Non-interventional Study Protocol

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Title:	**P**atients' **A**ssessment of **S**atisfaction for **S**troke Prevention in Atrial Fibrillation—**I**mpact of Conventional Oral Anticoagulant (**O**AC) Compared with Novel Oral Anticoagulant (**N**OAC)
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Research question and objectives:	**Objective 1** To describe the treatment perception from patients with non-valvular atrial fibrillation (NVAF) receiving Pradaxa® or VKA for stroke prevention by using the self-estimation questionnaire of PACT-Q during a 6-month study period. **Objective 2** To investigate the patient's characteristics.

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AP	Alkaline Phosphatase
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	Clinical Monitor Local
CRA	Clinical Research Associate
CrCl	Creatinine Clearance
CRF	Case Report Form
DMP	Data Management Plan
EC	Ethics Committee
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
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
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs and Alcohol
HRQoL	Health-Related Quality of Life
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
MAH	Marketing Authorisation Holder
NHI	National Health Insurance
NIS	Non-Interventional Study
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulation
PACT-Q©	Perception of Anticoagulant Treatment Questionnaire
PASS	Post-Authorization Safety Study
PT	Prothrombin Time
RWE	Real World Experience

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPAF	Stroke Prophylaxis (or Prevention) in Atrial Fibrillation
VKA	Vitamin K Antagonist

3. RESPONSIBLE PARTIES

Title	Name
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of Medical Affairs	
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Data /Biostatistician	
Clinical Research	

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: 15 March 2017	**Study number:** 1160-0286	**Version/Revision:** 1.0	**Version/Revision date:** 15 March 2017
Title of study:	**P**atients' **A**ssessment of **S**atisfaction for **S**troke Prevention in Atrial Fibrillation—**I**mpact of Conventional Oral Anticoagulant (**O**AC) Compared with Novel Oral Anticoagulant (**N**OAC)		
Rationale and background:	Non-interventional studies (NIS) observing patients treated with Pradaxa® for stroke prevention in atrial fibrillation (SPAF) to assess treatment satisfaction have not been conducted in Taiwan. Due to the limited data on patients' perception of conventional Vitamin K antagonist (VKA) or Pradaxa® treatment in real world experience (RWE), it remains an interesting topic to address. Therefore, the observational study is proposed to describe the perception of anticoagulant treatment according to the questionnaire—PACT-Q in the cohorts of patients switching from VKAs to Pradaxa® or newly initiating Pradaxa®/VKAs.		
Research question and objectives:	**Objective 1** To describe the treatment perception from patients with non-valvular atrial fibrillation (NVAF) receiving Pradaxa® or VKA for stroke prevention by using the self-estimation questionnaire of PACT-Q during a 6-month study period. **Objective 2** To investigate the patient's characteristics.		
Study design:	This non-interventional study enrolling patients in Taiwan with a previous VKA therapy, followed by switching to Pradaxa® OR patients being newly diagnosed with NVAF and initiated on Pradaxa® or VKA. The study is primarily based on questionnaire—PACT-Q.		
Population:	**Inclusion criteria**: Cohort A (patients switched from VKA to Pradaxa®) 1.A. Written informed consent prior to participation. 2.A. Female or male patients ≥ 20 years of age with a diagnosis of non-valvular atrial fibrillation (NVAF). 3.A. At least 3 months of continuous VKA treatment for stroke		

	prevention prior to baseline assessment. 4.A. Patients switched to Pradaxa® prior to baseline assessment according to the physician's discretion and the Summary of Product Characteristics (SmPCs)/reimbursement criteria. OR Cohort B (patients newly initiated Pradaxa® or VKA) 1.B. Written informed consent prior to participation. 2.B. Female or male patients ≥ 20 years of age, newly diagnosed with NVAF, and no previous treatment for stroke prevention (no use of any OAC within 1 year prior to enrolment). 3.B. Patients initiated stroke prevention treatment with Pradaxa® or VKA according to the physician's discretion and the SmPCs/reimbursement criteria. **Exclusion criteria**: 1. Contraindication to the use of Pradaxa® or VKA as described in the SmPCs. 2. Patients receiving Pradaxa® or VKA for any other condition than stroke prevention in NVAF. 3. Current participation in any clinical trial of a drug or device. 4. Current participation in an AF-related registry, e.g. the Gloria AF program. **Withdrawal Criteria**: 1. Patients withdraw informed consent. 2. Patients lost to follow-up. 3. Any pathological event, adverse event, or any change in the patient's status giving an indication to the physicians that further participation in the study may not be the best interest of the patient.
Variables:	**Primary outcome**: Cohort A (patients switched from VKA to Pradaxa®) • Mean PACT-Q2 scores at the second (30-45 days) and the last assessment (150-210 days) compared to baseline assessment. Cohort B (patients newly initiated Pradaxa® or VKA) • Mean PACT-Q2 scores at the second (30-45 days) and the last assessment (150-210 days) compared between 2 treatment groups. **Secondary outcome**: Cohort A (patients switched from VKA to Pradaxa®) • Mean PACT-Q2 score at the last assessment (150-210 days) compared to the second assessment (30-45 days). Cohort B (patients newly initiated Pradaxa® or VKA) • Description of mean PACT-Q1 score at baseline.

