with VKA for treatment of VTE has not been investigated in randomized clinical trials. Health authorities, however, have also requested the lower dose (110 mg b.i.d) for use in the treatment of VTE in special		

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	populations (e.g., elderly or patients concomitantly taking verapamil). This observational study provides an opportunity to collect clinical data in a broader patient population including all available dosages of dabigatran etexilate.		
Research question and objectives:	There are two primary objectives in this study: • To characterize the DVT / PE patient population including the initial acute event phase. All patients with a DVT and/or PE will be enrolled for cross-sectional characterization of the VTE patient population and descriptions of current treatment patterns, and stratified by geographical location. • To analyze the safety and effectiveness of dabigatran etexilate regimens in the treatment of DVT and PE over 1 year of follow-up in comparison to a VKA regimen. Additional further exploratory objectives are: • To evaluate geographical variations in health care resource utilization and patient satisfaction with their treatment in routine clinical practice. • To conduct stratified analysis for the safety and effectiveness of dabigatran etexilate according to dose. The following research questions will be investigated: • With the approval of dabigatran etexilate and other NOACs, what treatments are being administered for acute VTE in routine clinical practice in the different regions of the world? • When presenting with an acute VTE event, what factors influence the choice of treatment for the event? • What is the safety and effectiveness of dabigatran etexilate versus VKA under conditions of routine clinical practice? • What health care resources are utilized in patients who are treated with dabigatran etexilate or VKA for an acute VTE under conditions of routine clinical practice?		

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	• For patients who are treated with either dabigatran etexilate or VKA, what is patients' satisfaction with their treatment under conditions of routine clinical practice?		
Study design:	RE-COVERY is a large, multi-national, multi-center observational study based on new data collection. The study will enroll and characterize patients diagnosed with an acute DVT and/or PE. Patients treated with dabigatran etexilate or VKA will be followed up for the occurrence of outcome events for up to one year.		
Population:	Setting: Participation of a country requires the approval of dabigatran etexilate for the VTE indication prior to study initiation within that country. Selected sites within each country should include those physicians (e.g., specialist and general practitioners) and facilities (e.g., general practice offices, specialist offices, hospitals, outpatient care centers and anticoagulation clinics) that reflect the clinical practice within that country. Patient Population: Objective 1: The study will enroll and characterize patients diagnosed with an acute DVT and/or PE. Objective 2: Patients treated with dabigatran etexilate or VKA will be followed up for the occurrence of outcome events for up to one year.		
Variables:	For Objective 1: The patient's baseline characteristics including demographic information, co-medication and co-morbidities, basic physical examination and laboratory information, VTE event information including treatment selected, event type, and history of VTE event will be collected at the time of the acute VTE event. The following primary outcome measures will be analyzed on data that is collected at the time of the acute VTE event: • Demographic information (age and gender) • VTE event information (event type and treatment for event)		

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	For Objective 2: The same baseline outcome measures will be collected as described above at time of the acute VTE event. During the follow-up of patients treated with dabigatran etexilate or VKA, details regarding changes to their anticoagulation therapy (e.g., dose adjustments, discontinuation of treatment, and reason for discontinuation); outcome events, adverse drug reactions and changes to concomitant medications will be collected. Health care resource utilization and patient's satisfaction with their anticoagulation therapy will be assessed using the Perception of anticoagulation treatment questionnaire 2 (PACT-Q2). The following primary outcomes will be analyzed: • Primary safety outcome measure: Major bleeding and clinically relevant non major bleeding (International Society on Thrombosis and Haemostasis (ISTH) criteria) • Primary effectiveness outcome measure: symptomatic recurrent VTE including VTE-related mortality The following secondary outcomes will be analyzed: • Recurrent DVT and/or PE • VTE-related mortality • All-cause mortality		
Data sources:	RE-COVERY is a study based on new data collection. Data will be collected based on assessment of the patient (e.g., physical examination and patient interview), review of hospital / medical records and available laboratory and diagnostic test reports. Patient reported outcomes will be assessed using a validated questionnaire.		
Study size:	It is planned that approximately 6000 patients will be enrolled for Objective 1 and up to 5000 patients will be enrolled for Objective 2 from approximately 300 sites around the world		
Data analysis:	Patient demographics and baseline characteristics will be summarized descriptively. Multivariable regression models and		

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	propensity score based methods will be used for the comparative analyses of dabigatran etexilate and VKA patients.		
Milestones:	It is planned that data collection will start by August 2015 and is planned to be completed by December 2018. The final study report is planned to be completed in the first quarter of 2019 assuming recruitment is completed within 2 years.		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study Protocol	Amendment or update	Reason
1	16 Nov 2016	Cover page	Middle East added as a participating region.	Expanded country participation.
2	16 Nov 2016	Abstract	Reference to recruitment of patients within 30 days was removed.	The allowable window to recruit patients into Objective 1 was increased.
3	16 Nov 2016	9.1	The allowable window to recruit patients into Objective 1 was increased to 6 months.	To provide sites sufficient time to ensure consecutive enrollment of patients into the study.
4	16 Nov 2016	9.2.1	Revision to inclusion 2 criterion to allow up to 6 months to enroll patients into Objective 1.	To provide sites sufficient time to ensure consecutive enrollment of patients into the study.
5	16 Nov 2016	9.3.1.3	If the specific reversal agent for dabigatran is given to a patient, information will be collected.	To ensure that details regarding the use of the dabigatran reversal agent are collected in a consistent manner.
6	16 Nov 2016	11:3	The section was removed.	The relevant information for sites is located in the ISF.
7	16 Nov 2016	11.4	AE reporting to regulatory authorities will be done by the MAH in accordance with local and international regulatory requirements.	To provide clarification regarding reporting responsibilities.
8	18 Aug 2017	Cover page	Change in Author name	To reflect change of TCM
9	18 Aug 17	Abstract; 9.1; 9.3.2; 9.9	Primary outcome measure for obj 2 to include clinically relevant non major bleeds.	Expanded primary outcome

10		Abstract	Sample size for obj 2 changed to 5,000 and last patient out pushed to December 2018	Sample size and timelines revised based on expanded primary outcome
11		9.2.4	Added description on how to handle Obj 1 and 2 patients whose anticoagulation treatment was discontinued or changed	To provide guidance on ePRO collection and fup requirement for obj 2 patients whose anticoagulation treatment was discontinued or changed
12		9.3.3	Added ISTH criteria for clinically relevant non-major bleed	Provide definition in the protocol as CRNMB is now included in primary outcome
13		9.3.11	Added examples of objective testing for VTE	To provide clarification on what constitute objective testing of VTE
14		9.5; Table 9.5.2	Statistical analysis assumptions updated including sample size assessment for primary outcome	Statistical assumptions updated because of change in primary outcome
15		11.2	Serious and non-serious ADRs for DE will be collected and reported from time of event. Serious and non serious ADRs to VKA will be collected from time of event for obj2 only. All serious and non-serious ADRs will be collected from time of informed consent.	Clarification around ARDs collection and reporting for DE and VKA for obj 1 and 2

6. MILESTONES

Status reports will be generated on a regular basis and are dependent on recruitment, strategic decisions and regulatory requests, if applicable. The schedule of reports will be maintained throughout the study and will be filed with the study documentation. The planned major milestone dates are summarized below.

Milestone	**Date**
Start of data collection	01 February 2016 (actual)
End of data collection	31 December 2018 (planned)
Registration in the EU PAS register	22 October 2015 (actual)
Final report of study results:	Second quarter of 2019 (planned)

7. RATIONALE AND BACKGROUND

7.1 MEDICAL BACKGROUND

VTE includes 2 related events: DVT and PE. The venous thrombus usually develops in the deep veins of the leg or pelvis. Thrombus from a DVT can propagate and/or embolize to the pulmonary circulation, resulting in a PE, which can turn into an acute life-threatening condition. Up to 50% of patients with DVT have evidence of a silent PE, and up to 70% of patients with a PE have a DVT. About 90% of all PEs originate as a venous thrombus in a proximal, larger diameter leg or pelvic veins, leading to an occlusion or partial occlusion of larger sized pulmonary vessels.

Risk factors for the development of venous thrombosis include vessel wall injury or endothelial dysfunction, hemodynamic changes, and hypercoagulability, otherwise known as Virchow's triad [R12-2781]. Other risk factors include major trauma, hip or leg fracture, orthopedic replacement of joints in the leg, immobilization, certain malignancies, history of prior VTE and genetic thrombophilia.

