## Non-interventional Study Protocol

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<th>c09063488-07</th>
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<tr>
<td>BI Study Number:</td>
<td>1160.261</td>
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<tr>
<td><strong>BI Investigational</strong></td>
<td><strong>Dabigatran etexilate (Pradaxa®)</strong></td>
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<tr>
<td>Product(s):</td>
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<tr>
<td><strong>Title:</strong></td>
<td><strong>Non-interventional study describing patients’ perception on anticoagulant treatment and treatment convenience when treated with Pradaxa® or Vitamin K Antagonist for Stroke Prophylaxis in Atrial Fibrillation</strong></td>
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<td>Date of last version of</td>
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<td>Dabigatran etexilate</td>
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<td>EU/1/08/442/001-019</td>
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<td>Procedure number:</td>
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<td>Boehringer Ingelheim International GmbH</td>
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<td>holder(s):</td>
<td>Binger Str. 173</td>
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<td>D-55216 Ingelheim am Rhein, Germany</td>
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<td><strong>Joint PASS:</strong></td>
<td><strong>No</strong></td>
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<tr>
<td><strong>Research question and</strong></td>
<td><strong>Primary objective:</strong></td>
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<tr>
<td><strong>objectives:</strong></td>
<td>Describe the atrial fibrillation patient’s treatment perception by using the PACT-Q© (Perception on Anticoagulant Treatment Questionnaire).</td>
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<td><strong>Secondary objective:</strong></td>
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<td></td>
<td>Characterization of patient population (including dosing of Pradaxa®)</td>
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<tr>
<td><strong>Country(-ies) of study:</strong></td>
<td>6 SEASK countries (Indonesia, Malaysia, Singapore, South Korea, Thailand and Vietnam)</td>
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<tr>
<td><strong>Author:</strong></td>
<td>Phone:</td>
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<td>Email:</td>
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| **Marketing authorisation holder(s):** | Boehringer Ingelheim International GmbH  
Binger Str. 173  
D-55216 Ingelheim am Rhein, Germany |
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<td><strong>Date:</strong></td>
<td>25 Jan 2016</td>
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2. LIST OF ABBREVIATIONS

AE  Adverse Event
AESI  Adverse Event of Special interest
ADR  Adverse Drug Reaction
AF  Atrial Fibrillation
ANCOVA  Analysis of Covariance
BI  Boehringer Ingelheim
CA  Competent Authority
CHA₂DS₂-VASc score  Congestive heart failure, Hypertension, Age (≥ 75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex category
CI  Confidence Interval
CML  Local Clinical Monitor
CRA  Clinical Research Associate
CRF  Case Report Form
CTP  Clinical Trial Protocol
DEDP  Drug Exposure During Pregnancy
DMP  Data Management Plan
DVT  Deep Venous Thrombosis
eCRF  Electronic Case Report Form
EC  Ethics Committee
ECG  Electrocardiogram
EDC  Electronic Data Capture
EMA  European Medicine Agency
EudraCT  European Clinical Trials Database
FDA  Food and Drug Administration
GCP  Good Clinical Practice
GEP  Good Epidemiological Practice
GPP  Good Pharmacoepidemiology Practice
GVP  Good Pharmacovigilance Practices
GPV CTC  Global Pharmacovigilance Clinical Trial Coordinator
HAS-BLED  Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and Alcohol.
ICH  International Conference of Harmonisation
ICSR  Individual Case Safety Report
IEC  Independent Ethics Committee
INR  International Normalized Ratio
IRB  Institutional Review Board
ISF  Investigator Site File
MAH  Marketing Authorisation Holder
n.a.  Not applicable / not available
NIS  Non-Interventional Study
NVAF  Non valvular atrial fibrillation
OPU  Operative Unit
OAC  Oral Anticoagulation
PACT-Q©  Perception of Anticoagulant Treatment Questionnaire
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SDV</td>
<td>Source Data Verification</td>
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<tr>
<td>SEAP</td>
<td>Statistical and Epidemiological Analysis Plan</td>
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<tr>
<td>SEASK</td>
<td>South East Asia South Korea</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SPAF</td>
<td>Stroke Prophylaxis (or Prevention) in Atrial Fibrillation</td>
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<tr>
<td>TMF</td>
<td>Trial Master File</td>
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<tr>
<td>VKA</td>
<td>Vitamin K Antagonist</td>
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<td>Global Epidemiology (GEpi)</td>
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<td>Therapeutic Area Risk Management (TA RM), and Pharmacovigilance Working Group (PVWG)</td>
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<td>Trial Clinical Monitor (TCM)</td>
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<td>Trial Statistician (TSTAT)</td>
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## 4. ABSTRACT