<table>
<tr><td></td><td>Characterization of patients from both cohorts according to:
• Demographics: Age, gender, race, education level, height, weight, and BMI
• Co-morbidities
• Concomitant therapies
• Stroke- and/or bleeding related risk factors in the medical history
• CHA_2DS_2-VASc score
• HAS-BLED score
• Kidney function (creatinine clearance)
• Dosing of Pradaxa® and the reasons for dose change
• Duration of previous VKA treatment (for Cohort A only)</td></tr>
<tr><td>Data sources:</td><td>Source data are collected from medical charts and the questionnaires (PACT-Q) completed by the enrolled subjects at approximately 20 medical centers or regional hospitals. A case report form will be designed for data collection.</td></tr>
<tr><td>Study size:</td><td>It is planned that approximately total 1000 patients from around 20 medical centers or regional hospitals will be recruited in the study. An estimated sub-group allocation basing on real-world practice in Taiwan includes approximately 300 patients in Cohort A (patients switched from VKA to Pradaxa®) and around 700 patients in Cohort B (patients newly initiated Pradaxa® or VKA), with about 500 patients receiving Pradaxa® and 200 patients receiving VKA. Consecutive enrolment will be performed to minimize selection bias. The actual number of patients in each cohort will be according to the patient distribution in the real-world practice.
<table>
<tr><td colspan="3">Total number</td><td>1000</td></tr>
<tr><td rowspan="3">Estimated number in sub-grouping</td><td colspan="2">Cohort A—VKA switches to Pradaxa®</td><td>300</td></tr>
<tr><td rowspan="2">Cohort B—Newly initiator</td><td>Pradaxa®</td><td>500</td></tr>
<tr><td>VKA</td><td>200</td></tr>
</table>
</td></tr>
</table>

Data analysis:	A Data Management Plan (DMP) and Statistical Analysis Plan (SAP) will be prepared to describe all processes, variables, and specifications for data collection, cleaning, validation, and analyses. The study is essentially descriptive. All patients who have signed the informed consent and fulfilled study criteria will be included in the main analysis. **Baseline demographic and clinical characteristics** Descriptive summary will be presented for all patients enrolled in Cohort A, Cohort B Pradaxa® initiators, and Cohort B VKA initiators, respectively. For continuous variables, number of patients, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum will be presented. For categorical variables, frequency and percentage will be presented for each category. **Primary outcomes** For Cohort A, the PACT-Q2 score at Visit 2 and Visit 3 will be compared with the PACT-Q2 score at baseline visit, respectively, using paired t-test or Wilcoxon signed-rank test. For Cohort B, the patients newly initiated Pradaxa® or VKA will be matched with a ratio of 1:1 based on the propensity score. The covariates will be included in the propensity score model if available. Descriptive summary of the baseline characteristics will be compared between the matched patients to check the balance of baseline characteristics between the two sub-groups of Cohort B after propensity score matching (PSM). Standardized difference will be calculated as a measure of the balance of baseline characteristics after PSM. Analyses of PACT-Q2 score will be performed on propensity score matched Pradaxa® initiators and VKA initiators. PACT-Q2 score will be compared between matched Pradaxa® initiators and VKA initiators using paired t-test or Wilcoxon signed-rank test. **Secondary outcomes** For Cohort A, the PACT-Q2 score at Visit 2 and Visit 3 will be compared using paired t-test or Wilcoxon signed-rank test based on the distribution of the data. For Cohort B, descriptive summary will be presented for PACT-Q1 score at baseline visit on all patients in Cohort B and by treatment (Pradaxa® or VKA).
Milestones:	• IRB/IEC approval: 17 July 2017 • Start of data collection: 07 August 2017 • End of data collection: 27 September 2018 • Final report of study results: 20 December 2018

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	17 July 2017
Start of data collection	07 August 2017
End of data collection	27 September 2018
Final report of study results	20 December 2018

7. RATIONALE AND BACKGROUND

Pradaxa® (dabigatran etexilate), one of the novel oral anticoagulants (NOACs), is a direct thrombin inhibitor first approved in Europe in 2008 for the prevention of stroke and systemic embolism in adult patients suffering from non-valvular atrial fibrillation (NVAF) with one or more risk factors. In 2010, the Food and Drug Administration (FDA) confirmed the findings of the RE-LY study in 18,000 patients, which led to the approval of Pradaxa® for stroke prevention in AF worldwide.[1,2,3] In 2014, the FDA reported the study results comparing Pradaxa® to warfarin in 134,000 patients, and concluded that Pradaxa® was associated with a significantly reduced risk of ischaemic stroke and intracranial bleeding and a significant survival benefit compared with warfarin in elderly patients with NVAF.[1] Similar results were found in other observational studies, showing Pradaxa® was effective and safe with low rates of cardiovascular or major bleeding events.[4,5,6]

According to the previous study results, the decision in clinical practice to use Pradaxa® or established vitamin K antagonists (VKAs) depends on many factors related to: (a) The patient: health status, comorbid and demographic conditions, perception of anticoagulant treatment, understanding of the burden of the disease, access to the medication, educational measures informing about medications, and reimbursement status. (b) The treating physician: stroke risk assessment, bleeding risk assessment, adherence to guidelines, access and use of medical education, and overall local health care system. These factors in the real-world clinical practice vary in countries with different health care systems; patients who newly start anticoagulation treatment versus those have had anticoagulation experience already; and the initiation versus the mid-term follow-up on Pradaxa®. According to National Health Insurance (NHI) in Taiwan, Pradaxa® is prescribed to a newly diagnosed NVAF patient with stroke or systemic embolism, left ventricular ejection fraction < 40%, symptomatic heart failure (New York Heart Association Class ≥ 2), age ≥ 75 years, or age ≥ 65 years with one of the following risk factors: diabetes mellitus, coronary artery disease (CAD), or hypertension. Pradaxa® should not be considered if the patient has valvular heart disease, stroke within 14 days, serious stroke within 6 months, the risk of increasing ischemia, creatinine clearance (CrCl) < 30 mL/min, active liver disease, or pregnant.