7.2 EPIDEMIOLOGY

The annual incidence of VTE is approximately 1-2 per 1000 individuals in Western countries [R04-2883, R05-0300, R12-2781]. VTE is estimated to be the third most common cardiovascular disorder after coronary heart disease and stroke. VTE is responsible for more than 180,000 hospitalizations per year in the US [P11-07302, P12-04560]. Over 750,000 VTE events are estimated to occur per year in six major European Union (EU) countries (France, Germany, Italy, Spain, Sweden, and UK [R09-0200]).

Treatment Options

Anticoagulant therapy is the standard treatment for venous blood clots, preventing new blood clots from forming, and preventing existing blood clots from getting larger and leading to dissolution of the existing clot after successful treatment. Rapid anticoagulation will minimize the risk of thrombus extension and PE in patients with VTE. Treatment duration is determined by the individual patient's clinical presentation. There are a number of factors that influence the type of anticoagulant therapy and treatment duration, including: the presence or absence of one or more risk factors for VTE (i.e., major orthopedic surgery), the acuteness of the thrombotic condition, the risk of recurrence, the risk of bleeding including bleeding due to underlying conditions (e.g., cancer) and issues that can affect compliance (e.g., parenteral versus oral administration and the degree of medical monitoring necessary to ensure efficacy and safety of the treatment).

Current guidelines for the United States (American College of Chest Physicians antithrombotic guidelines) and Europe (European Society of Cardiology), for the acute treatment of VTE recommend the initial administration of a parenteral anticoagulant, usually a low-molecular-weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux for 5-10 days. Parenteral treatment is followed by treatment with an oral vitamin K antagonist (VKA) such as warfarin that is titrated to a target International Normalized Ratio (INR) of 2 to 3 or dabigatran etexilate or edoxaban. Alternatively rivaroxaban or apixaban may be started immediately or after 1 to 2 days of LMWH, UFH or fondaparinux. Both rivaroxaban and apixaban require dose increases over 3 weeks (for rivaroxaban) or 1 week (for apixaban).

Anticoagulation treatment should last at least 3 months. Longer treatment may be recommended depending on the nature of the initial event (i.e. DVT versus PE), the risk of recurrence and the risk for bleeding [P12-01518, P14-16368]. Patients with an unprovoked acute VTE should also receive extended anticoagulation therapy assuming that they are not at high risk for bleeding [P12-01518, P14-16368].

Optimal treatment duration for acute VTE and the secondary prevention of recurrent VTE is not definitively known. The two terms "acute treatment" and "secondary prevention" are not precisely defined and might overlap. Current guidelines recommend treatment for 3 months over shorter treatment durations [P12-01518, P14-16368]. An extended duration of anticoagulation treatment should be considered for those patients with the greatest risk of VTE recurrence, i.e., those with an unprovoked DVT and/or PE; recurrent VTE, co-morbidities, such as cancer, chronic inflammation of the peripheral veins, and a strong genetic pre-disposition to thrombosis.

For patients with a chronic risk of recurrent VTE, there is evidence that when oral anticoagulation therapy is stopped, the risk of recurrence will increase to pre-treatment levels [P08-08095, R09-4888]. Therefore, the decision to continue treatment for prevention of recurrent VTE must consider the risk factors for recurrence as well as any risk factors for bleeding. The risk of bleeding increases in patients with a prior history of bleeding events, the presence of certain co-morbidities (e.g., gastrointestinal ulceration, inflammation or malignancy or other metabolic disorders that might alter hemostasis such as cirrhosis or chronic renal disease or concomitant medications that alter hemostasis (i.e. antiplatelet agents)). These risks must be reviewed periodically, and therefore, treatment decisions should be individualized and periodically reviewed.

Another critical factor that must be taken into consideration is a patient's history of medication compliance. VKAs have been the standard of care for oral anticoagulation therapy for decades but because of the narrow therapeutic window and their mechanism of action which is sensitive to diet-related alterations in vitamin K absorption, VKAs have been challenging to administer. A recent review of the pattern of anticoagulation after VTE in over 46,000 patients in the UK showed that the mean percentage of time in the therapeutic range (TTR) (i.e., INR of 2 to 3) was only 57% [R12-2550]. Similarly, in another study conducted in the US, the mean TTR was 53.7% for patients with AF and being treated with warfarin for stroke prevention. The TTR improved with time on treatment, increasing from 47.6% for patients treated for less than 6 months to 57.5% for those patients treated for greater than 6 months. Female gender, younger age and lower income bracket were independently associated with poorer anticoagulation control. There was also a strong association between improved TTR and physician case load which could reflect better organization for warfarin management and drug familiarity [R15-0778]. Warfarin efficacy is directly related to the time spent in the therapeutic window. Therefore risk of recurrence and the risk of bleeding is highly dependent on patient adherence and persistence, the ability to monitor anticoagulant activity (i.e., INR monitoring) and managing the dose effectively.

NOAC therapy including Factor Xa inhibitors (e.g., apixaban, rivaroxaban or edoxaban) and direct thrombin inhibitors (e.g., DE) have been used more recently for prevention and treatment of VTE. In general these agents have fewer drug-drug or dietary interactions and do not require rigorous INR monitoring compared with VKA. Although lower bleeding rates were observed with NOACs compared to VKA in clinical trials, bleeding remains a major side effect. Unlike VKA, regulatory approved reversal agents are not yet available in cases of

life-threatening bleeding. The effects of VKA may be reversed through I.V. administration of Vitamin K or a prothrombin complex concentrate (Kcentra® in the U.S. or Beriplex® in other countries), which can reduce the INR to ≤ 1.3 within 30 minutes [R15-1423].

The efficacy and safety of dabigatran etexilate versus (vs) warfarin has been tested in 4 pivotal, randomized, double-blind, clinical trials. A dose of 150 mg b.i.d. of dabigatran etexilate was tested in all 4 trials. Two trials (RE-COVER and RE-COVER II) demonstrated that dabigatran etexilate was non-inferior to warfarin for treatment of acute VTE [U09-1400, U11-2298]. Two other trials focused on secondary prevention in high-risk (RE-MEDY) [U10-2533] and lower risk (RE-SONATE) patients [U11-2267-02]. Dabigatran etexilate was non-inferior to warfarin in secondary prevention of recurrent VTE events in high-risk patients and superior to placebo in lower risk patients. The safety profile of dabigatran etexilate from the pivotal studies is consistent with the available safety data from other indications. The most common related adverse events (AE) for dabigatran etexilate included bleeding and GI AEs (e.g., dyspepsia and gastritis) however, dabigatran etexilate had fewer major or clinically relevant bleeding events compared to warfarin.

The safety of dabigatran etexilate vs warfarin in VTE patients has not been assessed in routine clinical practice. However, dabigatran etexilate safety has been assessed in patients being treated for nonvalvular AF in a study of elderly Medicare patients [P14-15648]. A total of 67,494 dabigatran etexilate patients and 273,920 warfarin patients were eligible for the study. Compared with warfarin, dabigatran etexilate use was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and mortality but with an increased risk of gastrointestinal bleeding. The increased risk of gastrointestinal bleeding occurred in women aged ≥ 75 years and to men aged ≥85 years.

7.3 RATIONALE FOR THE STUDY

The collection of data under conditions of routine clinical practice is important for studying large patient numbers that include a broad spectrum of co-morbidities and co-medication use with the use of a new drug. Observational studies can provide supplementary data, including safety data with available doses of NOACs (e.g., 75 mg, 110 mg and 150 mg dabigatran etexilate) and health care resource utilization. This can complement previously collected data from randomized clinical trials, which generally have stricter entry criteria and structured monitoring schemes. This can lead to the exclusion of significant patient segments. But even patients theoretically eligible might often not be included in clinical trials, especially older, frail, and presumably non adherent/persistent patients. These facts make it desirable to generate high-quality non-trial data to complement the evidence obtained from clinical trials.

With the recent approval of NOACs for the treatment and prevention of recurrent VTE, the use of older, traditional treatments, such as VKA, may change, and it is therefore important to understand how patients with different characteristics are treated under conditions of routine clinical practice. In addition, there may be geographical or regional differences in treatment patterns based on a number of factors, including patient co-morbidities and co-medication use or cost and access to newer therapies.

Dabigatran etexilate safety and efficacy with the 150 mg b.i.d. dose has been demonstrated in large randomized clinical trials for several indications (e.g., VTE, stroke prevention in AF). However, the safety and effectiveness of 110 mg b.i.d. dabigatran etexilate compared with VKA for treatment of VTE has not been investigated in randomized clinical trials. Health

authorities, however, have requested the lower dose (110 mg b.i.d) for use in the treatment of VTE in special populations (e.g., elderly or patients concomitantly taking verapamil). This observational study provides an opportunity to collect clinical data in a broader patient population including all available dosages of dabigatran etexilate.

