Statistical Analysis Plan

Patients' **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)

PROTOCOL NO.	**1160-0286**
SAP VERSION	**V1.0**
SAP DATE	**Feb-18-2019**
SPONSOR	**Boehringer Ingelheim**
PREPARED BY	

CONFIDENTIAL

1 TITLE PAGE

Patients' **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)

PROTOCOL NO.	1160-0286
INVESTIGATIONAL DRUG	Dabigatran etexilate (Pradaxa®)
INDICATION	Stroke in Atrial Fibrillation
SPONSOR	Boehringer Ingelheim
PRINCIPAL INVESTIGATOR(S)	Dr. XXX-XXX XXX XXX Hospital
DATE OF FIRST ENROLLMENT	Jun-23-2017
DATE OF STUDY COMPLETION (LAST PATIENT LAST VISIT):	Jan-25-2019
DATE OF DATABASE LOCK	Expected on Apr-03-2019
SAP VERSION/DATE:	V1.0/Feb-18-2019

This study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents.

2   SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE

Patients' **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)

INVESTIGATIONAL DRUG	Dabigatran etexilate (Pradaxa®)
PROTOCOL NO.	1160-0286
SAP VERSION/DATE	V1.0/Feb-18-2019
SPONSOR	Boehringer Ingelheim
BUSINESS FUNCTION	/ of Medical Affairs

_____   _____
Signature   Date

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
CHA2DS2-VASc score	Congestive heart failure, Hypertension, Age (≥75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex category
CDMS	Clinical Data Management Systems
CRF	Case Report Form
CRO	Contract Research Organization
CrCl	Creatinine Clearance
CSR	Clinical Study Report
DM	Data Management
DVP	Data Validation Plan
GCP	Good Clinical Practice
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 on Harmonization
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
NVAF	Non-Valvular Atrial Fibrillation
PACT-Q©	Perception of Anticoagulant Treatment Questionnaire
PMS	Post-Marketing Surveillance
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System®

SOC	System Organ Class
SOP	Standard Operating Procedure

DRAFT

5 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final protocol 1160-0286 dated 15 March 2017 (version 1.0) and the protocol administrative memorandums that have been approved by Institutional Review Board (IRB). The SAP provides details on the planned statistical methodology for analysis of the study data, and also outlines the statistical programming specifications for the tables. It describes the safety variables, anticipated data transformations, manipulations, coding, and other details of the analyses not provided in the study protocol. A detailed description of the planned table and figures to be presented in the clinical study report (CSR) is provided in the accompanying mock-up tables documents. This SAP only covers the planned analysis of all safety and efficacy data collected on paper (source documents) and captured in case report forms (CRFs).

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports".

6   STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

<u>Objective 1</u>

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.

<u>Objective 2</u>

To investigate the patient's characteristics.

Two cohorts of patients will be recruited:

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

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

6.2 Endpoints

6.2.1   Primary Endpoint(s)

<u>Cohort A</u> (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.

<u>Cohort B</u> (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.

6.2.2   Secondary Endpoints

<u>Cohort A</u> (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).

<u>Cohort B</u> (patients newly initiated Pradaxa® or VKA)

- Description of mean PACT-Q1 score at baseline.

6.2.3 Safety Endpoints

- AEs (i.e. Pradaxa® relevant ADR (serious and non-serious), fatal AEs, and pregnancies)

Safety analyses will be performed separately for Cohort A and Cohort B.

7 STUDY METHOD

7.1 Overall Study Design and Plan

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).*

7.1.1 Schedule of Assessments

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.

However, below 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 7.1 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.

7.2 Selection of Population and Inclusion/Exclusion Criteria

7.2.1 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.

7.2.2 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.

7.3 Randomization and Blinding

This is a non-interventional, observational, and post-marketing study. Randomization and blinding are not applicable.