Although the clinical practice guide on the dosing and management of Pradaxa® is well established, the data on how patients perceive Pradaxa® treatment in the context of atrial fibrillation disease management only exist to a limited degree.[7] In the RE-LY study, over the course of one year, all the anticoagulated patients without outcome events (e.g. strokes or major bleedings) had stable results in Health-Related Quality of Life (HRQoL). To further describe patient's perception of anticoagulant treatment when using Pradaxa® to prevent stroke and systemic embolism while suffering from NVAF in comparison to standard care using VKA, some patient convenience studies are conducted in Europe (and and Asia at present. However, such a non-interventional study (NIS) observing patients treated with Pradaxa® for stroke prevention in atrial fibrillation (SPAF) to assess treatment satisfaction has not been conducted in Taiwan. Due to the limited data on patients' perception of conventional VKA or Pradaxa® treatment in real world experience (RWE), it remains an interesting topic to address. Therefore, the observational study is proposed to describe the perception of

anticoagulant treatment according to the questionnaire—PACT-Q in the cohorts of patients switching from VKAs to Pradaxa® or newly initiating Pradaxa®/VKAs.

8. RESEARCH QUESTION AND OBJECTIVES

Objective 1

To describe the treatment perception from patients with non-valvular atrial fibrillation (NVAF) receiving Pradaxa® or VKA for stroke prevention by using the self-estimation questionnaire of PACT-Q during a 6-month study period.

Objective 2

To investigate the patient's characteristics.

Two cohorts of patients will be recruited:

Cohort A:
Patients who had been treated with VKA and have switched to Pradaxa®.

Cohort B:
Patients who are newly diagnosed with NVAF and initiated on either Pradaxa® or VKA.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, single-country, multi-center study based on newly collected data. The study will enroll consented patients with NVAF in Taiwan with a previous VKA therapy, followed by switching to Pradaxa® (Cohort A) OR patients being newly diagnosed with NVAF and initiated on Pradaxa® or VKA (Cohort B). Patients will be followed up over an observation period of 6 months. Data will be collected at 3 time points:

1. Baseline (e.g., the enrolment date for Cohort A; the date of initiation on Pradaxa® or VKA for Cohort B).
2. 30 to 45 days after baseline (initiation period).
3. 150 to 210 days after baseline (continuation period).

9.2 SETTING

It is planned that data of approximately 1000 patients will be collected from approximately 20 medical centers or regional hospitals in Taiwan where Pradaxa® taken as one 110/150 mg capsule twice a day is listed as a prescription of SPAF in hospital formulary. Patients diagnosed with NVAF before the patient's baseline (inclusion) visit will be consecutively enrolled in the study. Selected subjects must meet all of the eligibility criteria described in Section 9.2.2.

After study initiation, the sites will include suitable patients where the decision for switching from VKA to Pradaxa® (Cohort A) or decision for initiation with Pradaxa® or VKA (Cohort B) has been made. Consecutive enrolment will be performed during whole recruitment period to minimize selection bias in the real-world practice.

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

9.2.1 Study sites

Cardiologist and non-cardiologist sites regularly prescribing Pradaxa® and VKA for stroke prevention in NVAF according to the respective Summary of Product Characteristics (SmPCs) will participate.

Selected sites include around 20 medical centers or regional hospitals in Taiwan, from Northern to Southern area, with physicians and facilities that reflect the locally clinical practice. The site selection criteria will help to ensure that the patients recruited into this study will represent the population with NVAF receiving Pradaxa® or VKA for stroke prevention in Taiwan.

9.2.2 Study population

Inclusion criteria

Cohort A (patients switched from VKA to Pradaxa®)

1.A. Written informed consent prior to participation.

2.A. Female or male patients ≥ 20 years of age with a diagnosis of non-valvular atrial fibrillation (NVAF).

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

4.A. Patients switched to Pradaxa® prior to baseline assessment according to the physician's discretion and the Summary of Product Characteristics (SmPCs)/reimbursement criteria.

OR

Cohort B (patients newly initiated Pradaxa® or VKA)

1.B. Written informed consent prior to participation.

2.B. Female or male patients ≥ 20 years of age, newly diagnosed with NVAF, and no previous treatment for stroke prevention (no use of any OAC within 1 year prior to enrolment).

3.B. Patients initiated stroke prevention treatment with Pradaxa® or VKA according to the physician's discretion and the SmPCs/reimbursement criteria.

Exclusion criteria

1. Contraindication to the use of Pradaxa® or VKA as described in the SmPCs.
2. Patients receiving Pradaxa® or VKA for any other condition than stroke prevention in NVAF.
3. Current participation in any clinical trial of a drug or device.
4. Current participation in an AF-related registry, e.g. the Gloria AF program.

Withdrawal criteria

Every patient has the right to withdraw consent at any time during the study, without the need for justification or any impact on the routine therapy. A patient is considered permanently discontinued or withdrawn from treatment if he/she does not complete the treatment with Pradaxa® or VKA in the 6-month study period or did not perform all three assessments. Withdrawal criteria includes:

1. Patients withdraw informed consent.
2. Patients lost to follow-up.
3. Any pathological event, adverse event, or any change in the patient's status giving an indication to the physicians that further participation in the study may not be the best interest of the patient.

9.2.3 Study visits

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, no visit 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 (PACT-Q). The planned collection time points are as follows:

1. Baseline (e.g., the enrolment date for Cohort A; the date of initiation on Pradaxa® or VKA for Cohort B)
2. 30 to 45 days after baseline (initiation period)
3. 150 to 210 days after baseline (continuation period)

Data will be collected and recorded on the CRF at baseline and follow-up visits according to **Table 1**, if available.