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<th>Name of company:</th>
<th>Boehringer Ingelheim</th>
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<tr>
<td>Name of finished medicinal product:</td>
<td>Pradaxa® (Dabigatran etexilate), or Vitamin K Antagonist (VKA)</td>
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<td>Name of active ingredient:</td>
<td>Dabigatran, or VKA</td>
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<tr>
<td>Protocol date:</td>
<td>25 January 2016</td>
</tr>
<tr>
<td>Study number:</td>
<td>1160.261</td>
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<tr>
<td>Version/Revision:</td>
<td>1.0</td>
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<tr>
<td>Version/Revision date:</td>
<td>n.a.</td>
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<td>Title of study:</td>
<td>Non-interventional study describing patients’ perception on anticoagulant treatment and treatment convenience when treated with Pradaxa® or Vitamin K Antagonist for Stroke Prophylaxis in Atrial Fibrillation.</td>
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<tr>
<td>Rationale and background:</td>
<td>Pradaxa® (Dabigatran etexilate) is a direct Thrombin inhibitor approved in Europe, USA and many other Asian countries worldwide for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. There is a lack of data on how atrial fibrillation patients in Asia perceive Pradaxa® treatment in the context of anticoagulation management. The decision in clinical practice to use Pradaxa® as the first novel anticoagulant or established vitamin K antagonists depends on many factors related to the patient and prescribing physician. The aim of this non-interventional study is to describe patients’ perception of anticoagulant treatment when using Pradaxa® to prevent stroke and systemic embolism while suffering from non-valvular atrial fibrillation (according to its approved indication at the approved dosages in respective countries) in comparison to using Vitamin K Antagonist (VKA).</td>
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<tr>
<td>Research question and objectives:</td>
<td>Objective 1: How do patients perceive anticoagulation treatment with Pradaxa® for stroke prevention in non-valvular atrial fibrillation (NVAF) in comparison with VKA?</td>
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<tr>
<td></td>
<td>• What is treatment expectation of newly diagnosed NVAF patients before they start treatment with VKA or Pradaxa®</td>
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<td>• Objective 2: What are the characteristics of patients receiving anticoagulation treatment for stroke prevention regarding demographics, physician rated scores, kidney function, treatment (choice of treatment, dosing)?</td>
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<td>Study design:</td>
<td>Non-interventional study of AF patients in Asia with a current VKA therapy and subsequent initiation of Pradaxa® OR patients being newly initiated on an anticoagulant due to their atrial fibrillation. This study will describe patients’ perception of anticoagulation treatment with Pradaxa® in comparison to Vitamin K Antagonist (VKA).</td>
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*Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies*
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<tr>
<th>Population:</th>
<th>Patients diagnosed with non-valvular atrial fibrillation (NVAF) and eligible for Pradaxa® or VKA treatment according to Pradaxa® or respective VKA label.</th>
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<tr>
<td>Variables:</td>
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<tr>
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<td><strong>Primary Outcome</strong></td>
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<td></td>
<td>For Cohort A (NVAF patients on VKA who are switched to Pradaxa®):</td>
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<td>- Mean PACT-Q2 scores at second and last assessment compared to baseline assessment.</td>
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<td>For Cohort B (newly diagnosed NVAF patients initiated to either VKA or Pradaxa®):</td>
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<td>- Mean PACT-Q2 scores at second and last assessment compared between treatment groups.</td>
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<td>For Cohort A (switched to Pradaxa®):</td>
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<td>- Mean PACT-Q2 scores at last assessment compared to second assessment.</td>
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<td>For Cohort B (newly initiated to VKA or Pradaxa®):</td>
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<td>- Description of PACT-Q1 items at baseline.</td>
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<td><strong>Primary outcome:</strong></td>
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<td>Characterization of patients from both cohorts according to</td>
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<td></td>
<td>- Age</td>
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<td></td>
<td>- Gender</td>
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<td>- CHA2DS2-VASc score (R10-5332)</td>
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<td>- HAS-BLED score (modified HAS-BLED for newly initiated patients) (R10-6394)</td>
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<td>- Kidney function (creatinine clearance)</td>
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<td>- Co-morbidities</td>
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<td>- Dosing of Pradaxa</td>
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<td></td>
<td>- Duration of previous VKA treatment (for Cohort A)</td>
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<tr>
<td>Data sources:</td>
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### Study size:
1790 patients in 6 SEASK countries

### Data analysis:
In this non-interventional study, baseline and longitudinal follow-up data over 6 months will be collected for non-valvular AF patients with a current VKA therapy and subsequent initiation of Pradaxa® in Cohort A, and for newly diagnosed AF patients initiated on Pradaxa® or VKA in Cohort B. Data from baseline and the longitudinal follow-up will be summarized descriptively. For Cohort A, mean PACT-Q2 scores between assessments will be compared using paired t-tests. For Cohort B, mean PACT-Q2 scores between Pradaxa® and VKA patients will be compared using propensity score matched analysis.

### Milestones:
- Planned start of data collection: 30 Apr 2016
- Planned end of data collection: 11 Jan 2018
- Planned final study report: 5 Jul 2018
5. AMENDMENTS AND UPDATES

None
6. **MILESTONES**

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<td>IRB/IEC approval</td>
<td>20 April 2016</td>
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<tr>
<td>Start of data collection</td>
<td>30 April 2016</td>
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<tr>
<td>End of data collection</td>
<td>11 January 2018</td>
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<tr>
<td>Final report of study results</td>
<td>05 July 2018</td>
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7. **RATIONALE AND BACKGROUND**

Pradaxa® (Dabigatran etexilate) is a direct Thrombin inhibitor approved in Europe, USA and many other Asian countries worldwide for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. Pradaxa® has been studied in the RELY study, one of the largest atrial fibrillation outcome studies (P13-05668). Over the course of one year, all anticoagulated patients without outcome events (e.g. strokes or major bleedings) had stable HRQoL. There is a lack of data on how atrial fibrillation patients in Asia perceive Pradaxa® treatment in the context of anticoagulation management.

The decision in clinical practice to use Pradaxa® as the first novel anticoagulant or established vitamin K antagonists depends on many factors related to:

a) The patient: Level of information, health status, comorbid conditions and demographic factors, perception of anticoagulant treatment, understanding of the burden of the disease, access to the medication, educational measures informing about medications and reimbursement status in a particular country.

b) The treating physician: Stroke risk assessment, bleeding risk assessment, understanding and adherence to guidelines, access and use of medical education, interaction with patients and overall local health care system.

It is assumed that these factors in real world clinical practice vary e.g. between countries with different health care systems, between patients who start anticoagulation treatment versus those who have anticoagulation experience already or between the treatment initiation versus the mid-term follow up on Pradaxa® or vitamin K antagonists.