8. RESEARCH QUESTION AND OBJECTIVES

There are two primary objectives in this study:

Objective 1: To characterize the DVT / PE patient population including the initial acute event phase. All patients with a DVT and/or PE will be enrolled for cross-sectional characterization of the VTE patient population and descriptions of current treatment patterns, and stratified by geographical location.

Objective 2: To analyze the safety and effectiveness of dabigatran etexilate regimens in the treatment of DVT and PE over 1 year of follow-up in comparison to a VKA regimen.

Additional further exploratory objectives are:

- To evaluate geographical variations in health care resource utilization and patient satisfaction with their treatment in routine clinical practice.
- To conduct stratified analysis for the safety and effectiveness of dabigatran etexilate according to dose.

The following research questions will be investigated:

- With the approval of dabigatran etexilate and other NOACs, what treatments are being administered for acute VTE in routine clinical practice in the different regions of the world?
- When presenting with an acute VTE event, what factors influence the choice of treatment for the event?
- What is the safety and effectiveness of dabigatran etexilate versus VKA under conditions of routine clinical practice?
- What health care resources are utilized in patients who are treated with dabigatran etexilate or VKA for an acute VTE under conditions of routine clinical practice?
- For patients who are treated with either dabigatran etexilate or VKA, what is patients' satisfaction with their treatment under conditions of routine clinical practice?

9. RESEARCH METHODS

9.1 STUDY DESIGN

RE-COVERY is a large, multi-national, multi-center observational study based on new data collection. The study will enroll and characterize all patients diagnosed with an acute DVT and/or PE. Patients treated with dabigatran etexilate or VKA will be followed up for the occurrence of outcome events for up to one year. The design is outlined in Figure 9.1:1.

To investigate Objective 1, a cross sectional design is selected to characterize the DVT/PE patient population at the time of an acute VTE event. The goal is to consecutively enroll approximately 6000 patients, who suffer from a DVT/PE independent of initial treatment choice and to allow for characterization of treatment patterns under conditions of routine clinical practice. Sites should utilize consecutive unselected enrollment (i.e., each patient who is seen with a VTE should be enrolled regardless of what treatment was provided) to avoid bias associated with preferential selection by physicians / site staff for the first objective (characterization of patient population). Patients should be enrolled ideally within 14 days of their acute VTE however sites will have up to 6 months to enroll the patient.

For Objective 2, that will compare patients who are being treated with dabigatran etexilate or VKA, a cohort design was selected to allow for comparisons between the two groups of patients regarding major and clinically relevant non-major bleeding events (primary safety outcome measure), and symptomatic recurrent DVT and PE events, including VTE-related mortality (primary effectiveness outcome measure). For the second objective, a balanced enrollment approach should be used so that the number of VKA patients does not vastly outnumber the dabigatran etexilate patients and both patient groups are collected at similar time points (i.e., for each dabigatran etexilate patient enrolled, the next VKA patient with the same index event (DVT/PE) should be recruited ideally at the same study site). Since the severity of the disease, treatment patterns and patient characteristics may differ considerably between patients with a DVT versus a PE, the treatment arms should have roughly equal numbers of patients with DVT and PE. To ensure global representation, regional recruitment caps will be employed to minimize under-or over-representation from a particular region. Patients should be enrolled ideally within 14 days but not more than 30 days of their acute VTE.

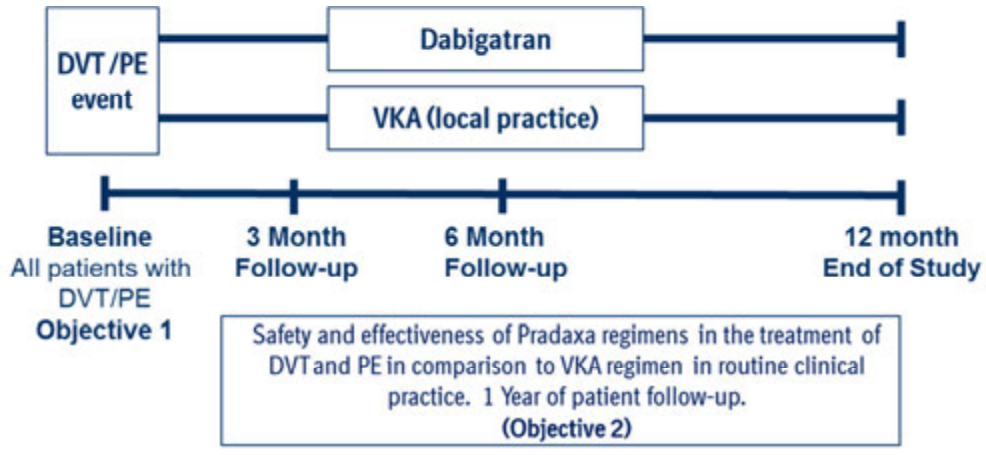

Figure 9.1:1 Study design

9.2 SETTING

It is planned that approximately 6000 patients will be enrolled for Objective 1 and up to 5000 patients will be enrolled for Objective 2 from approximately 300 sites around the world.

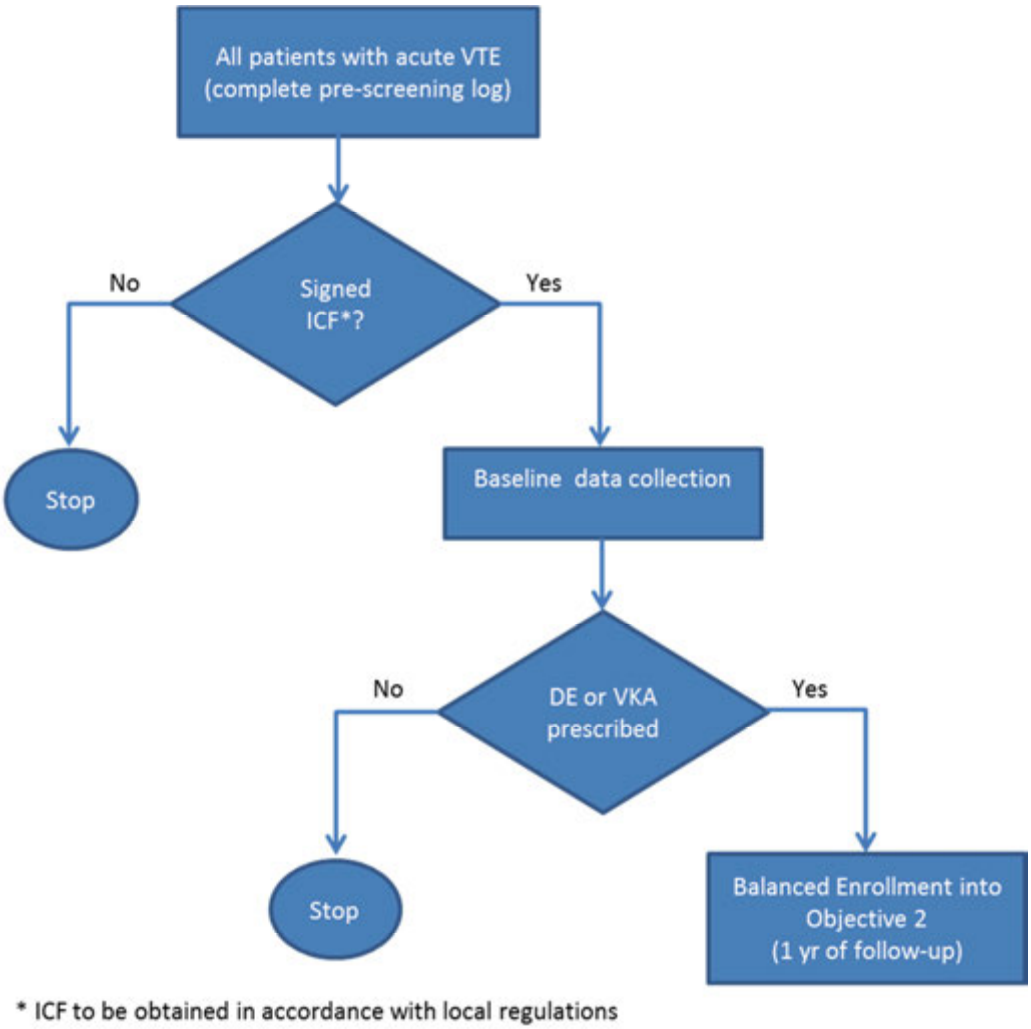

Figure 9.2:1 Enrollment of patients into the study

Participating countries require the approval of dabigatran etexilate for the VTE indication prior to study initiation within that country. Selected sites should include those physicians (e.g., specialists and general practitioners) and facilities (e.g., general practice offices, specialist offices, hospitals, outpatient-care centers and anticoagulation clinics) that reflect the clinical practice within that country. A robust site feasibility process will be undertaken to ensure that the participating sites represent the standard of care within that country. A pre-screening log will record minimal information about all potential patients (e.g., all patients who present with a VTE, age and gender will be collected if permissible by local law and if patient provided consent to participate in the study). This log will be maintained in the Investigator site file (ISF).

9.2.1 Inclusion criteria

1. Written informed consent provided by the patient or the patient's legal representative in accordance with local regulations
2. Diagnosis of an acute DVT irrespective of location and/or PE (For objective 1, assessment of patient for study participation should be done ideally within 14 days but not more than 6 months after diagnosis of the acute VTE. For Objective 2, patient assessment should occur ideally within 14 days but not more than 30 days from diagnosis)
3. Age ≥ 18 years
4. For Objective 2, the planned anticoagulation therapy should be for at least 3 months
5. For Objective 2, dabigatran etexilate and VKA patients should be available for follow-up data collection (clinic or via phone) at the specified timeframes

9.2.2 Exclusion criteria

1. On active or prophylactic anticoagulation therapy for conditions other than VTE. Ongoing anticoagulation treatment due to history of previous VTE is not considered an exclusion criterion. Anticoagulation therapy given for planned surgery is not considered an exclusion criterion.
2. Current participation in a clinical trial for VTE indication or current use of an unapproved (i.e., investigational) drug

The exclusion criteria were chosen for safety reasons and the number of patients thus excluded should be minimal.

9.2.3 Removal of subjects from the study

A patient can be withdrawn from the study for the following reasons:

1. A patient withdraws consent, without the need to justify the decision.
2. The patient was erroneously included in the study.

Boehringer Ingelheim (BI) reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study,
3. Violation of applicable sections of Good Clinical Practice (GCP), Good Pharmacoepidemiology Practice (GEP), the study protocol, or the contract by a study site or investigator.

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

9.2.4 Visit schedule

Collection of data in the study should be managed during routine practice visits or through telephone contacts with the patient, and follow the schedule in Table 9.2.4:1 as closely as possible.

Table 9.2.4:1 Schedule of data collection time-points

	Baseline	At hospital discharge (or 14 days)[1]	3 months	6 months	12 months
All patients	X	X			
DE or VKA patients followed for 1 year (objective 2 only)	X	X	X	X	X

1. Data will be collected at the date of hospital discharge or at 14 days post diagnosis, whichever is later.

Baseline

The "baseline" procedures and data to be collected may be done in one visit or over a series of contacts occurring after the acute VTE event based on information in the patient's medical record and/or information that is reported by the patient. Treatment with some NOACs (e.g., dabigatran etexilate or edoxaban) requires 5 to 10 days of pre-treatment with parenteral therapy; therefore, additional data will be collected according to the flowcharts (Table 9.3.1:1 and 9.3.1:2) at hospital discharge or 14 days after baseline, whichever is later.

Follow-up

Only patients who are treated with dabigatran etexilate or VKA are eligible to participate in the second objective that will include follow-up for up to 12 months after the index event. Balanced enrollment should be followed with regards to the treatment (i.e., dabigatran etexilate or VKA) and the type of index event (e.g., DVT or PE or DVT and PE). The decision to enroll a dabigatran etexilate or VKA patient for follow-up should be made as soon as the dabigatran etexilate or VKA has been prescribed and the patient has signed the study informed consent form (in accordance with local regulations). Patients should not be excluded from participation due to early outcome events (e.g., bleeding events). Data from all visits conducted under usual practice should be recorded in the electronic data capture (EDC) system at each data collection time-point even if the patient stops or changes treatment for the VTE event. Follow-up should be conducted by in-person clinic visits ideally. However, if no follow-up clinic visit occurs as part of clinical practice within one month of the planned data collection time-point (refer to Table 9.3.1:2), then follow-up contact with patient will be done by telephone, and email, if available.

If a patient discontinues the study for any reason, a follow-up assessment should be performed at the time of study discontinuation, if possible.

If the treatment for a patient changes during the study the following guidance should be followed:

- An objective 1 patient whose anticoagulation treatment is switched to DE or VKA can be enrolled into objective 2 as long as inclusion criteria 2 and 4 are met
- An objective 2 patient whose anticoagulant treatment is switched will be followed-up per protocol, including ePROs
- An objective 2 patient who stops taking anticoagulation treatment will be followed-up per protocol but will discontinue ePROs.

9.3 VARIABLES

9.3.1 Data points

Table 9.3.1:1 Flowchart for Objective 1

Data collection time point	**Baseline**	**At hospital discharge (or 14 days)[1]**
Informed consent	X	
Review of in- / exclusion criteria	X	
Demographics	X	
Medical history	X	
VTE disease characteristics	X	X
Treatment for VTE	X	X
Height	X	
Weight	X	
Blood pressure and heart rate	X	
Collect Laboratory data (if available)	X	
Adverse drug reactions (ADR)[2]	X	X
Adverse events with fatal outcomes[2]	X	X
Concomitant therapy	X	
Completion of patient participation		X

1. Data will be collected at the date of hospital discharge or at 14 days post diagnosis, whichever is later.
2. For collection and reporting of ADRs and AEs with fatal outcome please refer to Section 11.2.

Table 9.3.1:2 Flowchart for Objective 2

Data collection time point	Baseline	At hospital discharge (or 14 days)[1]	3 months	6 months	1 year
Informed consent	X				
Review of in- / exclusion criteria	X				
Demographics	X				
Medical history	X				
VTE disease characteristics	X	X			
Treatment for VTE	X	X	X	X	X
Concomitant diseases		X	X	X	X
Height	X				
Weight	X		X	X	X
Blood pressure and heart rate	X				
Collect Laboratory data (if available)	X	X	X	X	X
Adverse drug reactions (ADR)[2]	X	X	X	X	X
Adverse events with fatal outcomes[2]	X	X	X	X	X
Outcome events	X	X	X	X	X
Morisky Medication Adherence Scale			X	X	X
Health resource utilization			X	X	X
PACT-Q2			X	X	X
Concomitant therapy	X	X	X	X	X
Completion of patient participation					X
Vital status collection[3]			X	X	X

1. Data will be collected at the date of hospital discharge or at 14 days post diagnosis, whichever is later
2. For collection and reporting of ADRs and AEs with fatal outcome please refer to Section 11.2.
3. Vital status will be collected if the patient declines further clinic visits. See also 9.3.3.

9.3.1.1 Baseline visit data points

The Flowchart (Table 9.3.1:1 and Table 9.3.1:2) outlines all of the data points to be collected. No study procedures or data recorded in the EDC system should be performed unless the patient has consented to participate in the study or a waiver has been obtained in accordance with local regulations. As in any observational study, patients will be managed according to local clinical practice. The choice of treatment is solely at the discretion of the participating physicians. This means there are no additional medical or procedural risks to patients by

participating in this study. No additional medical procedures are required, over and above those that the patient would receive if not enrolled.

- Review of in- and exclusion criteria
- Demographic data will include year of birth, gender, race (as allowed by local regulations), insurance status
- Height, weight, blood pressure, and heart rate
- Available laboratory data (e.g., serum creatinine, hemoglobin, and INR)
- Information regarding the index VTE event including:
    - date of diagnosis,
    - risk factors for VTE (i.e., if the VTE was provoked or unprovoked),
    - clinical signs and symptoms and
    - the following variables based on objective testing (e.g. Venous compression ultrasonography, venography for DVT CT, MRI and any other examination that is deemed relevant per routine clinical practice for DVT diagnosis or ventilation-perfusion (V-Q) lung scan, pulmonary angiography or spiral (helical) computed tomography scan for PE):
        - Date of diagnostic testing
        - Location, extent and severity of venous thrombus
        - Impression or findings
- Treatment for VTE should include all treatment details including specific therapies provided for the event, start date(s) and stop dates (if applicable), dosage, planned treatment duration, and rationale for treatment choice.
- Medical history including current concomitant diseases, history of previous VTE (if any) risk factors (i.e., if the VTE was provoked or unprovoked) for VTE re-occurrence and risk factors for bleeding.
- Concomitant therapies that are being currently used by the patient including the name of the therapy and indication.