Remark: This is a non-interventional, observational study, all the tests collected at baseline and subsequent visits will be performed as judged appropriate by the treating physicians, and the results of interest will be recorded only if they are available. This study does not require additional tests or examinations to be performed throughout the entire study period.

Baseline visit (Visit 1):

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, and data will be collected from the medical chart and recorded on the CRF, **if available**:

- Sign informed consent form.
- Review of inclusion and exclusion criteria, and record date of inclusion.
- Collection of reimbursement status (reimbursed, partially reimbursed, or private pay).
- Collection of demographic data: age, gender, race, education level, height, weight[&], and BMI.
  [&]Weight will be used to calculate BMI and creatinine clearance (CrCl).
- Collection of concomitant diseases/comorbidities in the medical history and at baseline.
- Collection of concomitant diseases/comorbidities,[8] risk factors,[9,10] and medical history related to NVAF prior to enrolment, including diabetes mellitus, hypertension, ischaemic heart disease, congestive heart failure, left ventricular dysfunction, stroke, transient ischaemic attack, thromboembolism, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), abnormal renal function,

abnormal liver function (e.g. cirrhosis), bleeding (e.g. prior major bleeding, predisposition to bleeding/anemia), and alcohol usage. These data will be used to calculate CHA_2DS_2-VASc score and HAS-BLED score[#].

- Collection of current concomitant therapies within 1 month prior to enrolment. Detail information (e.g. indication, start/stop date or ongoing, dosage, route, unit, and frequency etc.) will be recorded if available.
  - For the concomitant therapy as an element for CHA_2DS_2-VASc score or HAS-BLED score calculation,[9,10] including chronic dialysis or renal transplant due to abnormal renal function and medication usage predisposing to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs (NSAIDs)), information prior to enrolment will only be collected as **active/past or never occurred**.
- Collection of serum creatinine, if available, to calculate creatinine clearance (CrCl). The most updated data of serum creatinine assessed prior to enrolment will be collected. CrCl will be calculated according to Cockcroft-Gault formula (using weight collected at the baseline visit and the most updated serum creatinine assessed prior to enrolment).
- Collect the most updated data of lab assessment assessed prior to enrolment for CHA_2DS_2-VASc score and HAS-BLED score calculation.[9,10] The lab assessments include renal function test (CrCl, as described above), liver function tests (bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP)), and international normalized ratio (INR), including prothrombin time (PT).
- For Cohort A only: Collect duration of previous treatment with VKA.
- For Cohort A only: Collect reasons for switching from VKA to Pradaxa®.
- Document the dosing of Pradaxa®.
- Patients will be asked to complete the following patient related questionnaires:
  - PACT-Q1 (Cohort B only)
  - PACT-Q2 (Cohort A only)
- Conduct safety reporting for Pradaxa® relevant adverse drug reaction (serious, non-serious), fatal AEs, and pregnancies; and record them on corresponding ADR forms and CRF pages.
- Complete the screening log for all patients that do not qualify at baseline*.
- Complete required CRFs.

[#]*Information to be collected, whenever available, for CHA_2DS_2-VASc score and HAS-BLED score calculation*

Age, gender, and part of concomitant diseases/comorbidities, risk factors, medical history, concomitant therapies, and lab assessments will be collected for the CHA_2DS_2-VASc score and HAS-BLED score calculation, **if available**. The data time frame on medical chart is defined as below:

- Demographics (age and gender): at the baseline visit.
- Comorbidities, risk factors, medical history, and concomitant therapies: prior to enrolment.

- Lab assessment: the most updated data conducted prior to enrolment, if regular practice available.

The description of scoring CHA_2DS_2-VASc and HAS-BLED is summarized in Section 9.3.4.

**Information to be collected on screening failures*

The screening log entry with demographic information and the primary reason for not continuing or ineligibility must be completed for all screened patients that do not qualify for baseline visit (Visit 1). No CRF other than the screening log will be collected for these patients. The subject number of these ineligible patients should be kept, and the following enrolments will be numbered in sequence.

Initiation period (Visit 2):

During a routine practice visit occurring at 30 to 45 days after baseline, the following assessments will be documented, **if available**:

- Weight will be recorded to calculate creatinine clearance (CrCl).
- New or changed concomitant diseases/comorbidities.
- Changes in concomitant therapies.
- Collection of serum creatinine, if available, to calculate creatinine clearance (CrCl). Serum creatinine assessed within 30 to 45 days after enrolment will be collected. CrCl will be calculated according to Cockcroft-Gault formula (using weight collected at Visit 2 and serum creatinine assessed within 30 to 45 days after enrolment).
- Collect dosing of Pradaxa® and reasons for dose change (if applicable).
- Patients will be asked to complete the PACT-Q2 questionnaire.
- Reasons for Pradaxa® or VKA discontinuation (if applicable).
- Conduct safety reporting for Pradaxa® relevant ADR (serious, non-serious), fatal AEs, and pregnancies; and record them on corresponding ADR forms and CRF pages.
- Complete required CRFs.

Continuation period (Visit 3):

During a routine practice visit occurring at 150 to 210 days after baseline, the following assessments will be documented, **if available**:

- Weight will be recorded to calculate creatinine clearance (CrCl).
- New or changed concomitant diseases/comorbidities.
- Changes in concomitant therapies.
- Collection of serum creatinine, if available, to calculate creatinine clearance (CrCl). Serum creatinine assessed within 150 to 210 days after enrolment will be collected. CrCl will be calculated according to Cockcroft-Gault formula (using weight collected at Visit 3 and serum creatinine assessed within 150 to 210 days after enrolment).
- Collect dosing of Pradaxa® and reasons for dose change (if applicable).
- Patients will be asked to complete the PACT-Q2 questionnaire.

