Boehringer Ingelheim

Non-interventional Study Protocol

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Product reference:	EU/1/08/442 (EMA registration number)
Procedure number:	n.a.
Marketing authorization holder:	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein, Germany
Joint PASS:	No
Research question and objectives:	Primary objective: Describe the atrial fibrillation patient´s treatment perception by using the PACT-Q© (Perception on Anticoagulant Treatment Questionnaire). Secondary objective: Characterization of patient population (including dosing of Pradaxa®)

Countries of study:	7 European countries (Belgium, Denmark, Greece, Norway, Portugal, Sweden and The Netherlands).
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Signature of EU-QPPV:	Not applicable
Date:	17 July 2015

1. TABLE OF CONTENTS

0. TITLE PAGE 1
1. TABLE OF CONTENTS 3
2. LIST OF ABBREVIATIONS 5
3. RESPONSIBLE PARTIES 7
4. ABSTRACT 8
5. AMENDMENTS AND UPDATES 11
6. MILESTONES 12
7. RATIONALE AND BACKGROUND 13
8. RESEARCH QUESTION AND OBJECTIVES 14
9.1 RESEARCH QUESTIONS 14
9.2 OBJECTIVES 14
9. RESEARCH METHODS 15
9.1 STUDY DESIGN 15
9.2 SETTING 15
9.2.1 Selection of sites 15
9.2.2 Inclusion criteria 16
9.2.3 Exclusion criteria 16
9.2.4 Removal of patients from the study 17
9.2.5 Visit schedule 17
9.2.6 Treatments 20
9.2.7 Concomitant medications and restrictions 21
9.2.8 Representativeness of the study population: 21
9.3 VARIABLES 21
9.3.1 Variables for objective 1 21
9.3.2 Variables for objective 2 22
9.4 DATA SOURCES 22
9.5 STUDY SIZE 22
9.6 DATA MANAGEMENT 24
9.7 DATA ANALYSIS 25
9.7.1 STUDY DESIGN 25
9.7.2 PLANNED ANALYSES 25
9.7.2.1 Main Analyses 25
[redacted] 26

9.7.2.3 Safety Analyses 27
9.7.2.4 Schedule of Planned Analyses 27
9.7.3 HANDLING OF MISSING DATA 28
9.8 QUALITY CONTROL 28
9.9 LIMITATIONS OF THE RESEARCH METHODS 28
9.10 OTHER ASPECTS 30
9.10.1 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS 30
9.10.1.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT 30
9.10.1.2 DATA QUALITY ASSURANCE 31
9.10.1.3 RECORDS 31
9.10.1.3.1 Source documents 31
9.10.1.3.2 Direct access to source data and documents 32
9.10.1.4 STATEMENT OF CONFIDENTIALITY 32
9.10.1.5 COMPLETION OF STUDY 32
10. PROTECTION OF HUMAN SUBJECTS 33
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 34
11.1 Definitions of adverse events 34
11.2 Adverse event and serious adverse event reporting 35
11.3 Reporting to health Authorities 37
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS. 38
13. REFERENCES 39
13.1 PUBLISHED REFERENCES 39
13.2 UNPUBLISHED REFERENCES 40
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS 41
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 42
ANNEX 3. ADDITIONAL INFORMATION 43
ANNEX 3.1 Perception of anticoagulant treatment Questionnaire, part 1 (PACT-Q1) 44
ANNEX 3.2 Perception of anticoagulant treatment Questionnaire, part 2 (PACT-Q2) 47

2. LIST OF ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
ADR	Adverse Drug Reaction
ANCOVA	Analysis of Covariance
BI	Boehringer Ingelheim
CA	Competent Authority
CHA_2DS_2-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
DMP	Data Management Plan
eCRF	Electronic Case Report Form
DEDP	Drug Exposure During Pregnancy
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EudraCT	European Clinical Trials Database
EU PAS Register	European Post- Authorization Study Register (current ENCePP electronic register of studies)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
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 Authorization Holder
n.a.	Not applicable / not available
NVAF	Non valvular atrial fibrillation
OPU	Operative Unit
OAC	Oral anticoagulation
PACT-Q©	Perception of Anticoagulant Treatment Questionnaire
SAE	Serious Adverse Event
SDV	Source Data Verification
SEAP	Statistical and Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPAF	Stroke Prophylaxis (or Prevention) in Atrial Fibrillation
VKA	Vitamin K Antagonist