9.3.1.2 Hospital discharge or at 14 days after diagnosis of VTE event (whichever occurs later)

For Objective 1, the additional data points will include:

- Any changes to the treatment for the VTE event
- Date of hospital discharge, if patient was admitted to hospital

For Objective 2, the additional data points will include:

- Any changes in VTE disease characteristics and/or treatment for the VTE event
- Concomitant diseases (current, any changes)
- Available laboratory data that is associated with outcome events (e.g., complete blood count (CBC) for major and clinically relevant non major bleeding events)
- INR for VKA patients
- Date of hospital discharge, if patient was admitted to hospital.
- Changes in concomitant therapies
- Information on any outcome events that may have occurred since study enrollment
- Adverse drug reactions

9.3.1.3 Follow-up visit data points

The flowchart (Table 9.3.1:2) outlines all of the data points to be collected for patients who are followed.

- Type of data collection (i.e., based on routine clinic visit or telephone contact)
- Concomitant diseases (current, any changes)
- Available laboratory data that is associated with outcome events (e.g., CBC for major and clinically relevant non major bleeding events)
- INR for VKA patients
- Anticoagulation treatment (current, any changes (start or stop dates) including adherence, reasons for dose change). Adherence will be assessed using the Morisky Medication Adherence Scale (refer to the Annex 3.1).
- Changes in concomitant therapies
- Information on any outcome events that may have occurred since the previous visit. If the specific reversal agent for dabigatran is given, information surrounding the clinical circumstances, treatment, and clinical outcome will be collected on the CRF.
- Adverse drug reactions
- PACT-Q2 to be completed by the patient (collection of the PACT-Q2 should occur as close to the data collection time-point as possible). Refer to the Annex 3.2.
- Details of health care resources utilization including:
    - Date, reason and duration of hospitalization occurring
    - Date and reason for visit to ER
    - Need to visit treating physician due to recurrent VTE event, bleeding event or for dose adjustment of anticoagulant therapy
    - For patients treated with VKA only:
        - The number of INR measurements and where the INR blood samples were drawn (e.g., physician's office, anticoagulation clinic, hospital, outpatient laboratory, self-monitoring)
        - At the 3 month data collection time-point *only*, the following details should be collected:
            - The distance traveled to have the INR measured
            - The time spent traveling to have the INR measured
            - If public transportation was used
        - If private transportation was used

9.3.2 Outcome measures

For Objective 1:

The following primary outcome measures will be analyzed on data that is collected at the time of the acute VTE event:

- Demographic information (age and gender)
- VTE event information (event type and treatment for event)

The following further outcome measures will be analyzed on the collected baseline data:

- co-medication
- co-morbidities,

- basic physical examination data
- laboratory information
- VTE event information including location, extent and severity of the thrombus
- VTE risk factors
- history of VTE event
- bleeding risk

For Objective 2:

The following primary outcomes will be analyzed from time of diagnosis of the index event to 12 months post diagnosis:

- Primary safety outcome measure: ISTH Major bleeding and ISTH clinically relevant non major bleeding (CRNMB)
- Primary effectiveness outcome measure: symptomatic recurrent VTE including VTE-related mortality

The following secondary outcomes will be analyzed from the time of diagnosis of the index event to 12 months post diagnosis:

- Recurrent DVT and/or PE
- VTE-related mortality
- All-cause mortality

The following further outcomes will be analyzed from time of diagnosis of the index event to 12 months post diagnosis:

- Life-threatening bleeding events
- Acute coronary syndrome (ACS)
- Serious adverse drug reactions
- Net clinical benefit (NCB)
- Satisfaction with anticoagulation treatment (PACT-Q2)
- Health care resource utilization

9.3.3 Assessment of outcome measures

Major bleeding, defined as meeting one or more of the following ISTH criteria [R05-0344, P11-05406]:

- Overt bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal, or intramuscular with compartmental syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding

Life-threatening bleeding, as defined as meeting one or more of the following criteria:

- Symptomatic intracranial bleed
- Reduction in hemoglobin of at least 50 grams per liter

- Transfusion of at least 4 units of packed cells, associated with hypotension requiring the use of intravenous inotropic agents
- Necessitated surgical intervention
- Fatal bleeding

Clinically relevant, non-major bleeding, defined as meeting one or more of the following ISTH criteria [P15-12889]

- Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
    - requiring medical intervention by a healthcare professional
    - leading to hospitalization or increased level of care
    - prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Recurrent DVT and/or PE: All recurrent VTE require objective verification by definitive diagnostic evaluation:

- any suspected DVT must be confirmed by venous compression ultrasonography conventional venography, CT or MRI to be entered as recurrent DVT in the CRF
- any suspected PE must be confirmed by one of the following: V-Q lung scan, pulmonary angiography, or spiral (helical) CT to be entered as recurrent DVT in the CRF

Deaths: Deaths will be classified as being:

- bleeding related (including bleeding events that contributed to deaths),
- VTE related (including VTE events that contributed to death based on investigator clinical judgment) and
- other.

ACS: will include ST elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina (UA) [P13-10618].

- STEMI: must have cardiac marker evidence of myocardial necrosis (e.g. positive cardiac troponin (Tn) or creatinine kinase isoenzymes CKM and CKB (CK-MB)) and new (or presumably new, if no prior electrocardiogram (ECG) is available) ST segment elevation or left bundle branch block on admission ECG.
- NSTEMI: will have cardiac marker evidence of myocardial necrosis (positive Tn or CK-MB) without new ST segment elevation.
- UA: is angina pectoris with any 1 of the 3 following features:
    - Angina occurring at rest and prolonged (usually ≥ 10 min)
    - New-onset angina of at least Canadian Cardiovascular Society (CCS) classification III severity
    - Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least CCS class III. The patient must also not have any biochemical evidence of necrosis.

Serious adverse drug reactions: refer to Section 11.1 and 11.2 for serious criteria and reporting requirements.

NCB: the event rate of recurrent symptomatic VTE or VTE-related mortality plus the major bleeding event rate will be compared for dabigatran etexilate versus VKA. [P14-17361]

Treatment adherence: adherence will be assessed using the Morisky Medication Adherence Scale.

Treatment persistence: will be assessed as time from treatment onset until permanent treatment discontinuation.

Exposure: will be assessed based on the anticoagulation treatment start date, dosage and the reported end date.

Perception of anticoagulation treatment satisfaction will be assessed using the PACT-Q2 (administered at follow-up time-points for those patients followed under Objective 2).

Health care resource utilization will be assessed as number of hospital admissions, emergency room visits, and physician's office visits calculated per-patient-per-month to account for variable follow-up time.

Vital status: if a patient is enrolled for follow-up (Objective 2) and then declines to return for clinic visits, the patient's vital status should be collected and reported after one year. If any outcome events (e.g., bleeding events, recurrent VTEs or other adverse drug reactions (ADRs)) occur, details should be recorded in the electronic Case Report Form (eCRF) and reported as appropriate. If the patient died, available data (e.g. date of death, cause of death) should be reported.

9.4 DATA SOURCES

RE-COVERY is a study based on new data collection. Data will be collected based on assessment of the patient (e.g., physical examination and patient interview), review of hospital / medical records and available laboratory and diagnostic test reports. Patient reported outcomes will be assessed using validated questionnaires. Refer to Section 9.10.2.1 for details regarding source documents.

9.5 STUDY SIZE

For Objective 1:

It is planned that a total of approximately 6000 patients will be enrolled. This is not based on formal sample size calculations as there are no hypotheses to be tested. If eligible, patients included in the cross-sectional assessment (Objective 1) who are treated with dabigatran etexilate and a similar number of those treated with VKA will be followed (Objective 2).

Baseline demographics and characteristics of the patient population will be described by estimates and confidence intervals (CI) overall and by relevant categories as specified in Section 9.7 and the statistical and epidemiological analysis plan SEAP. Categorical attributes will be estimated with the precision (i.e., width of descriptive 95% CI) described in Table 9.5:1, according to sample size and prevalence of the attribute.