- Reasons for Pradaxa® or VKA discontinuation (if applicable).
- Conduct safety reporting for Pradaxa® relevant ADR (serious, non-serious), fatal AEs, and pregnancies; and record them on corresponding ADR forms and CRF pages.
- Complete required CRFs.

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

Table 1 is the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most NVAF patients for stroke prevention. The sign "X" indicates when the data will be collected if available.

Table 1 Data Collection Schedule

Visit	**1**	**2**	**3**
Assessment	Baseline	Initiation period	Continuation period
Day(s) and allowed window*	1	30 to 45	150 to 210
Informed consent[1]	X		
Inclusion/exclusion criteria	X		
Reimbursement status[2]	X		
Patient demographics[3]	X		
Weight[4]	X	X	X
Concomitant diseases/comorbidities	X	X	X
Comorbidities, risk factors, and medical history related to NVAF[5]	X		
Concomitant therapies[6]	X	X	X
Concomitant therapies related to CHA_2DS_2-VASc and HAS-BLED[7]	X		
Collection of serum creatinine to calculate creatinine clearance[8]	X	X	X
Collection of lab data related to CHA_2DS_2-VASc and HAS-BLED[9]	X		
CHA_2DS_2-VASc score	X		
HAS-BLED score	X		
Duration of previous VKA treatment (Cohort A only)	X		
Reasons for switching from VKA to Pradaxa® (Cohort A only)	X		
Record Pradaxa® dosing (110 or 150mg) and reasons for dose changes if applicable	←	—	→
PACT-Q1 questionnaire	X (Cohort B only)		
PACT-Q2 questionnaire	X (Cohort A only)	X (both cohorts)	X (both cohorts)
Reason for Pradaxa® or VKA discontinuation	←	—	→
Safety reporting[10]	←	—	→

*Only lab data assessed within the following allowed window and according to regular practice will be collected:
-Baseline: the most updated data conducted prior to enrolment
-Visit 2: within 30-45 days after baseline
-Visit 3: within 150-210 days after baseline

1. Written informed consent must be obtained prior to the baseline visit assessment.
2. Reimbursement status includes reimbursed, partially reimbursed, or private pay.
3. Age, gender, race, education level, height, weight, and BMI.
4. Weight will be recorded at each visit if possible to calculate BMI (baseline only) and creatinine clearance.
5. Comorbidities, risk factors, and medical history related to NVAF include: diabetes mellitus, hypertension, ischaemic heart disease, congestive heart failure, left ventricular dysfunction, stroke, transient ischaemic attack, thromboembolism, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), abnormal renal function, abnormal liver function (e.g. cirrhosis), bleeding (e.g. prior major bleeding, predisposition to bleeding/anemia), and alcohol usage. The data prior to enrolment will be collected.
6. The current concomitant therapies within 1 month prior to enrolment will be collected. Changes in concomitant therapies will be collected at Visit 2 and Visit 3.
7. The concomitant therapies related to CHA_2DS_2-VASc and HAS-BLED score prior to enrolment will be collected, including chronic dialysis or renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs (NSAIDs)).
8. Serum creatinine assessment conducted within the allowed window of lab assessment* will be collected to calculate CrCl according to Cockcroft-Gault formula.
9. The lab assessments include: renal function test (serum creatinine, same as the collection of CrCl at baseline described in #8), liver function tests (bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP)), and international normalized ratio (INR, including prothrombin time (PT)). Only the most updated results of assessments conducted prior to enrolment will be collected.
10. Pradaxa® relevant ADR (serious and non-serious), fatal AEs, and pregnancies.

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. Emergence of any efficacy/safety information that could significantly affect the continuation of the study, or any other administrative reasons.
3. 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

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

9.3 VARIABLES

9.3.1 Exposures

Currently, Pradaxa® and VKA have been approved for treating NVAF patients for stroke prevention. The use of Pradaxa® and VKA will be according to the SmPCs and physician´s discretion. Prescription of Pradaxa® will be collected and recorded on the CRF during the

observational period, if available, including start/end date, dose, and the reason for dose adjustment or interruption.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Cohort A (patients switched from VKA to Pradaxa®)

- Mean PACT-Q2 scores at the second (30-45 days) and the last assessment (150-210 days) compared to baseline assessment.

Cohort B (patients newly initiated Pradaxa® or VKA)

- Mean PACT-Q2 scores at the second (30-45 days) and the last assessment (150-210 days) compared between 2 treatment groups.

9.3.2.2 Secondary outcome

Cohort A (patients switched from VKA to Pradaxa®)

- Mean PACT-Q2 score at the last assessment (150-210 days) compared to the second assessment (30-45 days).

Cohort B (patients newly initiated Pradaxa® or VKA)

- Description of mean PACT-Q1 score at baseline.

9.3.3 Covariates

Demographic and clinical characteristics, including age, gender, body weight, CHA2DS2-VASc score, HAS-BLED score, kidney function (creatinine clearance), stroke and/or bleeding related risk factors, co-morbidities, and/or concomitant therapies will be collected if available. If any covariates or confounding/interacting variables that may be possibly predictive of the outcome under study are noted, additional analyses may be carried out to identify its effect. Details of handling covariates will be given in the statistical analysis plan (SAP), if any covariates of interest are detected.