3. RESPONSIBLE PARTIES

Therapeutic Area [redacted] Cardiovascular Medicine (TA[redacted]	[redacted]
Team Member Medical Affairs (TM MA)	
Team Member Epidemiology (TM Epi)	
[redacted] Global Epidemiology [redacted] GEpi)	
Therapeutic Area [redacted] Risk Management (TA[redacted] RM), and Pharmacovigilance Working Group (PVWG) [redacted]	
Trial Clinical Monitor (TCM)	
Trial Statistician (TSTAT)	
Coordinating Investigator (CI)	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa® (Dabigatran etexilate), or Vitamin K Antagonist (VKA)			
Name of active ingredient: Dabigatran, or VKA			
Protocol date: 17 JUL 2015	**Study number:** 1160.247	**Version/Revision:** 01	**Version/Revision date:** n.a.
Title of study:	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.		
Rationale and background:	Pradaxa® (Dabigatran etexilate) is a direct Thrombin inhibitor approved in Europe, USA and many other countries worldwide for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. Data on how patients perceive Pradaxa® treatment in the context of atrial fibrillation and anticoagulation management do only exist to a limited degree in Europe. (R15-1312). 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 in the approved dosages of 110 mg or 150 mg twice daily) in comparison to using Vitamin K Antagonist (VKA).		
Research question and objectives:	• Objective 1: How do patients perceive anticoagulation treatment with Pradaxa® for stroke prevention in non-valvular atrial fibrillation (NVAF) in comparison with VKA? o With further exploratory objectives: o Is there a variation of treatment convenience and treatment satisfaction among different age groups? Is there a difference in treatment convenience and treatment satisfaction between switchers and newly initiated patients? o What is treatment expectation of newly diagnosed NVAF patients before they start treatment with VKA or Pradaxa® o Is there any geographical variation in treatment perception?		

	• 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)?
Study design:	Non-interventional study of AF patients in Europe with a current VKA therapy and subsequent initiation of Pradaxa® OR patients being newly diagnosed with AF and initiated on Pradaxa® or VKA.
Population:	Patients diagnosed with non-valvular atrial fibrillation (NVAF) and eligible for Pradaxa® or VKA treatment according to Pradaxa® or respective VKA label.
Variables:	**For objective 1:** **Primary outcome** **For Cohort A (NVAF patients on VKA who are switched to Pradaxa®)):** - Mean PACT-Q2 scores at second and last assessment compared to baseline assessment. **For Cohort B (newly diagnosed NVAF patients initiated to either VKA or Pradaxa®)):** - Mean PACT-Q2 scores at second and last assessment compared between treatment groups. **Secondary outcome** **For Cohort A (switched to Pradaxa®):** - Mean PACT-Q2 scores at last assessment compared to second assessment. **For Cohort B (newly initiated to VKA or Pradaxa®):** - Description of PACT-Q1 items at baseline. **Further exploratory outcomes**: - Variation of PACT-Q2 scores at baseline, during initiation period and during the continuation period in respective treatment cohorts between countries (both cohorts). - Variation of PACT-Q2 scores in different age groups (both cohorts). - Variation of treatment expectations, measured with PACT-Q1 items at baseline in different age groups (cohort B). - Geographical variation in treatment perception **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)

	- Co-morbidities - Co-medication - Dosing of Pradaxa - Duration of previous VKA treatment (for Cohort A)
Data sources:	- New data collection - Questionnaires completed by patients - Patient characteristics completed by physician's judgement and records.
Study size:	3.000 patients in 7 European 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: 08-Sep-2015 Planned end of data collection: 05-Oct 2015 Planned final study report: 10-May-2017

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Start of data collection	08-SEP-2015
End of data collection	05-OCT-2016
Registration in the EU PAS register	will be done before study initiation
Final report of study results:	10-MAY-2017

7. RATIONALE AND BACKGROUND

Pradaxa® (Dabigatran etexilate) is a direct Thrombin inhibitor approved in Europe, USA and many other 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. Other data on how patients perceive Pradaxa® treatment in the context of atrial fibrillation disease management only exist to a limited degree in Europe. (R15-1312)

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

9.1 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)?
  - Is there a variation of treatment convenience and treatment satisfaction among different age groups?
  - Is there a difference in treatment convenience and treatment satisfaction between switchers and newly initiated patients?
  - Is there any geographical variation in treatment expectations?
- 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:
Cohort A:
Patients having been treated with VKA and now being switched to Pradaxa®
Cohort B:
Patients newly diagnosed with non-valvular atrial fibrillation and initiated on either Pradaxa® or VKA.