It is the aim of this non-interventional study to describe the patient perception of anticoagulation when treated with Pradaxa® to prevent stroke and systemic embolism while suffering from non-valvular atrial fibrillation (according to its approved indication in the approved dosages of 110 mg or 150 mg twice daily). To evaluate patient understanding of treatment and patient values it is important to assess patient’s perception of the treatment in the context of overall disease management as close as possible to the clinical practice. Furthermore it is important to anchor the Pradaxa® treatment perception data in different ways, in order to determine on how previously and newly diagnosed NVAF patients perceive treatment with Pradaxa®, in comparison to vitamin K antagonist treatment (being considered the standard anticoagulation treatment for stroke prevention in non-valvular atrial fibrillation over decades):

- Compare the treatment perception data of patients, who are switched to Pradaxa® treatment, to their perception about their previous anticoagulation (VKA) therapy, and
- Compare the treatment perception data of patients who are newly initiated Pradaxa® treatment to the treatment perception data of patients who are newly initiated to VKA treatment

These real world data are needed to guide the scientific community in designing educational efforts for doctors and their patients and to assess the potential values of patient adherence programs when using Pradaxa® as the first novel anticoagulant. Also such data, describing patient’s perception on Pradaxa® anticoagulation in the context of
patient-physician interaction managing stroke prevention in atrial fibrillation cannot be obtained by market research.
8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTIONS

This non-interventional study will address the following questions:

- How do patients with non-valvular atrial fibrillation perceive anticoagulation treatment for stroke prevention (stratified in cohorts of patients switched from previous treatment to Pradaxa®, newly initiated treatment with Pradaxa®, newly initiated treatment with VKA)?

- What are the characteristics of patients receiving anticoagulation treatment for stroke prevention regarding demographics, physician rated risk scores, kidney function, concomitant diseases and concomitant medications, treatment for SPAF (choice of treatment, dosing)?

Two cohorts of patients will be recruited:

CohortA: Patients having been treated with VKA and now being switched to Pradaxa®

CohortB: Patients newly diagnosed with non-valvular atrial fibrillation and initiated on either Pradaxa® or VKA.

8.2 OBJECTIVE

Primary objective

- Describe the atrial fibrillation patient’s treatment perception by using the PACT-Q at three time-points at baseline, during initiation period and during the continuation period.

Secondary objective

- Characterization of patient population (incl. dosing) in the participating SEASK countries.
9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional multi-national, multi-centre study based on newly collected data.

The study will enrol consented patients with non-valvular atrial fibrillation (AF) in SEASK with a current VKA therapy and subsequent initiation of Pradaxa® (Cohort A) OR patients being newly diagnosed with AF and initiated on Pradaxa® or VKA (Cohort B).

Patients will be followed over an observation period of 6 months. Data will be collected at three time points:

1. At Baseline (initiation on Pradaxa® or VKA)
2. 30-45 days after initiation on Pradaxa® or VKA (initiation period)
3. 150-210 days after initiation on Pradaxa® or VKA (continuation period)

9.2 SETTING

It is planned that data of approximately 1790 patients will be collected from approximately 80 sites in 6 SEASK countries. Planned participating countries are Indonesia, Malaysia, Singapore, South Korea, Thailand and Vietnam.

9.2.1 Study sites

Cardiologists and non-cardiologist sites regularly prescribing Pradaxa® and VKA for stroke prevention in atrial fibrillation according to the respective country approved label will participate.

Selected sites within each country should include those physicians (e.g. cardiologists, non-cardiologists) and facilities (e.g. specialist offices, hospitals, outpatient care centres etc.) that reflect the clinical practice in that country. Investigators that are currently participating in the BI registry program 1160.129 (GLORIA) are not allowed to participate in this study.

These site selection criteria will help to ensure that the patients recruited into this study will represent the patients treated within that country. After initiation, every site should include the first consecutive suitable patients where decision for switch to Pradaxa® (Cohort A) or decision for initiation on Pradaxa® or VKA (Cohort B) has been made. In consecutive sampling, every eligible patient is selected until the required sample size is enrolled. This approach helps to reduce the likelihood of selection bias.

Balance between Cohorts within each country

Within each participating country, the recruitment of patients in Cohort A and Cohort B needs to be balanced (A:B = 1:2). Within Cohort B, the patient enrolment will be controlled as well, in order to ensure that an equal amount of data will be collected of AF patients newly treated with Pradaxa® (sub-Cohort B1) or with VKA (sub-Cohort B2).
(Pradaxa®:VKA = 1:1). Therefore, the sponsor may have to decide to close the enrolment of patients for one of the Cohorts (or sub-Cohorts) during the recruitment period, if the other (sub) Cohort is exceeding the maximum number of enrolled patients planned for that country/site.

The decision for therapy has to be taken prior to and independently of enrolment into the study. Only after the treatment decision for the patient is taken, the investigator can check and decide if a patient can be enrolled in Cohort A or Cohort B. Patients will then have to sign informed consent before they can take part in the non-interventional study.

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

9.2.2 Study population

9.2.2.1 Inclusion Criteria

Cohort A:
1A. Written informed consent prior to participation

2A. Female and male patient’s ≥ 18 years of age with a diagnosis of non-valvular atrial fibrillation.

3A. At least 3 months of continuous VKA treatment for stroke prevention prior to baseline assessment.

4A. Patients switched to Pradaxa® according approved country label and physician’s discretion.

OR

Cohort B:
1B. Written informed consent prior to participation.

2B. Female and male patients ≥ 18 years of age newly diagnosed with non-valvular atrial fibrillation and no previous treatment for stroke prevention (no use of any OAC within one year prior to enrolment).

3B. Stroke prevention treatment initiated with Pradaxa® or VKA according to approved country label and physician’s discretion.

Exclusion Criteria

1. Contraindication to the use of Pradaxa® or VKA as described in the approved country label
2. Patients receiving Pradaxa® or VKA for any other condition than stroke prevention in atrial fibrillation.

3. Current participation in any clinical trial of a drug or device

4. Current participation in a Registry, e.g. the Gloria registry program, on the use of oral anticoagulation in AF

9.2.2.2 Removal of patients from the study

Every patient has the right to withdraw consent at any time during the study, without the need for justification and without any impact on the routine therapy.