9.3.4 Baseline characteristics and general information

Baseline characteristics of patients include:

- Demographics: Age, gender, race, education level, height, weight, and BMI
- Comorbidities
- Concomitant therapies
- Stroke- and/or bleeding related risk factors in the medical history
- CHA_2DS_2-VASc score
- HAS-BLED score
- Kidney function (creatinine clearance)
- Dosing of Pradaxa® and the reasons for dose change
- Duration of previous VKA treatment (for Cohort A only)

For the following 6 sections, data collection detail is described in Section 9.2.3.

1. Concomitant diseases/comorbidities

All the concomitant diseases/comorbidities in the medical history will be collected at Baseline visit (Visit 1). Newly occurred or changed concomitant diseases/comorbidities compared with the previous visit will be collected at the initiation period (Visit 2) and the continuation period (Visit 3).

2. Comorbidities/Risk factors/Medical history related to NVAF[8]

For the comorbidities/risk factors/medical history related to NVAF, the status (active/past or never occurred, no retrospective time limit is set) should be documented at enrolment, if available. The comorbidities/risk factors/medical history related to NVAF include diabetes mellitus, hypertension, ischaemic heart disease, heart failure, stroke, transient ischaemic attack, and thromboembolism.

3. Concomitant therapies

Current concomitant therapies within 1 month prior to enrolment will be collected. Changes in concomitant therapies compared with the previous visit will be collected at the initiation period (Visit 2) and the continuation period (Visit 3). Data of interest include start/stop date or ongoing, dose, unit, and frequency.

For the concomitant therapy as an element for the CHA2DS2-VASc score or HAS-BLED score calculation, including chronic dialysis or renal transplant due to abnormal renal function and medication usage predisposing to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs (NSAIDs)), information will only be collected as active/past or never occurred prior to enrolment (no retrospective time limit is set).

4. Calculation of CHA_2DS_2-VASc score[9]

The CHA_2DS_2-VASc score is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF. The CHA_2DS_2-VASc score is composed of 8 items with a maximum score of 9. Among all the items, 2 of them have extra weight with 2 points,

including “age 75 and above” and “stroke, transient ischemic attack, and thromboembolism”, while the other 6 items are counted as 1 point of each. A higher score corresponds to a greater risk of stroke. The available information for verifying the items in CHA_2DS_2-VASc score will be collected from source data and will be recorded on the CRFs. The CHA_2DS_2-VASc score will be calculated according to **Table 2**.

Table 2 The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2-VASc

Letter	Clinical Characteristic	Score
C	Congestive heart failure or left ventricular dysfunction	1
H	Hypertension	1
A_2	Age ≥ 75 years	2
D	Diabetes Mellitus	1
S_2	Previous stroke, transient ischemic attack, or thromboembolism	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

5. Calculation of HAS-BLED score[10]

HAS-BLED is a scoring system developed to assess 1-year risk of major bleeding in patients with AF. The HAS-BLED score is composed of 7 items with a maximum score of 9. Among all the items, 2 of them will be scored with 1 or 2 points depending on the number of corresponded description, including “abnormal renal and liver function” and “drugs or alcohol”, while the other 5 items are counted as 1 point of each. A higher score corresponds to a greater risk of bleeding, and a score of ≥ 3 points indicates "high risk". The available information for verifying the items in HAS-BLED score will be collected from source data and will be recorded on the CRFs. The HAS-BLED score will be calculated according to **Table 3**.

Table 3 Clinical Characteristics Composing the HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristic	Score
H	Hypertension[1]	1
A	Abnormal renal function[2] and abnormal liver function[3] (1 point each)	1 or 2
S	Stroke[4]	1
B	Bleeding[5]	1
L	Labile INRs[6]	1
E	Elderly, age > 65 years	1

D	Drugs or alcohol (1 point each)[7]	1 or 2

1. Hypertension should be uncontrolled, with systolic blood pressure > 160 mmHg.
2. Abnormal kidney function is classified as a presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 200 µmol/L.
3. Abnormal liver function is defined as the chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/AP > 3 × upper limit normal, and so forth.)
4. Previous history, particularly lacunar.
5. Bleeding history, such as prior major bleeding or predisposition to bleeding (e.g., anemia).
6. Labile international normalized ratio (INR, e.g., therapeutic time in range < 60%).
7. Drugs are medication usage predisposing to bleeding (e.g. antiplatelet agents or NSAIDs). Ethanol abuse is classified as ≥ 8 units of alcoholic consumption per week.

6. Calculation of creatinine clearance (CrCl)

Kidney function will be evaluated according to creatinine clearance (CrCl). Serum creatinine available from medical chart and weight assessed according to the visit schedule will be collected to calculate the CrCl value by Cockcroft-Gault formula*. In addition, only serum creatinine data assessed within the allowed window will be collected. The allowed window at each visit is listed as below:

- Baseline: the most updated data assessed prior to enrolment
- Visit 2 (initiation period): within 30-45 days after baseline
- Visit 3 (continuation period): within 150-210 days after baseline

*Cockcroft-Gault formula:

If the information of serum creatinine and weight are both collected and recorded on the CRFs, the CrCl will be calculated via Cockcroft-Gault formula which could be measured in different serum creatinine units (mg/dL or µmol/L):[11,12]

- When serum creatinine is measured in mg/dL:

  The resulting value is multiplied by a constant of 0.85 if the patient is female.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

- When serum creatinine is measured in µmol/L:

  Constant is 1.23 for male and 1.04 for female.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

9.3.5 Description and justification of patient questionnaires (PACT-Q©)

The Perception of Anticoagulant Treatment Questionnaire (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).[13,14] The PACT-Q is a self-administered questionnaire. It can be completed in about 10 minutes. No specific training is required to complete this document.