7.4 Sample 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

8   GENERAL CONSIDERATIONS

8.1 Relevant SOPs and Policies

The data management (DM) will carry out verification procedures upon double data entry completion. Data entered in the first database has to be verified against the data entered in the second database for comparison and verification purposes. All discrepancies shall be recorded and data verification output shall be generated after this process. The data management will verify the discrepancies between first entry and second entry against the hard copy CRF. All verified data must be uploaded to the updated database(s). Data verification output and relevant records will be stored properly and securely.

To ensure the data reliability, data management will validate data based on data validation plan and reconfirm those unreliable values for all collected data includes safety and efficacy data. The locked data will be treated as the analyzable data.

Statistical Analysis Plan (SAP) will be developed from first patient enrollment. The draft SAP

will be issued based on the approved protocol, approved amendments and the CRF.

All process will follow the relevant SOPs as follow:

DM 1709	Data Entry Procedure
DM 1710	Data Verification Procedure
DM 1711	Data Validation Procedure
DM 1712	Data Clarification Procedure
DM 1713	Data Lock Procedure
DM 1719	Statistical Analysis Plan

8.2 Timing of Analyses

The final analysis will take place when all enrolled patients complete the study or permanently discontinued from the study. After the relevant data management processes are completed and data clean status is claimed, the database will be locked. The final analysis will be conducted based on the lock data.

8.3 Analysis Populations

In this study, there will be two populations, Full Analysis Set (FAS), and Safety population set up for analysis. The populations for analysis applied into this study are defined as following:

Full Analysis Set (FAS)

All eligible patients.

Safety Population

All enrolled patients with an actual follow-up.

8.4 Covariates and Subgroups

Demographic and clinical characteristics, including age, gender, BMI classification (BMI<18.5, 18.5≤BMI<24, 24≤BMI<27, BMI≥27), CHA2DS2-VASc score, HAS-BLED score, kidney function (creatinine clearance), stroke and/or bleeding related risk factors, will be

considered as covariates/predictors for conducting propensity score matching the two subgroups in cohort B.

8.5 Missing Data

No imputation method will be performed to estimate the missing values for efficacy and safety variables.

8.6 Interim Analyses and Data Monitoring

Interim analysis is not defined in protocol and will not be performed in this study.

8.7 Adjustments for Multiplicity

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). There will be no multiple comparisons in this study. As a result, adjustment for multiplicity is not applicable in the analysis.

8.8 Multi-center Studies

1000 patients will be enrolled from 20 sites in Taiwan. With the intention of pooling the data for analysis, all the investigators from participating institutions will follow the study protocol and conduct the clinical trial to improve the consistency across centers. All the data defined on CRF will be collected and managed via a centralized process. The collected clinical data will be summarized with respect to demographic characteristics, and efficacy and safety observations.

8.9 Data Management System and Analysis Software

The data collected will be entered into the study database against the paper CRF and stored in the Clinical Data Management Systems (CDMS). The data backup is exhibited by data management personnel. The data will be exported to Statistical Analysis System® (SAS) for Windows (Version 9.4 or higher, SAS Institute, Cary, North Carolina, USA) to generate the subject listings, tabulations, and statistical analyses.

8.10   Coding Dictionary

In order to create a standard language that is comparable across all therapeutic teams and provide standardization for statistical analysis, adverse events recorded on the paper CRF will be coded by medical dictionaries/thesaurus. In this study, the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or higher will be used to map adverse events verbatim to Preferred Terms (PT) and System Organ Class (SOC).

8.11   Data Handling and Transfer

All collected clinical data will be collected via paper CRF by study coordinator, and will be managed centralized and stored in the clinical data management systems. No external data will be imported to the system. The system of variable coding will follow rules of   SOPs. During the study, Data manager will follow the SOP to enter and manage the CRFs. After data clean and data lock process, all the clinical data will be exported as SAS datasets and stored in a read-only space. Statistician will perform the statistical analysis based on the SAS datasets.

8.12   Programming Specifications

The summary statistics for continuous variables will be entitled as Number, Mean±SD, Median, Range, inter-quartile range (IQR), 25th percentile, 75th percentile and 95% C.I. in the table, which represent the number of observations, mean value plus/minus standard deviation, median value of observations, minimum and maximum, lower bound and upper bound of the 95% confidence interval. Range (minimum and maximum) and 95% confidence interval (lower and upper bound) are given in parentheses.