A patient is considered permanently discontinued or withdrawn from treatment if the patient did not complete the treatment with Pradaxa or VKA for the entire continuation period until Visit 3 and did not perform all visit 3 assessments.

Boehringer Ingelheim 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 enrolment goals overall or at a particular study site.
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons.
3. Violation of the protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study.

In the framework of NIS study, the Investigators are responsible for treatment and may remove patients at any time according to his/her medical judgement.

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

9.2.2.3 Visit schedule

Collection of patient data should be managed during routine practice visits. The time-schedule below can only be a recommendation; if a patient does not visit the site at these time points, data will not be collected (no visits will be conducted solely for study purposes).

Visits must be performed face-to-face and cannot be performed by phone, email or fax, as the patient has to complete the self-administered questionnaires.

1. At Baseline (at initiation on Pradaxa® or VKA)

2. 30-45 days after initiation on Pradaxa® or VKA (initiation period)
3. 150-210 days after initiation on Pradaxa® or VKA (continuation period)

Table 9.2.2.3: 1 Flow Chart / Schedule of Data Collection

<table>
<thead>
<tr>
<th>Visit</th>
<th>Assessment</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Baseline</td>
<td>Initiation period</td>
<td>Continuation period</td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient demographics: age, gender</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant diseases / co-morbidities</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant therapies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Healthcare system characteristics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED score (to be calculated in the eCRF)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc score (to be calculated in the eCRF)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of previous VKA treatment (for Cohort A)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasons for switch to Pradaxa® (for Cohort A)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start Pradaxa® or VKA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pradaxa® dosing (110 or 150 mg) and reasons for dose changes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance calculation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ADR (serious and non-serious), fatal AE, pregnancy collection</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for Pradaxa®/VKA discontinuation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACT-Q1 questionnaire</td>
<td>X (for Cohort B only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACT-Q2 questionnaire</td>
<td>X (for Cohort A only)</td>
<td>X (both Cohorts)</td>
<td>X (both Cohorts)</td>
<td></td>
</tr>
</tbody>
</table>

Footnotes:
1. Written Informed Consent must be obtained prior to the baseline visit assessments.
2. The type of hospital/practice and speciality of treating physician must be entered.
3. Creatinine clearance can only be calculated in the eCRF (via Cockroft-Gault Formula) if serum creatinine value is available from already existing laboratory reports. No lab assessment must be performed for the study at the baseline Visit 1, Visit 2 and/or Visit 3. See also footnote 4.
4. Weight must be determined at Visit 1. At Visit 2 and/or 3, only if existing serum creatinine value is available at Visit 2 and/or 3.
9.2.3 Study visits

**Baseline visit:**

No data collection for study purposes must be performed unless the patient has consented to participate in the study. Once the patient has signed the informed consent form, the patient is considered to be enrolled in the study and patient details should be recorded on the enrolment log.

The following procedures will be performed at the baseline visit:

- Sign informed consent form
- Review of inclusion and exclusion criteria
- Collection of demographic data: age, gender,
- Collection of concomitant diseases/co-morbidities in the medical history and at baseline
- Collection of current concomitant therapies
- Weight
- Creatinine Clearance: serum creatinine value (if available) to be entered on eCRF, Creatinine Clearance according to Cockcroft-Gault formula to be automatically calculated CHA2DS2-VASc and HAS-BLED score calculation in eCRF
- For Cohort A only: duration of previous treatment with VKA to be documented
- For Cohort A only: reasons for switch to Pradaxa® to be documented
- Documentation of Pradaxa® dosing
- Patient will be asked to complete the following patient related questionnaires:
  - PACT-Q2 (Cohort A only)
  - PACT-Q1 (Cohort B only)
- Treatment with Pradaxa® or VKA will be initiated

**Initiation period:**

During a routine practice visit occurring at 30 – 45 days after initiation of treatment, the following assessments will be documented:

- Current dosing of Pradaxa® and reasons for dose change (if applicable)
- New or changed concomitant diseases/co-morbidities
- Changes in concomitant therapies
- Creatinine Clearance: serum creatinine value (if available) to be entered on eCRF, Creatinine Clearance according to Cockcroft-Gault formula to be automatically calculated
- Weight (if needed for creatinine clearance calculation at V2)
- Collection and reporting of ADR (serious and non-serious), fatal AEs, or pregnancies (if applicable)
- Reasons for Pradaxa® or VKA discontinuation (if applicable)
- Patients will be asked to complete the PACT-Q2 questionnaire

**Continuation period:**
During a routine practice visit occurring at 150-210 days after initiation of treatment, the following assessments will be documented:

- Current dosing of Pradaxa® and reasons for dose change (if applicable)
- New or changed concomitant diseases/co-morbidities
- Changes in concomitant therapies
- Creatinine Clearance: serum creatinine value (if available) to be entered on eCRF, Creatinine Clearance according to Cockcroft-Gault formula to be automatically calculated
- Weight (if needed for creatinine clearance calculation at V3)
- Collection and reporting of ADR (serious and non-serious), fatal AEs, or pregnancies (if applicable)
- Reasons for Pradaxa® or VKA discontinuation (if applicable)
- Patients will be asked to complete the PACT-Q2 questionnaire

With this visit, the patient’s participation in the study will be completed.

Description and justification of patient questionnaires:

- **PACT-Q**: The PACT-Q was developed as a means to investigate patients’ satisfaction with anticoagulant treatment and treatment convenience in patients with deep venous thrombosis (DVT), pulmonary embolism (PE) or atrial fibrillation (AF) (R15-1314; R15-1316). The PACT-Q is a self-administered questionnaire. It can be completed in about ten minutes. No specific training is required to complete this document.