The original PACT-Q consists of 2 parts and contains 27 items:

1. 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. Only patients in Cohort B (newly initiator) will receive the PACT-Q1 questionnaire at baseline.
2. The PACT-Q2 is composed of 3 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. The patients in Cohort A (switchers) will receive PACT-Q2 at all the 3 visits, while the ones in Cohort B (initiators) will receive the questionnaire at Visit 2 and Visit 3.

9.4 DATA SOURCES

As this is a non-interventional study, no diagnostic or monitoring procedures additional to the standard of care and routine practice will be applied to the patients. All the assessment will be performed by the investigator if they are deemed necessary for the medical treatment procedure.

This non-interventional study will collect the data onto the designed paper case report form (CRF) if available by the investigators or delegated site staffs. Data source includes patient questionnaires (PACT-Q), hospital discharge files, abstracts of primary clinical records, electronic medical records, ad hoc clinical databases, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, etc. during the routine clinical practice.

Each patient is identified by a unique central patient identification code, which is only used for study purposes.

9.5 STUDY SIZE

It is planned that approximately 1000 patients from around 20 medical centers or regional hospitals will be recruited in the study. An estimated sub-group allocation basing on real-world practice in Taiwan includes approximately 300 patients in Cohort A (patients switched from VKA to Pradaxa®) and around 700 patients in Cohort B (patients newly initiated Pradaxa® or VKA), with about 500 patients receiving Pradaxa® and 200 patients receiving VKA. Consecutive enrolment will be performed during whole recruitment period to minimize selection bias. The actual number of patients in each cohort will be according to the patient distribution in the real-world practice.

Total number			1000
Estimated number in sub-grouping	**Cohort A**—VKA switches to Pradaxa®		300
	Cohort B—Newly initiator	Pradaxa®	500
		VKA	200

9.6 DATA MANAGEMENT

The data from enrolled patients in this study will be recorded on a CRF or other applicable forms. The designated CRO will capture, check, store and analyze the data. The designated CRO will follow Boehringer Ingelheim standard operating procedures (SOPs) and their own internal SOPs.

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning, and validation.

Data will be transferred to Boehringer Ingelheim after the closure of the study.

9.7 DATA ANALYSIS

Analyses will be performed by a designated CRO. The main analysis population will consist of all eligible patients (i.e. all patients who have signed the informed consent and fulfilled all inclusion criteria and no exclusion criteria). In addition, all eligible patients will be categorized into Cohort A (patients switched from VKA to Pradaxa®) and Cohort B (patients newly initiated Pradaxa® or VKA). Cohort B will be further classified into 2 groups, the Pradaxa® initiators or the VKA initiators. The 2 cohorts and the 2 subgroups will be used in corresponding PACT-Q analyses.

Analytic specifications, including tables and listings, will be detailed in the statistical analysis plan (SAP) that is separate from the full study protocol.

Statistical analysis of all data will be performed using the latest version of SAS® statistical software (SAS Institute, Cary, NC, USA). All statistical tests are two sided and statistical significance level of 0.05 will be used.

9.7.1 Main analysis

Baseline demographic and clinical characteristics

Descriptive summary will be presented for baseline demographic and clinical characteristics of all patients enrolled in Cohort A, Cohort B Pradaxa® initiators, and Cohort B VKA initiators, respectively. For continuous variables, number of patients, mean, standard deviation (SD), median, Q1 (lower quartile), Q3 (upper quartile), minimum, and maximum will be presented. For categorical variables, frequency and percentage will be presented for each category.

Primary outcomes

For Cohort A, descriptive summary will be presented for PACT-Q2 score at baseline visit (Visit 1), Visit 2, and Visit 3 using measure of central tendency and variation (mean ± SD, or median with inter-quartile range (IQR)). The PACT-Q2 score at Visit 2 and Visit 3 will be compared with the PACT-Q2 score at baseline visit, respectively, using paired t-test or Wilcoxon signed-rank test based on the distribution of the data.

For Cohort B, the patients newly initiated Pradaxa® or VKA will be matched with a ratio of 1:1 based on the propensity score. The covariates age, gender, body weight, CHA_2DS_2-VASc score, HAS-BLED score, kidney function (creatinine clearance), stroke and/or bleeding related risk factors, co-morbidities, and/or concomitant therapies, **if available**, will be included in the propensity score model. Details of the propensity score model and the matching procedure, such as the choice of algorithm and caliper width will be specified in the SAP. Descriptive summary of the baseline characteristics will be presented for and compared between the matched patients to check the balance of baseline characteristics between the two groups of Cohort B after propensity score matching. Moreover, standardized difference will be calculated as a measure of the balance of baseline characteristics after propensity score matching. Analyses of PACT-Q2 score will be performed on propensity score matched Pradaxa® initiators and VKA initiators. Descriptive summary will be presented for PACT-Q2 score at Visit 2 and Visit 3 using mean ± SD, or median with IQR. PACT-Q2 score will be compared between matched Pradaxa® initiators and VKA initiators using paired t-test or Wilcoxon signed-rank test.

Secondary outcomes

For Cohort A, the PACT-Q2 score at Visit 2 and Visit 3 will be compared using paired t-test or Wilcoxon signed-rank test based on the distribution of the data.

For Cohort B, descriptive summary will be presented for PACT-Q1score at baseline visit using mean ± standard deviation, or median with IQR, and will be performed on all patients in Cohort B and by treatment (Pradaxa® or VKA).