Unless otherwise noted, the summary statistics for continuous variables will be printed out to one decimal place except for the standard deviation and confidence interval. The standard deviation and confidence interval will be expressed to 2 decimal places. If the summary statistics cannot be obtained, it will be printed as "--"

For categorical variables, number and percentage will be presented as summary statistics. All table percentages will be reported with one decimal point unless otherwise specified.

The p-value will be reported to 4 decimal places. An asterisk indicates the statistical significance. P-value less than 0.0001 will be reported as "<0.0001*" and p-value greater than 0.9999 will be expressed as ">0.9999". If the p-value cannot be computed, p-value

will be printed as 'NA'.

9   SUMMARY OF STUDY DATA

Continuous variables will be summarized by descriptive statistics: number of observations, mean, median, standard deviation, range, and quartiles. Frequency counts and percentages of observed levels will be reported for categorical variables. The denominator of percentages will be the number of subjects with valid assessment results. Subjects with missing data will not be included in the number of denominator.

Efficacy analysis will be performed based on FAS. Safety analysis will be conducted based on Safety population. The relevant population size will be annotated in the tables.

9.1 Disposition of Subjects

The number of subjects screened, number of eligible subjects, and number of subject reached study completion will be counted and summarized. The denominator of percentage of number of eligible subjects will be the number of subject screened. The denominator of percentage of number of subject complete the study will be the number of eligible subjects. The summary of reason for early termination will be provided as well. The denominator of the reason will be the number of subjects not complete the study.

The number of subjects in Full Analysis Set, and number of subjects in PP population will also be presented with count and percentage. The denominator of the percentage will be the number of eligible subjects.

9.2 Protocol Violations and Deviations

This is a PMS study. Investigator could follow their practice and judgment. No protocol violation and deviation will be defined.

9.3 Demographic and Baseline Characteristics

The demographic characteristics including reimbursement status, date of birth, gender, race, education level, height, weight, concomitant diseases/comorbidities, risk factors, and medical history related to NVAF, Concomitant Therapies Related to CHA2DS2-VASc and HAS-BLED, Lab Data Related to CHA2DS2-VASc and HAS-BLED, Duration of previous VKA treatment (Cohort A only), PACT-Q1 Questionnaire (Cohort B only), and PACT-Q2 Questionnaire (Cohort A only) will be collected at visit 1 (baseline). Age will be calculated based on the date of birth and date of informed consent.

$$Age = \frac{(Date\ of\ informed\ consent - Date\ of\ birth)}{365.25}$$

BMI will be calculated based on the height and weight.

$$BMI = \frac{Weight\ (kg)}{Height\ (m)^2}$$

Gender, race, education level, concomitant diseases/comorbidities, risk factors, and medical history related to NVAF, Concomitant Therapies Related to CHA2DS2-VASc and HAS-BLED, Lab Data Related to CHA2DS2-VASc and HAS-BLED, Duration of previous VKA treatment (Cohort A only), PACT-Q1 Questionnaire (Cohort B only), and PACT-Q2 Questionnaire (Cohort A only) will be summarized as count and percentage. Demographics and baseline characteristic will be analyzed based on FAS.

9.4 Medical History

Medical history will be collected as Concomitant Diseases/Comorbidities at visit 1 (baseline). No coding or analysis item for medical history of subjects will be planned. The data listing will present the raw medical history record of subjects.

10 DEFINITION AND DETERMINATION OF ANALYSIS VARIABLES

10.1 Treatment Exposure and Compliance

Treatment duration will be counted from the date of visit 1 to the discontinued date in the Pradaxa® / VKA Discontinuation page. For those continuing using study drug, Treatment duration will be counted from the date of visit 1 to the date of visit 3. Treatment duration will be summarized as continuous variables. The reason for treatment discontinuation will be summarized as categorical data.