The original PACT-Q consists of two parts and contains 27 items:

- The PACT-Q1 is composed of a single dimension (7 items), covering the expectations of patients regarding their anticoagulant treatment, and is to be administered before treatment initiation.
- The PACT-Q2 is composed of three dimensions covering: convenience (11 items), burden of disease and treatment (2 items), and anticoagulant treatment satisfaction (7 items). The PACT-Q2 is to be administered to patients once treatment is ongoing.

Patients will either be switched from VKA treatment to Pradaxa® (cohort A) or newly initiated on Pradaxa® or VKA (cohort B).

- Pradaxa® 110 mg hard capsules
- Pradaxa® 150 mg hard capsules
- Vitamin K antagonist

9.2.3.1 Treatments
Pradaxa® 110 mg and Pradaxa® 150 mg hard capsules contain Dabigatran etexilate (active moiety: Dabigatran).
Patients will receive daily dose of Pradaxa® according to the approved country label and physician’s discretion.

The choice of vitamin K antagonist and the appropriate dosing is in the discretion of the physician. The applicable approved country label of the chosen treatment should be referred to.

9.2.3.2 Concomitant medications and restrictions

All concomitant medications are prescribed based on the underlying medical condition and upon the discretion of the treating physician. No treatment will be withheld from the patients. Any prescription is in the responsibility of the treating physician.

9.2.3.3 Representativeness of the study population

Inclusion and exclusion criteria have been limited to the respective approved country label of Pradaxa® and VKA. Therefore the patient population recruited in this non-interventional study can be seen as representative for patients receiving an oral anticoagulation for stroke prevention in non-valvular atrial fibrillation.

9.2.4 Study discontinuation

Boehringer Ingelheim 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 enrolment goals overall or at a particular study site
2. Violation of Good Clinical Practice (GCP) (as applicable), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study
3. Any other administrative reasons

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

9.3 VARIABLES

9.3.1 Variables for objective 1

Primary outcome
For Cohort A (switcher):
- Mean PACT-Q2 scores at second and last assessment compared to baseline assessment
For Cohort B (newly initiated):
- Mean PACT-Q2 scores at second and last assessment between treatment groups

Secondary outcome:
For Cohort A (switcher):
- Mean PACT-Q2 score at last assessment compared to second assessment

For Cohort B (newly initiated):
- Description of PACT-Q1 items at baseline

9.3.2 Variables for objective 2

Primary outcome:
Characterization of patients from both cohorts according to
- Age
- Gender
- CHA2DS2-VASc score (R10-5332)
- HAS-BLED score (modified HAS-BLED for newly initiated patients) (R10-6394)
- Kidney function (creatinine clearance)
- Stroke- and/or bleeding related risk factors in medical history and at baseline
- Co-morbidities
- Concomitant therapies
- Dosing of Pradaxa®
- Duration of previous VKA treatment (for Cohort A)

9.4 DATA SOURCES

Data will be newly collected from the patient by the investigator and recorded as source data at the site, i.e. the physicians records, and entered in the eCRF by the investigator or site staff. Patients will be asked to complete the respective questionnaires during their routine visits. Patient demographic data, concomitant diseases and concomitant therapies will be completed based on the physician’s records. Information on Pradaxa® and/or VKA dosing will be collected from physician’s records. Creatinine clearance for assessment of kidney function will be calculated within the eCRF, by entering Creatinine values (from existing lab reports, if available), and weight (if applicable) to be measured by the physician or delegated site staff.
9.5 STUDY SIZE

It is planned that a total of approximately 1790 patients from 6 SEASK countries will be recruited for Cohort A and Cohort B.

Baseline demographics and disease characteristics of the patient population will be described by estimates and confidence intervals (CIs) overall (for Cohort A), by anticoagulation treatment (for Cohort B), and by additional relevant categories as specified in Section 9.7.2 and the SEAP. Categorical attributes will be estimated with the precision (i.e. width of descriptive 95% confidence interval) described in Table 9.5: 1, according to sample size and prevalence of the attribute.

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

<table>
<thead>
<tr>
<th>Prevalence of attribute</th>
<th>Sample size (overall or per subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200</td>
</tr>
<tr>
<td>10% Expected n</td>
<td>20</td>
</tr>
<tr>
<td>95% CI width</td>
<td>8.80</td>
</tr>
<tr>
<td>20% Expected n</td>
<td>40</td>
</tr>
<tr>
<td>95% CI width</td>
<td>11.53</td>
</tr>
<tr>
<td>30% Expected n</td>
<td>60</td>
</tr>
<tr>
<td>95% CI width</td>
<td>13.13</td>
</tr>
<tr>
<td>40% Expected n</td>
<td>80</td>
</tr>
<tr>
<td>95% CI width</td>
<td>13.99</td>
</tr>
<tr>
<td>50% Expected n</td>
<td>100</td>
</tr>
<tr>
<td>95% CI width</td>
<td>14.26</td>
</tr>
</tbody>
</table>
* Calculations are based on the Clopper-Pearson method.

For example, for a population attribute with a prevalence of 20%, a total sample size of 1000 patients for Cohort A allows this proportion to be estimated with a precision of 5.05% (i.e. width of 95% CI).

The planned total sample size of 1790 patients is jointly determined by the following sample size assessments and additional non-statistical considerations, including feasibility assessments for the participating countries.

Due to the limited number of publications on PACT-Q2 and the lack of information regarding the clinical meaning of changes in PACT-Q2 scores, sample size assessments are performed using standardized mean differences. In the context of this study, they represent the mean differences in PACT-Q2 scores between two assessments (for Cohort A) or between the Pradaxa® and VKA groups (for Cohort B) divided by the corresponding standard deviations. In general, a standardized effect size of 0.2 is considered a small change, 0.5 a moderate change, and 0.8 a large change.

For Cohort A, assuming a 2-sided alpha of 0.05 and a 20% loss to follow-up, a total sample size of 598 patients will provide over 80% power to detect a standardized mean difference of 0.13 in PACT-Q2 scores between two assessments.