9.2 OBJECTIVES

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 European 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 Europe 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 3.000 patients will be collected from approximately 220 sites in 7 European countries. Planned participating countries are Belgium, Denmark, Greece, Norway, Portugal, Sweden and The Netherlands.

9.2.1 Selection of sites

Cardiologists and non-cardiologist sites regularly prescribing Pradaxa® and VKA for stroke prevention in atrial fibrillation according to the respective Summary of Product Characteristics 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 1160.136 (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 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 Inclusion criteria

Cohort A:

1A. Written informed consent prior to participation

2A. Female and male patients ≥ 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 Summary of Product Characteristics 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 Summary of Product Characteristics and physician`s discretion.

9.2.3 Exclusion criteria

1. Contraindication to the use of Pradaxa® or VKA as described in the Summary of Product Characteristics (SmPC)

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

9.2.4 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.

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

9.2.5 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 9.2.5: 1 Flow Chart / Schedule of Data Collection

Visit	**1**	**2**	**3**
Assessment	**Baseline**	**Initiation period**	**Continuation period**
Day	**1**	**30-45 days**	**150 – 210 days**
Informed Consent[1]	X		
Patient demographics: age, gender	X		
Concomitant diseases / co-morbidities	X	X	X
Concomitant therapies	X	X	X
Healthcare system characteristics[2]	X		
HAS- BLED score (to be calculated in the eCRF)	X		
CHA_2DS_2-VASc score (to be calculated in the eCRF)	X		
Inclusion/exclusion criteria	X		
Duration of previous VKA treatment (for Cohort A)	X		
Reasons for switch to Pradaxa® (for Cohort A)	X		
Start Pradaxa® or VKA	X		
Pradaxa® dosing (110 or 150 mg) and reasons for dose changes	X	X	X
Creatinine clearance calculation[3]	X	X	X
Weight[4]	X	X[4]	X[4]
ADR (serious and non-serious), fatal AE, pregnancy collection		X	X
Reason for Pradaxa®/VKA discontinuation		X	X
PACT-Q1 questionnaire	X (for Cohort B only)		
PACT-Q2 questionnaire	X (for Cohort A only)	X (both Cohorts)	X (both Cohorts)

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.

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.

9.2.6 Treatments

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

Pradaxa® 110 mg and Pradaxa® 150 mg hard capsules contain Dabigatran etexilate (active ingredient: Dabigatran).
Patients will receive daily dose of Pradaxa® according to the Summary of Product characteristics and physician´s discretion.

The choice of vitamin K antagonist and the appropriate dosing is in the discretion of the physician. The applicable Summary of Product characteristics of the chosen treatment should

be referred to. The following website, accessed on 16 July 2015, shows the full list of products by active substance registered in the EU:
http://ec.europa.eu/health/documents/community-register/html/inn_full_a.htm

Dosing of VKA has to be monitored and individually adapted by regular measurements of INR values (International Normalized Ratio).

The current version of Pradaxa® Summary of Product Characteristics (SmPC) can be found on the EMA Webpage.

The following link is updated with the most recent version of the approved SmPC:
http://ec.europa.eu/health/documents/community-register/html/h442.htm

9.2.7 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.

9.2.8 Representativeness of the study population:

Inclusion and exclusion criteria have been limited to the respective SmPCs 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.