10.2 Primary Endpoint(s)

<u>Cohort A</u> (patients switched from VKA to Pradaxa®)

- Mean change in the PACT-Q2 scores at the second assessment (30-45 days) and the last assessment (150-210 days) compared to baseline assessment. The changes will be calculated as (PACT-Q2 scores at Visit 2 minus PACT-Q2 scores at visit 1, PACT-Q2 scores at Last Visit minus PACT-Q2 scores at visit 1).

<u>Cohort B</u> (patients newly initiated Pradaxa® or VKA)

- Mean difference in the PACT-Q2 scores at the second (30-45 days) and the last assessment (150-210 days) compared between 2 treatment groups. The difference will be calculated as (PACT-Q2 scores of *Pradaxa®* minus PACT-Q2 scores of VKA at Visit 2, PACT-Q2 scores of *Pradaxa®* minus PACT-Q2 scores of VKA at Last Visit).

10.3 Secondary Endpoints

<u>Cohort A</u> (patients switched from VKA to Pradaxa®)

- Mean change in the PACT-Q2 score at the last assessment (150-210 days) compared to the second assessment (30-45 days). The change will be calculated as (PACT-Q2 scores at Last Visit minus PACT-Q2 scores at visit 2).

<u>Cohort B</u> (patients newly initiated Pradaxa® or VKA)

- Description of mean PACT-Q1 score at baseline.

10.4   Safety Endpoints

- AEs (i.e. Pradaxa® relevant ADR (serious and non-serious), fatal AEs, and pregnancies)

Safety analyses will be performed separately for Cohort A and Cohort B.

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

11 STATISTICAL METHODS

11.1 Primary Hypothesis

This study is aim 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. The hypothesis for the testing is

$$H_0: \text{Change} = 0 \text{ vs. } H_a: \text{Change} \neq 0$$

11.2 Test of Assumptions

The primary hypothesis will be tested by paired t-test. The assumption of normality will be tested by using the Shapiro-Wilk test. Wilcoxon signed rank test will be used if the assumption of normally distributed is violated.

11.3 Primary Endpoint Analysis

Mean values and mean change from baseline of PACT-Q2 scores will be presented as descriptive statistics including Number, Mean±SD, Median, Range, inter-quartile range (IQR), 25th percentile, 75th percentile and 95% C.I. The changes under Cohort A will be calculated as (PACT-Q2 scores at Visit 2 minus PACT-Q2 scores at visit 1, PACT-Q2 scores at Last Visit minus PACT-Q2 scores at visit 1). The difference under cohort B will be calculated as (PACT-Q2 scores of Pradaxa® minus PACT-Q2 scores of VKA at Visit 2, PACT-Q2 scores of Pradaxa® minus PACT-Q2 scores of VKA at Last Visit). Shapiro-Wilk test will be conducted for testing the normality. If the null hypothesis of normally distributed of Shapiro-Wilk test is not reject, two-sided paired t-test will be performed and obtain the p-value. Significant level of the test will be set as 0.05. Once significant result of Shapiro-Wilk test is lower than 0.05, Wilcoxon signed rank test will be used instead.

For cohort B, the patients newly initiated Pradaxa® or VKA will be matched with a ratio of 1:1 based on the propensity score with caliper matching. After the propensity score each patient is generated, both Pradaxa® group and VKA group should be randomly sorted and then the first VKA unit is selected to find its closest

Pradaxa® match in terms of the propensity score. The random seed will be set as 20190218. The caliper will be set as 0.001.

11.4 Secondary Endpoint Analyses

<u>Cohort A</u> (patients switched from VKA to Pradaxa®)

- Mean change in the PACT-Q2 score at the last assessment (150-210 days) compared to the second assessment (30-45 days). The change will be calculated as (PACT-Q2 scores at Last Visit minus PACT-Q2 scores at visit 2). The test hypothesis of MMSE will be H0: Change = 0 vs. Ha: Change ≠ 0. Shapiro-Wilk test will be conducted for testing the normality. If the null hypothesis of normally distributed of Shapiro-Wilk test is not reject, two-sided paired t-test will be performed and obtain the p-value. Significant level of the test will be set as 0.05. Once significant result of Shapiro-Wilk test is lower than 0.05, Wilcoxon signed rank test will be used instead.

<u>Cohort B</u> (patients newly initiated Pradaxa® or VKA)

- Description of mean PACT-Q1 score at baseline. Mean values of PACT-Q2 scores will be presented as descriptive statistics including Number, Mean ±SD, Median, Range, inter-quartile range (IQR), 25th percentile, 75th percentile and 95% C.I.

11.5 Safety Analyses

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.

AE will be coded using the MedDRA dictionary. All adverse events will be classified

using MedDRA terminology. The number of subjects and percentage of subjects will be computed by System Organ Class and Preferred Term to show the incidence of AE.

11.6   Interpretation and Conclusion

The study objective is to provide evidence to show if significant change of PACT-Q2 scores in patients treated with Pradaxa® or VKA. The hypothesis testing for the primary endpoint will be two-sided and significant level will be 0.05. Once the significant is found (p-value < 0.05), the study shows the significant change of PACT-Q2 scores in patients treated with Pradaxa® or VKA.

12 SUMMARY OF CHANGES TO THE PROTOCOL

The initial statistical analysis plan will follow the protocol design and no changes or differences will be planned in the initial statistical analysis plan.

13 APPENDIX

13.1 Mock-up Tables

All statistical tables will be presented corresponding to the content of mock-up tables.

14 REFERENCES

1   Graham J. et al. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for non-valvular atrial fibrillation. Circulation. 2014. doi: 10.1161/CIRCULATIONAHA.114.012061 Published online October 30, 2014.

2 Connolly SJ. et al. The Long Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study. Circulation. 2013;128:237-43.

3 Connolly SJ. et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.

4 J. Beyer-Westendorf, F. Ebertz, V. Gelbricht, K. Foerster, L. Tittl, S. Werth, C. Koehler. Real life efficacy and safety of dabigatran for stroke prevention in atrial fibrillation: updated results of the prospective NOAC registry. European Heart Journal. 1 August 2013. DOI: http://dx.doi.org/10.1093/eurheartj/eht310.P4871.

5 Urooj F, Kulkarni A, Stapleton D, Kaluski E. New Oral Anticoagulants in Nonvalvular Atrial Fibrillation. Clin Cardiol. 2016 Dec;39(12):739-746. doi: 10.1002/clc.22582. Epub 2016 Oct 7.

6 Kailas SD, Thambuluru SR. Efficacy and Safety of Direct Oral Anticoagulants Compared to Warfarin in Prevention of Thromboembolic Events Among Elderly Patients with Atrial Fibrillation. Muacevic A, Adler JR, eds. Cureus. 2016;8(10):e836. doi:10.7759/cureus.836.

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

8 Carroll K, Majeed A. Comorbidity associated with atrial fibrillation: a general practice-based study. The British Journal of General Practice. 2001;51(472):884-891.

9 Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 137 (2), 263 - 272 (2010).

10 Pisters R, Lane DA, Nieuwlaat R, Vos CB de, Crijns HJGM, Lip GYH A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 138 (5), 1093 - 1100 (2010).

11 Cockcroft D, W, Gault M, H, Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976;16:31-41

12 Gault M, H, Longerich L, L, Harnett J, D, Wesolowski C, Predicting Glomerular Function from Adjusted Serum Creatinine. Nephron 1992;62:249-256

13 Prins MH, Guillemin I, Gilet H, Gabriel S, Essers B, Raskob G, Kahn SR. Scoring and psychometric validation of the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). Health Qual Life Outcomes 7, 30 (2009)

14 Prins MH, Marrel A, Carita P, Anerson D, Bousser MG, Crijns H, Consoli S,

Arnould B. Multinational development of a questionnaire assessing patient satisfaction with anticoagulant treatment: the 'Perception of Anticoagulant Treatment Questionnaire' (PACT-Q). Health Qual Life Outcomes 7, 9 (2009)