9.7.3 Safety analysis

Safety analyses will be performed separately for Cohort A and Cohort B, and will include all enrolled patients with an actual follow-up. Statistical analysis and reporting of AEs (i.e. Pradaxa® relevant ADR (serious and non-serious), fatal AEs, and pregnancies) will be descriptive in nature and based on BI standards. No hypothesis testing is planned. The assessment of safety will be based mainly on the frequency of adverse events, which includes

all serious adverse events. All adverse events will be summarized with the coding term, severity, and relationship to study drug by frequency tables with the counts and percentage.

In addition, occurrences of Pradaxa® relevant ADRs will be analyzed relative to the number of patients treated as well as observed person-years (i.e. time at risk). If no concurrent Pradaxa® treatment is administered, then events occurring within a washout period of 3 days after discontinuation of Pradaxa® 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 Pradaxa® treatment prescribed at baseline, during periods without Pradaxa® 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.

Furthermore, serious adverse events will be listed with event narration. Adverse events will be coded using the latest version of Medical dictionary for regulatory activities (MedDRA) terminology.

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

9.7.4 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 SAP.

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 are lost to follow-up in comparison to patients who have completed follow-up.

9.8 QUALITY CONTROL

Before the study launch, participating physicians will be trained on the protocol, safety reporting (as described in Section 11) and study conduct procedures by Boehringer Ingelheim (or designee).

In keeping with the non-interventional design employed in this study, site interaction (e.g., direct contact between site study staff or patients and representatives of the call center or the Study Coordinating Center) is minimized.

Twenty percent source data verification is planned in this study. At any time during the course of the study, the site study staff may contact designated personnel for clarification of study conduct. All information will be kept confidential.

During the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the clinical database has been declared to be complete and accurate, it will be locked.

To ensure the data accuracy, completeness, and reliability, quality control will be the ongoing, concurrent review of data collection forms for completion and logic. The research staffs will preserve documented data from all sources on CRF, including lab test results, chart records, treatment conditions, physical examination, concomitant medication, and any safety information.

Boehringer Ingelheim or designated CRO will assure database quality processes are followed including the review of the data entered into the CRFs by investigational staffs for completeness and accuracy, and in accordance with the data validation plan.

9.9 LIMITATIONS OF THE RESEARCH METHODS

A non-interventional study is the most suitable design for obtaining information about the use of medicines in everyday therapeutic practice and thus for clarifying questions in everyday therapeutic practice. However, observational methodology inherits the limitation of selection bias and generalizability. In addition, the observational design intends to collect available data that are recorded on medical charts. The lack of data of interest may be one of the limitations.

A number of different types of bias that could influence the data collection and analysis from these cohorts are summarized below. Consecutive enrolment will be employed to minimize selection bias. The entry criteria are non-restrictive and will permit the enrolment of a broad patient population. The choice of treatment is at the discretion of the investigator. Missing data will be handled as appropriate (see Section 9.7.4) to lower the effect of missing values. All efforts will be made to minimize loss to follow-up in patients who are enrolled. Adjustment for covariates and propensity score matching (PSM) will be used to correct for identified confounders and channeling bias which could 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). Patient reported outcomes will be assessed using validated questionnaires within a limited period of time to minimize recall bias which 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.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

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

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via paper. All paper CRFs should be typed or filled out with a black ball-point pen and must be legible.

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Authority Form. No erasers, correction fluid, or tape may be used.
- The principal investigator will sign and date the indicated places on the CRFs. These signatures will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

9.10.2.1 Source documents

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data).

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

For paper CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth, etc.)
- 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 concomitant diseases and concomitant, if applicable)

- Adverse drug reactions and outcome events (onset date [mandatory], and end date [if available])
- fatal adverse events (SAEs) (onset date (mandatory), and end date (if available))
- Pregnancy record
- Originals or copies of laboratory results or examinations (in validated electronic format, if available)
- Conclusion of Patient's Participation in the study

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Authority Form.

No information in source documents about the identity of the patients will be disclosed. No study document should be destroyed without prior written agreement between Boehringer Ingelheim and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Boehringer Ingelheim in advance.

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes, 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. US Food and Drug Administration [FDA]). The Clinical Research Associate (CRA)/Clinical Monitor Local (CML) and the auditor may review all CRFs 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

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 Harmonized 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 finalization of the Study Report and consent from sponsor.

Insurance Cover: The requirements for insurance depend on local law and legislations. 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).

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 to 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. Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate

assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

The patient must be informed that his/her medical records may be examined by authorized 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.

No subject names will be supplied to Boehringer Ingelheim or other responsible parties. Only the subject number and subject initials will be recorded on the CRF, and if the subject's name appears on any other document (e.g., laboratory report), it must be obliterated before a copy of the document is supplied to Boehringer Ingelheim or other responsible parties. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

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. All personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can, therefore, be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. The 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 the 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 is defined as any AE which

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization

or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse event of special interest (AESI)

The term 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 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 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 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 should carefully assess 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 the pattern of reaction, temporal relationship, de-challenge or re-challenge, and 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 the 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:

Type of Report	Timeline
All **serious ADRs** 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	7 calendar days

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

Results of this non-interventional study will be disclosed on external websites according to BI SOP. 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 finalization of the study report.

13. REFERENCES

13.1 PUBLISHED REFERENCE

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anticoagulant treatment: the 'Perception of Anticoagulant Treatment Questionnaire' (PACT-Q). Health Qual Life Outcomes 7, 9 (2009)

13.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	Not applicable	23 September 2016	PACT-Q1 - Taiwan/Mandarin
2	Not applicable	23 September 2016	PACT-Q2 - Taiwan/Mandarin

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

As attached.

ANNEX 3. ADDITIONAL INFORMATION

None.