Table 9.5:1 Width of 95% CI by sample size and prevalence of attribute

Prevalence of attribute		Sample size (overall or per subgroup)					
		500	1000	2000	3000	4000	6000
5%	Expected n	25	50	100	150	200	300
	95% CI width	4.03	2.81	1.96	1.59	1.38	1.12
10%	Expected n	50	100	200	300	400	600
	95% CI width	5.46	3.82	2.68	2.18	1.88	1.54
20%	Expected n	100	200	400	600	800	1200
	95% CI width	7.20	5.05	3.55	2.90	2.50	2.04
30%	Expected n	150	300	600	900	1200	1800
	95% CI width	8.21	5.77	4.06	3.28	2.86	2.34
40%	Expected n	200	400	800	1200	1600	2400
	95% CI width	8.77	6.17	4.34	3.54	3.06	2.49
50%	Expected n	250	500	1000	1500	2000	3000
	95% CI width	8.94	6.29	4.43	3.61	3.12	2.54

* Calculations are based on the Clopper-Pearson method.

For example, if an attribute has a prevalence of 40% in the population of acute VTE patients, with a sample size of 2000 patients, this proportion can be estimated with a precision of 4.34% (i.e. width of 95% CI). Furthermore, in a subgroup that consists of 1000 patients, this same proportion can be estimated with a precision of 6.17%.

For Objective 2:

Baseline data will be summarized descriptively for eligible patients using a similar approach as described above for Objective 1. Categorical attributes will be estimated with the precision described in Table 9.5:1. For example, a sample size of 2000 patients allows a population attribute with a 30% prevalence to be estimated with a precision of 4.06%.

The primary and further outcomes will be analyzed for dabigatran etexilate patients in comparison to VKA patients over 1 year. To support the sample size determination, assessments were performed for the primary safety outcome of major and clinically relevant non-major bleeding based on the observed event rate for VKA in the pooled analysis of the RE-COVER and RE-COVER II trials, and additional assumptions including a 1:1 ratio of dabigatran etexilate and VKA patients, one-year fixed follow-up, one-sided alpha of 0.025, and 15% loss to follow-up (Table 9.5:2). With these assumptions, a total sample size of 5000

patients would provide 90% power to detect a hazard ratio of 0.69 between dabigatran etexilate and VKA.

Table 9.5:2 Sample size assessments for the primary safety outcome of major and clinically relevant non-major bleeding

Event rates		Hazard ratio	Power	Loss to follow-up	Total N
Dabigatran etexilate	VKA*				
5.3%	7.7%	0.69	90%	15%	5000
5.2%	7.7%	0.67			4500
5.1%	7.7%	0.65			4000
4.9%	7.7%	0.63			3500
4.7%	7.7%	0.60			3000

* The VKA event rate is based on the pooled RE-COVER and RE-COVER II analysis of the oral treatment period [P13-09153, U12-3306-01]. The Freedman formula was used for the calculations.

In combination with additional non-statistical considerations, a total sample size of up to 5000 patients (i.e., 2,500 patients per group) is deemed appropriate for the planned analyses for Objective 2 on an exploratory basis. The actual power of the analysis will be dependent upon the actual rates of major bleeding and loss to follow-up in the current study, the covariates included in the statistical model, their degree of imbalance between the treatment groups, their strength of association with the outcome, and the use of propensity score matching, and may therefore be different.

9.6 DATA MANAGEMENT

A study specific Data Operations Plan will be created to describe the software, functions, processes and specifications used for data collection, cleaning and validation. The eCRF will include programmable edit checks to obtain feedback if data is missing, out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data, or complex cross-form verifications such as lab result deviations across visits. Concurrent manual data review may be performed based on parameters outlined in the Data Operations Plan. Ad hoc queries to sites may be generated and followed up for resolution.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the ICH guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

9.7.1 Study design

For Objective 1, the population of acute VTE patients will be described using cross-sectional data collected at baseline. No follow-up data will be collected or analyzed.

For Objective 2, both cross-sectional data at baseline and longitudinal follow-up data up to 1 year will be collected for acute VTE patients treated with either dabigatran etexilate or VKA. Baseline data will be described using a cross-sectional approach. Data from the longitudinal follow-up will be summarized descriptively, and dabigatran etexilate patients will be analyzed in comparison to VKA patients using multivariable regression, as well as analytical methods based on propensity scores.

Due to the nature of this observational study, there is no (confirmatory) hypothesis testing foreseen in a strict statistical sense. Analyses are descriptive in nature and CIs and p-values from statistical models are used for explorative purposes.

9.7.2 Planned analyses

Analyses will be performed by BI or BI's designees.

The main analysis population will consist of all eligible patients (i.e., all patients who provide informed consent and fulfill all inclusion criteria and no exclusion criteria).

Summary statistics for continuous variables will include the N, mean, standard deviation, minimum, Q1 (lower quartile), median, Q2 (upper quartile), and maximum value; tabulations of categorical variables will include all possible categories and will display the number of observations per category as well as percentages based on the relevant denominators. Estimates from statistical models will be presented with 95% CIs.

Additional details of the planned analysis will be provided in the statistical and epidemiological analysis plan (SEAP).

9.7.2.1 Main analyses

For Objective 1:

Baseline patient demographics and disease characteristics, including information regarding the index VTE event, medical history, concomitant therapies, and laboratory data as specified in Section 9.3.1, will be summarized descriptively for all eligible patients overall and by anticoagulation treatment at baseline. The analysis will be repeated by region and by additional relevant patient attributes.

Patterns of anticoagulation treatment at baseline will be described overall, by region, and by additional relevant patient attributes.

For Objective 2:

Patient demographics and disease characteristics at baseline as described above for Objective 1 will be summarized descriptively for all eligible patients by their initial anticoagulation treatment (i.e. dabigatran etexilate or VKA). This analysis will be repeated by region and by additional relevant patient attributes.

Given the observational nature of this study, patients in the dabigatran etexilate and VKA groups may differ with regard to important baseline demographics and disease characteristics. When the target sample size is reached, propensity scores that estimate the probabilities that patients would be initiated on dabigatran etexilate will be calculated using a logistic regression model that considers variables that are risk factors for the occurrence of VTE or bleeding events or affect the choice of anticoagulation treatment (details of the model will be provided in the SEAP). Overlap of propensity scores between the dabigatran etexilate and VKA groups will be examined to assess the comparability of the two patient populations, and to estimate the loss of patients from the comparative analysis if trimming or matching is to be performed.

The primary safety and effectiveness outcomes will be analyzed for dabigatran etexilate patients in comparison to VKA patients using Cox proportional hazards models. Confounding will be controlled for using appropriate methods, including adjustment of covariates in the Cox regression model, trimming of extreme observations, and/or propensity score matching, based on the evaluation of the comparability of dabigatran etexilate and VKA patients (i.e. overlap of propensity scores) as described above. Details of the analytical methods and the selection rules of the appropriate analysis strategy will be provided in the SEAP.

The primary comparative analyses will be based on the actual anticoagulation treatment the patients receive (i.e. “as treated” analysis). Patients who complete the planned anticoagulation treatment prior to one year or discontinue initial anticoagulation treatment permanently will be censored at date of last drug intake + 6 days for both dabigatran etexilate and VKA or at first intake of another relevant anticoagulation treatment, whichever occurs first. A patient is considered to have permanently stopped initial anticoagulation treatment if other relevant anticoagulation treatment is initiated or otherwise dependent on the duration of treatment interruption. Details of the censoring rules will be described in the SEAP.

9.7.2.3 Safety analyses

Statistical analysis and reporting of safety data will be descriptive in nature, will be based on BI standards, and will focus on ADRs to dabigatran etexilate or VKA. No hypothesis testing is planned.

Occurrences of ADRs will be analyzed relative to the number of patients treated as well as observed person-years (i.e., time at risk). Safety analysis will be based on the concept of treatment emergent ADRs. Patients will be analyzed according to the anticoagulation treatment received at the time of the event. If no concurrent anticoagulation treatment is administered, then events occurring within a washout period of 6 days after discontinuation of anticoagulation treatment will be assigned to the last treatment given. This washout period will also be included as time at risk for derivation of total person-years. ADRs that deteriorate under treatment will also be considered as "treatment emergent". Events occurring prior to first intake of anticoagulation treatment prescribed at baseline, during periods without any anticoagulation treatment (excluding washout periods), or after the end of the 1 year follow-up (excluding washout periods) will not be considered treatment emergent events and will not be included in the summary tables.

The following parameters will be included in the safety analyses:

- Adverse drug reactions
- Adverse drug reactions leading to discontinuation of anticoagulation treatment
- Serious adverse drug reactions
- Adverse drug reactions leading to deaths

9.7.2.4 Schedule of planned analyses

For Objective 1:

It is planned that one interim analysis will be performed when approximately 3,000 patients have been enrolled. The final analysis as specified in Section 9.7.2 will be performed once the data collection is completed, the data sets are cleaned, and the database is locked for Objective 1.

For Objective 2:

It is planned that an interim analysis that assesses the comparability of patients in the dabigatran etexilate and VKA groups based on propensity scores will be performed when the target sample size is reached (see details in Section 9.7.2.1). The final analysis as specified in Section 9.7.2 will be performed once the data collection is completed for Objective 2.

Additional reports (e.g. for region/country-specific analyses) may be prepared if deemed appropriate and will be specified in the SEAP.

9.7.3 Handling of missing data

Every reasonable attempt will be undertaken to ensure completeness of data collection. Imputation will be permitted, if deemed appropriate and on a case-by-case basis, depending on the extent and distribution of missing values, and will be described in the SEAP.

For Objective 1, the presence of missing data is expected to be low, since the variables are expected to be collected in routine clinical practice and should therefore be available in the patient's medical record.

For Objective 2, the percentage of and reason for loss to follow-up will be summarized by treatment and by other relevant factors (e.g., region). In addition, if the proportion of loss to follow-up is large enough to warrant further investigation, baseline characteristics will be described for patients who were lost to follow-up in comparison to patients who have completed follow-up.

9.8 QUALITY CONTROL

The Clinical Research Associate (CRA) or on-site monitor may review the eCRFs and written informed consents. Approximately 15% of sites will have a routine on-site visit by the CRA. All sites will receive remote monitoring phone calls throughout the study. The accuracy of the data will be verified by reviewing the source documents with the entered data. Details of the monitoring activities will be outlined in the Site Management Plan.

9.9 LIMITATIONS OF THE RESEARCH METHODS

For Objective 1, a cross sectional design will be used to characterize the VTE patient population. Consecutive unselected enrollment will be employed to ensure that specific types of patients are not selected by site staff to participate. It is expected that accrual for this objective will occur rapidly as there are no requirements to ensure balance between the types of anticoagulation treatments prescribed. To ensure global representation, regional recruitment caps will be employed to minimize over- or under-representation from a particular region. There is also the potential that prescribing patterns may change for a variety of reasons such as antidotes for NOACs are approved for use.

For Objective 2, two cohorts of patients (dabigatran etexilate vs VKA) will be followed for 12 months. VKA has been the mainstay of treatment of VTE for many years. It is widely available, affordable, but does require regular INR monitoring. Dabigatran etexilate is more expensive, may or may not be reimbursed, but does not require the continual INR monitoring. There are a number of different types of bias that could influence the analysis from these cohorts such as selection bias and recall bias.

The study is designed to collect new data. The entry criteria are non-restrictive which will permit the enrollment of a broad patient population. The choice of treatment is at the discretion of the investigator. Therefore the data collected in this study should reflect the treatment patterns and patient characteristics under conditions of routine clinical practice.

The primary safety outcome measure is major bleeding and clinically relevant non-major bleeding events (CRNMB) according to the ISTH definition. Clinically relevant non-major bleeding events and major bleeding events were combined in the phase III clinical trial safety analysis, and, although it is probable that clinically relevant non-major bleeding events may

be harder to detect, new recommendations for the ISTH are now available for reporting them in a consistent manner in a routine clinical practice setting. The enlargement of the main variable, in a validated and consistent manner, will maximize the efficiency of the clinical trial in order to not prolong excessively the study duration. As a result, the primary safety outcome measure will include major bleeding and CRNMB events and the sample size calculations have been adjusted accordingly.

Selection bias:

Selection bias could occur at both the site level and the patient level. If sites where dabigatran etexilate is used frequently differ systematically with respect to patient or the routine procedures from sites that use dabigatran etexilate less frequently, the between site difference could lead to non-comparability between the dabigatran etexilate patients. To minimize the site level selection bias, a robust site feasibility process will be performed to ensure that the participating centers that have access to all available treatment options for VTE that are approved for use in that country and that those physicians follow the standard of care that is accepted within the country.

Selection bias at the patient level could occur if sites preferentially enroll specific patients into the study. To minimize selection bias at the patient level, at a minimum, dabigatran etexilate and VKA treatment options must be available. Consecutive unselected enrollment of patients will be used for the recruitment of patients into Objective 1 which will address issues associated with preferential patient selection by the site staff however; this could potentially create other sources of bias. A balanced approach for enrollment will be used for Objective 2. The balanced approach will also minimize effects of potential temporal changes in prescribing patients, as dabigatran etexilate and VKA patients are enrolled in similar time periods.

Survivor bias:

Survivor bias can occur if patients who have had an early outcome event (e.g. major bleeding) are not enrolled into the study due to the early outcome event. To minimize survivor bias, sites will receive training to ensure that they understand the importance of not selectively excluding patients who may have had an early outcome event. Sites will also be encouraged to enroll patients as soon as possible after the patient's VTE has been diagnosed so that early outcome events will be captured as part of follow-up.

Channelling bias:

Channelling bias is a type of selection bias that can occur due to preferential prescribing in relation to different risks for events of interest. For example, if dabigatran etexilate is prescribed more frequently to high risk patients than to other treatments, a high rate of outcome events could be expected in the dabigatran etexilate group. In order to control for potential channelling bias, an interim assessment will be conducted to monitor the comparability of important patient baseline characteristics. The use of estimated propensity score methods can further address bias.

Loss to follow-up:

All efforts will be made to minimize loss to follow-up in patients who are enrolled into the follow-up cohort (Objective 2). Patients who are lost to follow-up will be characterized and compared to the remaining patients and the reason and time point of lost to follow-up will be evaluated.

Recall bias:

Recall bias refers to the phenomenon when the outcomes of treatment (either good or bad) may influence the patient's recollection of events prior to, or during, the treatment. To minimize recall bias, patient reported outcomes and adherence will be assessed using validated scales that are administered at regular time intervals so that the time intervals from event to collection of the PRO will be limited.

Confounding:

Confounding occurs when an observed association is due to three factors: the exposure, the outcome of interest and a third factor which is independently associated with both the outcome of interest and the exposure. Statistical techniques, such as adjustment for covariates, stratified analysis, matching, etc. can be used to correct for identified confounders. However, as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain. The employed methods are described in the data analysis section.

In addition, sites will be encouraged to enroll patients as soon as possible after the acute index event.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees, or by Institutional Review Board (IRBs)/Independent Ethics Committee (IECs), or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

All of the clinical data and site/investigator characteristics will be captured via a web-based EDC system. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The Investigator will approve the data using an electronic signature that is 21 CFR Part 11 compliant.

Patients must not be identified on the eCRF by name. Appropriately coded identification (i.e. Patient numbers) must be used. The Investigator must make a separate confidential record of these details (Patient enrollment log) to permit the identification of all patients enrolled in the study in case follow-up is required. Any supporting documentation must be redacted of any patient identifying information and the patient ID number must be clearly written on the documents.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data entered into the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to

request previous medical records or transfer records, depending on the study; also, current medical records must be available. For eCRFs, all data must be derived from source documents. The approved clinical data entered into the EDC system will be made available to the investigator at the end of the study. The investigator will be responsible for retaining all records pertaining to the study as specified in the contract and per local regulations.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all informed consent forms and related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. Food and Drug Administration). The CRA/ on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.3 Completion of study

The EC/competent authority (CA) in each participating EU member state needs to be notified about the end of the study (last patient/patient out) or early termination of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the applicable sections of GCP, guidelines for Good Epidemiological Practice (GEP) [R10-4560], Good Pharmacoepidemiology Practice (GPP) [R09-0182], relevant BI Standard Operating Procedures and local regulations. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/International Conference on Harmonization (ICH) GCP / GPP if applicable.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study 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.

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

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

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

Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities i.e. the Competent Authority (CA).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. 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 drug reaction

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

Serious adverse event

A serious adverse event (SAE) is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

The following are considered as AESIs:

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection and reporting of AEs

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

For Objective 1

Data collected on the eCRF once informed consent or waiver is obtained

- Serious and non-serious ADRs to DE from the time of VTE until the end of the study for a patient
- ALL serious and non-serious ADRs other than DE from time of informed consent/ waiver until the end of the study for a patient
- All AEs with fatal outcome

Data reported on the NIS AE form once informed consent or waiver is obtained

- Serious and non-serious ADRs to DE from the time of VTE until the end of the study for a patient
- All AEs with fatal outcome in patients exposed to DE

For Objective 2

Data collected on the eCRF once informed consent is obtained

- Serious and non-serious ADRs to DE and VKA from the time of VTE until the end of the study for a patient.

Data reported on the NIS AE form once informed consent is obtained

- Serious and non-serious ADRs to DE form time of VTE until the end of the study for a patient
- All AEs with fatal outcome in patients exposed to DE

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse drug reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse drug reaction, in contrast to an adverse event, is characterized 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 **a reasonable 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 etiologies** that could explain the event (e.g. preexisting 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 study drug treatment continues or remains unchanged.

<u>Intensity of adverse event</u>

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

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

Pregnancy

In rare cases, pregnancy might occur in a study. Once a female subject has been enrolled into the study, after having taken dabigatran etexilate, the investigator must report any drug exposure during pregnancy to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Timelines for Expedited Reporting of AEs on the NIS AE form and Drug Exposure During Pregnancy

Type of Report	Timeline
All **Serious ADRs** associated with dabigatran etexilate (DE)	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to dabigatran etexilate (DE)	immediately within 24 hours
All **non-serious ADRs** associated with dabigatran etexilate (DE)	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor or the Sponsor's designee (i.e., the CRO) upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form if applicable.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than dabigatran etexilate according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the marketing authorization holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Any publication must be consistent with the BI publication policy and guided by the current version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journals.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents have not been finalized at the time of protocol finalization. The final version of these documents will be archived in the study master file.

Number	Document Reference Number	Date	Title
1			Site Management Plan
2			Data Operations Plan
3			Statistical and Epidemiological Analysis Plan
4			List of Investigators

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Cha**R**act**E**rization of patients following a**C**ute venous thr**O**mboembolism (**V**T**E**) and assessment of safety and effectiveness of dabigatran etexilate(DE) in the t**R**eatment and secondar**Y** prevention of acute deep vein thrombosis (**DVT**) and pulmonary embolism (**PE**) in comparison to vitamin K antagonist (VKA) in routine clinical practice - **RE-COVERY DVT/PE**
Study reference number: 1160.188

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	15
1.1.6 Final report of study results	☒	☒	☐	15

Comments:

Status reports will be generated on a regular basis and are dependent on recruitment, strategic decisions and regulatory requests, if applicable.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	18-19
2.1.2 The objectives of the study?	☒	☐	☐	20
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	21
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

No formal hypothesis are being tested. The research questions, study objectives and analysis are defined in the protocol.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	21

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	28-29
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	32-34

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	15 & 21
4.2.2 Age and sex?	☒	☐	☐	23
4.2.3 Country of origin?	☒	☐	☐	2
4.2.4 Disease/indication?	☒	☐	☐	23
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	23

Comments:

Patient recruitment is not restricted. Therefore co-morbitities are not part of the entry criteria. The planned recruitment period is over 2 years with no reference to seasonality.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	32
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	35
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	35
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	23

Comments:

No pharmacokinetic information will be collected in this study.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	30-32
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	32-34

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	38-40
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	38-40

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	32
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	29-30
8.1.3 Covariates?	☒	☐	☐	27-29
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	30
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	27-29
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	27-29
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	40

Comments:

Coding system will be described in detail in the data management plan.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	31-33

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	34-36
10.2 Is the choice of statistical techniques described?	☒	☐	☐	34-36
10.3 Are descriptive analyses included?	☒	☐	☐	34-36
10.4 Are stratified analyses included?	☒	☐	☐	34-36
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	34-36
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	34-36

Comments:

Additional information will be included in the SEAP.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	37
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	33
11.3 Are methods of quality assurance described?	☒	☐	☐	37
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	37-39
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

There are no plans for an independent adjudication or data monitoring committee at time of protocol finalization.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	37-39
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	37-39

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19-20
12.3 Does the protocol address other limitations?	☒	☐	☐	37-39

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	39
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	39

Comments:

The protocol has not yet been submitted to an ethics review board.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	46
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

Publication plan to be developed as a separate document.

Name of the main author of the protocol: _____

Date: dd/mm/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

ANNEX 3.1 MORISKY MEDICATION ADHERENCE SCALE

©Morisky Medication Adherence Scale (MMAS-8-Item).

You indicated that you are taking medication(s) for your Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE). Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your anticoagulation medication.

(Please check your answer below)

	No=1	Yes=0
1. Do you sometimes forget to take your anticoagulation medication(s)?		
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your anticoagulation medication(s)?		
3. Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring along your anticoagulation medication(s)?		
5. Did you take your anticoagulation medication(s) yesterday?		
6. When you feel like your anticoagulation is under control, do you sometimes stop taking your medication(s)?		
7. Taking medication(s) everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your [health concern] treatment plan?		

8. How often do you have difficulty remembering to take all your medication(s)?

(Please check your answer below)

Never/Rarely	4
Once in a while	3
Sometimes	2
Usually	1
All the time	0

Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive Validity of a Medication Adherence Measure for Hypertension Control. *Journal of Clinical Hypertension* 2008; 10(5):348-354

Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New Medication Adherence Scale Versus Pharmacy Fill Rates in Seniors With Hypertension. *Am J Manag Care* 2009;15(1):59-66.

Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemio 2011; 64:258-263. PMID:21144706

MMAS8 - United States/English - Mapi.
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ANNEX 3.2 PERCEPTION OF ANTICOAGULANT TREATMENT QUESTIONNAIRE 2

PACT-Q2
(Perception AntiCoagulant Treatment Questionnaire)

- The purpose of this questionnaire is to understand your expectations and to assess your satisfaction with your anticoagulant treatment (treatment that stops the blood from clotting).
- Throughout the questionnaire, the term "taking" refers to how you take your anticoagulant treatment (either by pill or injection).
- Please read each question carefully, answering as openly as you can and without help from anyone. There are no wrong answers.
- All of the information you provide will be kept confidential.
- This questionnaire will take about **10 minutes** to complete.

Convenience

Please answer the following questions to help us understand how convenient it is to take your treatment.

Please check one box per line.

B1 - How difficult is it to take your anticoagulant treatment (i.e., pills or injections, number of pills or injections, frequency of intake ...)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B2 - How bothered are you by taking your anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B3 - Some anticoagulant treatments may need dose adjustments; how difficult is this for you?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B4 - Certain medications CANNOT be taken with anticoagulant treatments; how difficult is this for you?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B5 - It is recommended that certain foods be avoided while taking an anticoagulant treatment; how difficult is this for you?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B6 - How difficult is it for you to take your anticoagulant treatment when you are away from home?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B7 - How difficult is it for you to plan your time around your anticoagulant treatment (i.e., appointments with nurses, doctors or labs ...)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B8 - How bothered are you by the medical follow-up required with your anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B9 - How difficult is it for you to take your anticoagulant treatment as directed on a regular basis?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B10 - Do you feel more dependent on others (i.e partner, family, nurse…) because of your anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

B11 - How worried are you about having to interrupt or stop your anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

Burden of Disease and Treatment

Please answer the following questions to help us understand how your disease and its treatment affect you.

Please check one box per line.

C1 - Because of potential side effects (i.e., minor bruises, bleeding…), do you limit your usual activities (i.e., work, leisure, social, or physical activities…)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Extremely

C2 - How much physical discomfort do you have due to bruises or pain?

☐1	☐2	☐3	☐4	☐5
None	A little	Moderate	A lot	Extreme

Anticoagulant Treatment Satisfaction

Please answer the following questions to help us understand how satisfied you are with your treatment.

Please check one box per line.

D1 - How reassured do you feel by your anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Somewhat	Very	Completely

D2 - Do you feel that your anticoagulant treatment has decreased your symptoms (i.e., leg pain or swelling, palpitations, shortness of breath, or chest pain…)?

☐1	☐2	☐3	☐4	☐5
Not at all	A little	Moderately	A lot	Completely

D3 - How did your experience with side effects such as minor bruises or bleeding (i.e., while shaving, cooking, after small cuts…) compare to what you expected?

☐1	☐2	☐3	☐4	☐5
It is much worse than what I expected	It is worse than what I expected	It is exactly what I expected	It is better than what I expected	It is much better than what I expected

D4 - Regarding the follow-up of your disease and anticoagulant treatment, how satisfied are you with your level of independence?

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

D5 - How satisfied are you with the methods (i.e., appointments with nurses, doctors, labs…) used to ensure the follow-up of your disease and anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

D6 - How satisfied are you with the form of your anticoagulant treatment (oral pill / injection)?

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

D7 - **Overall**, how satisfied are you with your anticoagulant treatment?

☐1	☐2	☐3	☐4	☐5
Extremely dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Extremely satisfied

Please make sure you answered all questions.

Thank you for your time.