For Cohort B, assuming a 2-sided alpha of 0.05, a 1:1 ratio of Pradaxa® and VKA patients, and a 30% loss to follow-up and matching, a total sample size of 1192 patients will provide over 80% power to detect a standardized mean difference of 0.14 in PACT-Q2 scores between the Pradaxa® and VKA groups at each assessment.

Based on results from the PREFER in AF registry study, a reasonable expected standard deviation for the PACT-Q2 convenience and treatment satisfaction scores is 16. Based on this estimate, a standardized mean difference of 0.1 corresponds to an actual mean difference of 1.6 in the PACT-Q2 convenience and treatment satisfaction scores.

The PREFER in AF study also reported a mean difference between patients receiving novel oral anticoagulants and those receiving VKA of -0.6 for the convenience score, and of 1.1 for the treatment satisfaction score. Since the clinical meaningfulness of such small mean differences in PACT-Q2 scores is unclear, the
current study is by design not powered to detect statistically significant differences of such small magnitudes.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic CRFs (eCRFs) will include programmable edits to obtain immediate feedback if data are 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 dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate. Source data verification (SDV) will be performed at sites identified by a risk-based approach outlined in the monitoring plan, as needed.

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 International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

9.7.1 Study Design

In this non-interventional study, cross-sectional data at study baseline and longitudinal follow-up data over 6 months will be collected for non-valvular AF patients with a current VKA therapy and subsequent initiation of Pradaxa® in Cohort A, and for newly diagnosed AF patients initiated on Pradaxa® or VKA in Cohort B.

Baseline data will be analyzed using a descriptive approach. Data from the longitudinal follow-up will be summarized descriptively. For Cohort A, mean differences in PACT-Q2 scores between assessments will be assessed using paired t-tests. For Cohort B, mean differences in PACT-Q2 scores between Pradaxa® and VKA patients will be assessed using propensity score matched analysis.

Due to the nature of this non-interventional study, there is no (confirmatory) hypothesis testing foreseen in a strict statistical sense. Analyses are descriptive in nature and confidence intervals and p-values from statistical models are used for exploratory purposes.
9.7.2 Planned Analysis

Analyses will be performed by Boehringer Ingelheim or Boehringer Ingelheim’s designees. The main analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria) from all participating countries.

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 present all possible categories and will display the number of observations per category as well as percentages. Estimates will be presented with 95% confidence intervals.

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

9.7.3 Main analysis

Patient demographics and disease characteristics at baseline as described in section 9.3.2 will be summarized descriptively for all eligible patients in Cohort A and by treatment in Cohort B. This analysis may be repeated by additional relevant factors (e.g. country) that will be specified in the SEAP.

For Cohort A, the mean PACT-Q2 scores at the second and last assessments will be compared with the baseline assessment using paired t-tests.

For Cohort B, mean PACT-Q2 scores will be compared between Pradaxa® and VKA patients at the second and last assessments. Given the nature of this non-interventional study, patient in the two treatment groups may differ with regard to important baseline demographics and disease characteristics. When approximately half of the target sample size is reached, propensity scores that estimate the probabilities that patients would be initiated on Pradaxa® will be calculated using a logistic regression model including relevant baseline factors. The percentage of Pradaxa® and VKA patients that are matched with a 1:1 ratio and without replacement based on propensity scores will be calculated to assess the comparability of the two patient populations, and to estimate the loss of patients from the comparative analysis. Details of the propensity score model and the matching procedure, such as the choice of algorithm and caliper width will be described in the SEAP. If a sufficient percentage of matching (e.g. 90%) is achieved, the loss is considered minimal. If the percentage is considered not to be sufficient, the target sample size might be raised to increase the power of the comparative analysis.

For the final comparative analysis for Cohort B, Pradaxa® and VKA patients will be matched based on propensity scores following the same approach as described above. To assess the performance of the propensity score matching procedure, patient demographics and disease characteristics at baseline will be descriptively summarized again for the matched patients by treatment. Finally, the mean PACT-Q2 scores at each of the second and last assessments will be compared between the matched Pradaxa® and VKA patients using a paired t-test.
For both cohorts, the primary analyses will be based on the actual anticoagulation treatment the patients receive (i.e. “as treated” analysis). A patient is considered to have permanently discontinued initial anticoagulation treatment if other relevant anticoagulation treatment is initiated or otherwise dependent on the duration of treatment interruption (details will be provided in the SEAP). Patients who have permanently discontinued initial anticoagulation treatment at the time of an assessment will be excluded from all analyses where data from that assessment is included.

9.7.5 Safety Analyses

Safety analyses will be performed separately for Cohort A and B, and will include all enrolled patients with an actual follow-up. Statistical analysis and reporting of AEs will be descriptive in nature, will be based on BI standards, and will focus on adverse drug reactions (ADRs) to Pradaxa® and 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 3 days (for Pradaxa®) or 6 days (for VKA) 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 6 month 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 events leading to deaths

Schedule of Planned Analyses

No interim analysis is planned for Cohort A.

For Cohort B, it is planned that an interim analysis that assesses the comparability of patients in the Pradaxa® and VKA groups based on propensity scores will be performed when approximately half of the target sample size is reached (see details in Section 9.7.2.1).

For each cohort, the final analyses 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 that cohort. The final analysis for both cohorts may be performed together, if their complete data becomes available at the same time. One final report will be prepared at the completion of both cohorts.

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

9.7.6 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.

The percentage of and reason for loss to follow-up will be summarized overall in Cohort A, by treatment in Cohort B, and by other relevant factors. In addition, if the proportion of
patients with loss to follow-up is substantial enough (e.g. ≥ 10%) 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 following processes will be implemented to ensure data completeness and data quality:

Data Edit Checks:

The electronic CRF (eCRF) will include programmable edit checks to obtain feedback if data is missing, out of range, illogical or potentially erroneous.

These checks will be performed once data is entered into the eCRF. Thus the data entered in to the eCRF will be validated within the system and the physician will receive alerts for missing or inconsistent data. In case any changes of already entered data will be required, an audit trail will be available.

Medical monitoring:

A review of applicable entered eCRF data will be performed to verify patient eligibility to ensure that the analysed patient population corresponds to the protocol–described population. In addition eCRFs/completed patient related questionnaires will also be reviewed for verification that no non reported safety event is present.

Source data verification:

No regular source data verification is planned in this non-interventional study. However, in case of issues (i.e. high amount of missing data, data discrepancies, protocol violations, etcetera) detected at a site with the measures described above, a for-cause onsite visit can be planned to perform a sample check of source data.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Consecutive enrolment will be employed to ensure that specific types of patients are not selected by site staff to participate.

VKA has been the mainstay of SPAF for many years. It is widely available, affordable but does require regular INR monitoring. Pradaxa® is more expensive, may or may not be reimbursed but doesn’t require the continual INR monitoring. There are a number of different types of bias that could influence the data collection and analysis from these cohorts such as selection bias, information bias and channelling bias.

The study is designed to collect new data. The entry criteria are non-restrictive which will permit the enrolment 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 real world treatment patterns and patient characteristics.

Selection bias:
Selection bias could occur at both the site (physician) level and the patient level. If sites where Pradaxa® is used frequently differ systematically with respect to patient or the routine procedures from sites that use Pradaxa® less frequently, the between site difference could lead to non-comparability between the patients. To minimize the site level selection bias, the goal is to have participating centres that have access to all available treatment options for SPAF that are approved for use in that country.

Selection bias at the patient level could occur if sites preferentially enrol specific patients into the study. To minimize selection bias at the patient level, consecutive enrolment is performed.

- **Information / observer bias:**
  Information or observer bias may occur when information is collected differently between two groups. E.g. if the observer/physician has more knowledge about the use of VKA treatment, the patients exposure to VKA treatment or the disease status and development as compared to Pradaxa®. Also, a VKA patient will be more often seen. Such information may result in differences in the way information is collected, measured or interpreted by the investigator in each of the treatment groups (cohort A or B (B1, B2)). The use of a standardized protocol and eCRF for data collection, but also the use of standardized questionnaires (PACT-Q) which have to be completed by the patients themselves, will minimize the information/observer bias.

- **Loss to follow-up:**
  All efforts will be made to minimize loss to follow-up in patients who are enrolled. 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.

**Channelling bias:**
Channelling bias can occur due to preferential prescribing in relation to different risks for events of interest e.g. if Pradaxa® is prescribed more frequently to high risk patients than to other treatments, a high rate of outcome events could be expected in the Pradaxa® group. In order to control for potential channelling, an assessment will be conducted to monitor the comparability of important patient baseline characteristics. Propensity score matching is planned to account for potential differences.

**Recall bias:**
Recall bias refers to the phenomenon when the outcomes of treatment (either good or bad) may colour the patient’s recollection of events prior to or during the treatment. To minimize recall bias, patient reported outcomes will be assessed using validated questionnaires within a limited period of time to minimize recall bias.

**Confounding:**
Statistical techniques, such as adjustment for covariates and propensity score matching will be used to correct for identified confounders. However unidentified confounders cannot be controlled for using statistical analysis. The employed methods are described in the data analysis section.
9.10 OTHER ASPECTS

9.10.1 Informed Consent, Data Protection, Study Records

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, and as close as possible to the standards of the International Conference of Harmonisation (ICH) Tripartite Guideline, Good Clinical Practice (GCP), Guidelines for Good Epidemiological Practice (GEP) [R10-4560], Good Pharmacoepidemiology Practice (GPP) [R09-0182] and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

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

9.10.2 Study Approval, Patient Information, And Informed Consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to 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 trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative. ICH-GCP will be used as guidance where applicable.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the 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 Boehringer
Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

9.10.3 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.

9.10.4 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. 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 enrolment 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.

9.10.4.1 Source documents

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

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

For eCRFs all data must be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the study (substance, study number, patient number, date patient was informed)
- Dates of Patient’s visits, including prescription of study medication
- Medical history (including study indication and concomitant diseases, if applicable)
- Medication history
• PACT-Q 1 and 2 questionnaires: the original paper questionnaires completed by the patients
• Adverse drug reactions (non-serious) (onset date (mandatory), and end date (if available))
• Serious adverse drug reactions (onset date (mandatory), and end date (if available))
• Fatal adverse events (onset date (mandatory), and end date (if available))
• Pregnancy
• Concomitant therapy (start date, changes)
• Originals or copies of laboratory results (in validated electronic format, if available)
• Conclusion of Patient’s Participation in the study

9.10.4.2 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 related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor’s clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.
10. PROTECTION OF HUMAN SUBJECTS

Safeguards in order to comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation (safety) studies.

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

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. As a general rule, no study results should be published prior to finalisation of the Study Report.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to 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 Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, 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.

Treatment data may be given to the patient’s personal physician or to other appropriate medical personnel responsible for the patient’s welfare. Data generated as a result of the 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.

10.3 COMPLETION OF STUDY

The EC/competent authority in each participating country needs to be notified about the end of the study (last patient out) or early termination of the study.
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 unfavourable 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 reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- 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 judgement 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 hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

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 of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. 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.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome,
- all pregnancies

Note: For all patients on Pradaxa® these data must be recorded on the AE pages in the eCRF. The separate NIS AE form or Pregnancy Monitoring Form must be used for Pradaxa® patient only (see 'Expedited Reporting' below).

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

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

Intensity of adverse event
The intensity of the AE should be judged based on the following:
- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Pradaxa®, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject 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.
Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

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<tr>
<th>Type of Report</th>
<th>Timeline</th>
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<tr>
<td>All serious ADRs associated with Pradaxa®</td>
<td>immediately within 24 hours</td>
</tr>
<tr>
<td>All AEs with fatal outcome in patients exposed to Pradaxa®</td>
<td>immediately within 24 hours</td>
</tr>
<tr>
<td>All non-serious ADRs associated with Pradaxa®</td>
<td>7 calendar days</td>
</tr>
<tr>
<td>All pregnancy monitoring forms associated with Pradaxa®</td>
<td>7 calendar days</td>
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</tbody>
</table>

Note: the NIS AE form or Pregnancy Monitoring Form is required only for Pradaxa® patients, not for VKA patients.

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor 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.

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 Pradaxa® 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 MAH according to local and international regulatory requirements.
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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. As a general rule, no study results should be published prior to finalisation of the Study Report.

Results of this non-interventional study will be disclosed on external websites according to BI SOP.
In addition, a study specific publication plan will be developed to describe planned publications per country and for overall study results.
13. REFERENCES

13.1 PUBLISHED REFERENCES


R15-1312  Caterina R de, Brueggenjuergen B, Darius H, Heuzey JY le, Renda G, Schilling RJ, Schmitt J, Zamorano JL, Kirchhof P Quality of life and patient satisfaction data in atrial fibrillation patients stably treated with a VKA vs patients switched from a VKA to NOAC. The PREFER in AF registry. ESC 2014, 36th Cong of the European Society of Cardiology (ESC), Barcelona, 30 Aug - 3 Sep 2014 (Poster)


13.2 UNPUBLISHED REFERENCES

None
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The following stand-alone documents have not been finalized at the time of protocol finalization. The final version of these documents will be archived in the Trial Master File (TMF)

- Statistical and Epidemiological Analysis Plan (SEAP)
- List of participating investigators
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable
ANNEX 3. ADDITIONAL INFORMATION

The Perception of Anticoagulant Treatment Questionnaires (PACT-Q®) will be shown on the next pages (in English). Validated translations of these PACT-Q1 and PACT-Q2 questionnaires will be provided to the patients participating in this study (in their local language).
ANNEX 3.1 PERCEPTION OF ANTICOAGULANT TREATMENT QUESTIONNAIRE, PART 1 (PACT-Q1)

PACT-Q1
(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.

PACT-Q © 2007 Sanofi-Aventis, France, All rights reserved
Treatment Expectations

Please answer the following questions to help us understand your treatment expectations. Please check one box per line.

A1 - How confident are you that your anticoagulant treatment will prevent blood clots?

\[
\begin{array}{|c|c|c|c|c|}
\hline
& 1 & 2 & 3 & 4 \\
\hline
Not at all & A little & Moderately & A lot & Extremely \\
\hline
\end{array}
\]

A2 - Do you expect that your anticoagulant treatment will relieve some of the symptoms you experience (i.e., leg pain, swelling, palpitations, shortness of breath, or chest pain ...)?

\[
\begin{array}{|c|c|c|c|c|}
\hline
& 1 & 2 & 3 & 4 \\
\hline
Not at all & A little & Moderately & A lot & Completely \\
\hline
\end{array}
\]

A3 - Do you expect that your anticoagulant treatment will cause side effects such as minor bruises or bleeding (i.e., while shaving, cooking, after small cuts ...)?

\[
\begin{array}{|c|c|c|c|c|}
\hline
& 1 & 2 & 3 & 4 \\
\hline
Not at all & A little & Moderately & A lot & Very much \\
\hline
\end{array}
\]

FACT-Q © 2007 Sanofi-Aventis, France, All rights reserved
**A4 - How important is it for you to have an anticoagulant treatment that is easy to take?**

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**A5 - How concerned are you about making mistakes when taking your anticoagulant treatment (i.e., in the way you take it, the time you take it, or in the dosage that you take)?**

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**A6 - How important is it for you to take care of your anticoagulant treatment by yourself?**

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**A7 - How concerned are you about how much you may have to pay for your anticoagulant treatment?**

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Please make sure you answered all questions.

Thank you for your time.

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ANNEX 3.2 PERCEPTION OF ANTICOAGULANT TREATMENT QUESTIONNAIRE, PART 2 (PACT-Q2)

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.

PACT-Q © 2007 Sanoit-Avantia, Texas, All rights reserved
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 ...)?

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

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

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

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PACT-Q © 2007 Sanofi-Aventis, France, All rights reserved
B5 - It is recommended that certain foods be avoided while taking an anticoagulant treatment; how difficult is this for you?

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

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

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

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

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

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

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### 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.

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

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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Not at all</td>
<td>A little</td>
<td>Moderately</td>
<td>A lot</td>
<td>Extremely</td>
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</table>

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

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<td>Moderate</td>
<td>A lot</td>
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**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.

**Q1** - How reassured do you feel by your anticoagulant treatment?

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<tr>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
<th>L5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>A little</td>
<td>Somewhat</td>
<td>Very</td>
<td>Completely</td>
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</tbody>
</table>

**Q2** - Do you feel that your anticoagulant treatment has decreased your symptoms (i.e., leg pain or swelling, palpitations, shortness of breath, or chest pain?)

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<tr>
<th>L1</th>
<th>L2</th>
<th>L3</th>
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<th>L5</th>
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<td>Not at all</td>
<td>A little</td>
<td>Moderately</td>
<td>A lot</td>
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**Q3** - 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?

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<tr>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
<th>L5</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is much worse than what I expected</td>
<td>It is worse than what I expected</td>
<td>It is exactly what I expected</td>
<td>It is better than what I expected</td>
<td>It is much better than what I expected</td>
</tr>
</tbody>
</table>

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

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<td>1</td>
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<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Extremely dissatisfied</td>
<td>Dissatisfied</td>
<td>Neither satisfied nor dissatisfied</td>
<td>Satisfied</td>
<td>Extremely satisfied</td>
</tr>
</tbody>
</table>

**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?

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

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

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</table>

Please make sure you answered all questions.

Thank you for your time.

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