9.3 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

Further exploratory outcomes:

- Variation of PACT-Q2 scores at baseline, during initiation period and during the continuation period in respective treatment cohorts between countries(both cohorts)

- Variation of PACT-Q2 scores in different age groups (both cohorts)
- Variation of treatment expectations, measured with PACT-Q1 items at baseline in different age groups (cohort B)
- Geographical variation in treatment perception

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 3000 patients from 7 European 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

Prevalence of attribute		Sample size (overall or per subgroup)				
		200	500	1000	2000	3000
10%	Expected n	20	50	100	200	300
	95% CI width	8.80	5.46	3.82	2.68	2.18
20%	Expected n	40	100	200	400	600
	95% CI width	11.53	7.20	5.05	3.55	2.90
30%	Expected n	60	150	300	600	900
	95% CI width	13.13	8.21	5.77	4.06	3.28
40%	Expected n	80	200	400	800	1200
	95% CI width	13.99	8.77	6.17	4.34	3.54
50%	Expected n	100	250	500	1000	1500
	95% CI width	14.26	8.94	6.29	4.43	3.61

* 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). In addition, for a population attribute with a prevalence of 30%, a sample size of 500 Pradaxa® patients in a particular subgroup in Cohort B allows this proportion to be estimated with a precision of 8.21%.

The planned total sample size of 3000 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 (R15-1314, R15-1316, R15-1359) 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 1000 patients will provide over 80% power to detect a standardized mean difference of 0.1 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 2000 patients will provide over 80% power to detect a standardized mean difference of 0.11 in PACT-Q2 scores between the Pradaxa® and VKA groups at each assessment.

Based on results from the PREFER in AF (R15-1312) 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 (R15-1312) 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 ANALYSES

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).

9.7.2.1 Main Analyses

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.

[redacted]

9.7.2.3 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

9.7.2.4 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.

9.7.3 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.

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.

Insurance Cover: The requirements for an insurance depend on local law and legislations in the participating country. If required, the terms and conditions of the insurance cover are made available to the investigator and the patients, and the documentation must be archived in the Investigator Site File (ISF).

9.10.1.1 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 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.

9.10.1.2 DATA QUALITY ASSURANCE

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

9.10.1.3 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.

9.10.1.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents:

- 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

9.10.1.3.2 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 9.10.1.3.1.

9.10.1.4 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, i.e. the competent authority (CA).

9.10.1.5 COMPLETION OF STUDY

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

10. PROTECTION OF HUMAN SUBJECTS

Please refer to section 9.10.1

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 drug reaction
An adverse drug reaction (ADR) 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 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 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 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 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 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.

The following must be collected by the investigator in the eCRF from signing the informed consent onwards until the end of the study:

- all ADRs (serious and non-serious)*,
- all AEs with fatal outcome*
- all pregnancies*

Note: For all patients (on Pradaxa® or VKA) these data must be recorded on the AE pages in the eCRF. The separate NIS (S)AE 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 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.

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 paper NIS (S)AE form is to be completed and forwarded (by fax/e-mail) to the responsible contact (person) for each country 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 (S)AE form** from signing the informed consent onwards until the end of the study:

Table 11.2: 1 Report types and timelines

Type of Report*	Timeline
All **SADRs** associated with Pradaxa®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Pradaxa®	immediately within 24 hours
All **non-serious ADRs** associated with Pradaxa®	7 calendar days
All **pregnancy monitoring** forms associated with Pradaxa®	7 calendar days

Note: the NIS (S)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 (S)AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF pages and the NIS (S)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

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

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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.

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?

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

A2 - Do you expect that your anticoagulant treatment will relieve some of the symptoms you experience (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

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 …)?

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

A4 - How important is it for you to have an anticoagulant treatment that is easy to take?

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

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)?

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

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

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

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

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

Please make sure you answered all questions.

Thank you for your time.

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.

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.

APPROVAL / SIGNATURE PAGE

Document Number: c03518692 **Technical Version Number:1.0**

Document Name: 1160-0247-clinical-trial-protocol

Title: Non-interventional study describing patients´ perception on anticoagulant treatment and treatment convenience when treated with Pradaxa or standard care VKA for SPAF

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medical Affairs	[redacted]	17 Jul 2015 13:19 CEST
Approval-[redacted] Safety Evaluation Therapeutic Area		19 Jul 2015 15:18 CEST
Author-Trial Statistician		20 Jul 2015 15:12 CEST
Approval-Other		20 Jul 2015 18:25 CEST
Approval-[redacted] of Global Epidemiology		21 Jul 2015 09:17 CEST
Approval-Therapeutic Area [redacted]		22 Jul 2015 10:46 CEST
Approval-Other		22 Jul 2015 11:14 CEST
Approval-Trial Clinical Monitor		22 Jul 2015 11:35 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed