Statistical and Epidemiological Analysis Plan

c10496131-03

BI Trial No.:	1160.261
Title:	Non-interventional study describing patients' perception on anticoagulant treatment and treatment convenience when treated with Pradaxa® or Vitamin K Antagonist for Stroke Prophylaxis in Atrial Fibrillation
Investigational Product:	Dabigatran etexilate (Pradaxa®)
Responsible trial statisticians:	Telephone: Telephone:
Responsible trial epidemiologist:	NA
Date of statistical and epidemiological analysis plan:	02 JAN 2018 REVISED
Version:	Revised

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
CHA_2DS_2-VASc score	Congestive heart failure, Hypertension, Age (≥ 75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex category
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End-Of-Text
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and Alcohol.
IC	Informed Consent
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IPV	Important Protocol Violation
ISPE	International Society for Pharmaceutical Engineering
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NVAF	Non-Valvular Atrial Fibrillation
PACT-Q©	Perception of Anticoagulant Treatment Questionnaire
SD	Standard Deviation
SEAP	Statistical and Epidemiological Analysis Plan
SEASK	South East Asia South Korea
VKA	Vitamin K Antagonist
WHO	World Health Organization

3. INTRODUCTION

As per ICH E9 (1) and the ISPE Guidelines of Good Pharmacoepidemiology Practice (2), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the data. This document describes the final analysis at the end of trial as well as the preliminary assessment which will be performed for Cohort B when approximately half of the target sample size is reached.

This SEAP assumes familiarity with the registry protocol, including Protocol Amendments (if present). In particular, the SEAP is based on the planned analysis specification as written in the registry protocol Section 9 “Research Methods”. Therefore, SEAP readers may consult the registry protocol for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

SAS® Version 9.3 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

4.1 SUMMARY OF CHANGES TO THE STUDY

Patient analysis set has been updated to include all patients who took the prescribed treatment and without an important protocol violation.

For Cohort B, no formal interim analysis will be performed; instead a preliminary analysis will be performed to assess the comparability of the matched Pradaxa® and VKA patients based on propensity scores matching analysis when approximately half of the target sample size is reached.

5. OUTCOMES

This non-interventional study is designed to describe the non-valvular atrial fibrillation patient's treatment perception by using the PACT-Q at three time-points (at baseline, during initiation period and during the continuation period) (objective 1) and to characterize the patient population (incl. dosing) in the participating SEASK countries (objective 2).

The data will be collected for two cohorts of patients:

Cohort A: Patients having been treated with VKA and now being switched to Pradaxa®
Cohort B: Patients newly diagnosed with non-valvular atrial fibrillation and initiated on either Pradaxa® or VKA.

5.1 MAIN OUTCOMES

For objective 1, the main variables of interest are mean PACT-Q2 scores at second and last assessment compared to baseline assessment for Cohort A (switcher), and mean PACT-Q2 scores at second and last assessment between treatment groups for Cohort B (newly initiated).

For objective 2, the main variables of interest are patient baseline characteristics and demographics, including age, gender, CHA_2DS_2-VASc score, HAS-BLED score (modified HAS-BLED for newly initiated patients), kidney function (creatinine clearance), stroke and/or bleeding related risk factors in medical history and at baseline, co-morbidities, concomitant therapies, dosing of Pradaxa®, as well as duration of previous VKA treatment (for Cohort A).

5.2 SECONDARY OUTCOMES

The secondary outcomes to be analysed are mean PACT-Q2 score at last assessment compared to second assessment for Cohort A (switcher), and description of PACT-Q1 items at baseline for Cohort B (newly initiated).

6. GENERAL ANALYSIS DEFINITIONS

6.1 EXPOSURE

This is a non-interventional multi-national, multi-centre study based on newly collected data. Patients will either be switched from vitamin K antagonist (VKA) treatment to Pradaxa® (Cohort A) or newly initiated on Pradaxa® or VKA (Cohort B).

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

Patients will receive daily dose of Pradaxa® (hard capsules contain Dabigatran etexilate) according to the Summary of Product characteristics and physician's discretion. The choice of VKA and the appropriate dosing is in the discretion of the physician.

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

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

The visit windows above for Visit 2 and Visit 3 should be seen as guidance for the treating physician. Visit schedule deviations are expected as the visits are being scheduled according to local clinical routine. For analysis purpose, Visit 2 data that were collected between 7 and 124 days after initiation will be included (rationale for the lower limit is that steady state on Pradaxa is achieved after 3 days, and first side effects also might occur after a 1st or 2nd intake; rationale for the higher limit is to make sure that there is no overlap with Visit 3). Visit 3 data that were collected between 125 and 365 days after initiation will be included for analysis.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Patients with important protocol violations (IPVs) will be documented. The following list of IPVs will be used. Additional IPVs may be defined during the course of the study. Those will be assessed during the Medical and Quality Review meetings (MQRM); if the list of IPVs needs to be enlarged, it will be documented in the report planning meeting minutes before database lock.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met		
	A1.1	Informed consent not given	Date of written informed consent missing	All
	A1.2	Informed consent given too late	Date of written informed consent after date of baseline visit, date of first dose taken, or PACT-Q date	All

Table 6.2: 1 (continued) Important protocol violations

Category / Code		Description	Requirements	Excluded from
	A1.3	Age < 18 years		All
	A1.4	No diagnosis of non-valvular atrial fibrillation (NVAF)	For Cohort A, no existing diagnosis of NVAF, or for Cohort B, no new diagnosis of NVAF	All
	A1.5	< 3 months of continuous VKA treatment for stroke prevention prior to baseline assessment	For Cohort A only, less than 3 months of continuous VKA treatment for stroke prevention prior to baseline assessment	All
	A1.6	Previous treatment for stroke prevention	For Cohort B only, patients had previous treatment (i.e. used an oral anticoagulant within 1 year prior to enrolment) for stroke prevention	All
	A1.7	IC prior to site initiation visit	Date of written informed consent prior to site initiation	All
	A2	Exclusion criteria violated		
	A2.1	Contraindication to the use of Pradaxa® or VKA		All
	A2.2	Pradaxa® or VKA used for any other conditions	Patients receiving Pradaxa® or VKA for any other condition than stroke prevention in atrial fibrillation	All
	A2.3	Participating in other clinical trial	Current participation in any clinical trial of a drug or device	All
	A2.4	Participating in a Registry on the use of oral anticoagulation in AF	Current participation in a Registry, e.g. the Gloria registry program, on the use of oral anticoagulation in AF	All
Z		**Other**		
	Z1	Patients on Pradaxa with CrCl < 30 ml/min		All

6.3 PATIENT SETS ANALYSED

The main analysis population will consist of all eligible patients [i.e. all patients who took the prescribed treatment and without an important protocol violation (see Table 6.2: 1)] from all participating countries.

6.5 POOLING OF CENTRES

Centre will not be used as a factor in any analysis model; therefore this topic is not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

The percentage of and reason for discontinuation from treatment and study 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 discontinued patients is substantial enough (e.g. ≥ 10%) to warrant further investigation, baseline characteristics will be described for patients who discontinued prematurely in comparison to patients who have completed the treatment or study follow-up up to Visit 3.

As to PACT-Q2, the convenience and satisfaction dimension scores are calculated separately only if at least 50% of items of the dimension are completed for a patient at a visit. (3) See Section 7.6 for imputation details when at least 50% of items of a dimension are completed.

The amount of missing data will be described and assessed in the report based on the descriptive summary tables by topic (category 'Missing' will be displayed if missing occurs in the data).

Missing or incomplete ADR or fatal AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (4).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline visit is defined as the physical visit where the patient is enrolled in the registry. Baseline values are the values collected at baseline visit (Visit 1).

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

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

As indicated in Section 6.1, Visit 2 data that were collected between 7 and 124 days after baseline will be included for analysis; Visit 3 data that were collected between 125 and 365 days after baseline will be included for analysis.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

The summary of data will be done by cohort and by treatment (Pradaxa® or VKA) within Cohort B.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Analysis of demographic and other baseline characteristics is defined as a main analysis for Objective 2. Details regarding the main analysis can be found in Section 7.6.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only the information on the pre-specified medical history/concomitant diseases and pre-specified concomitant therapies is collected in the eCRF.

The pre-specified diseases in the past and those while on treatment will be summarized by pre-specified category and condition / diagnosis.

The pre-specified therapies have already been named in accordance with the WHO Drug coding dictionary. The pre-specified therapies taken in the past and those taken concomitantly while on treatment will be summarized by pre-specified term. Analysis of concomitant diseases and concomitant therapies at the time of baseline visit is defined as a main analysis for Objective 2. Details regarding the main analysis can be found in Section 7.6.

7.3 TREATMENT ADHERENCE

Not applicable for this study. Treatment adherence is not assessed in this study.

7.4 METHODS ADDRESSING BIAS

See registry protocol Section 9.9.

7.5 METHODS ADDRESSING CONFOUNDING/EFFECT MEASURE MODIFICATION

Propensity score matching will be used to correct for identified confounders. However unidentified confounders cannot be controlled for using statistical analysis. For details on the propensity score matching method, see Section 7.6.

7.6 MAIN ANALYSES

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

For the PACT-Q1, no global score is calculated as each item is analysed individually (3).

Within the PACT-Q2, items for convenience and for burden of disease and treatment are reversed (reversed score = 6 – item score), added together and rescaled on a 0-100 scale to obtain the convenience dimension score. Items for anticoagulant treatment satisfaction are summed and rescaled on a 0-100 scale to determine the satisfaction dimension score (3).

The convenience and satisfaction scores are calculated separately only if at least 50% of items of the dimension for a patient at a visit are completed. For convenience and satisfaction dimension scores, if at least 50% of items are completed (non-missing) for a dimension, the missing items of a patient at a visit are replaced by the mean of non-missing items of the dimension obtained at the same visit for the same patient. Then sums of items of dimensions are calculated and rescaled on a 0-100 scale as follow (3):

Score = 100 × (sum – minimal possible sum) / (highest possible sum – minimal possible sum)

The PACT-Q1 scores which were collected after first dose, the PACT-Q2 scores which were collected more than 1 day after patients discontinued from the treatment, and the PACT-Q scores which were collected using incorrect PACT-Q procedure will be excluded from the summaries or analyses.

For Cohort A, the mean convenience and satisfaction dimension scores of PACT-Q2 at the second assessment (Visit 2) and last assessment (Visit 3) will be compared with the baseline assessment (Visit 1) using paired t-tests.

For Cohort B, mean Convenience and Satisfaction dimension scores of PACT-Q2 will be compared between Pradaxa® and VKA patients at the second and last assessments. Given the nature of this non-interventional study, patient in the two treatment groups may differ with regard to important baseline demographics and disease characteristics. Therefore, a preliminary assessment of the comparability of the Pradaxa® and VKA patients based on propensity scores will be performed when approximately half of the target sample size is reached. As a first step of the assessment, propensity scores that estimate the probabilities that patients would be initiated on Pradaxa® will be calculated using a logistic regression model as specified below:

- Dependent variable in the propensity score model is treatment choice (Pradaxa® or VKA).
- The following baseline variables that are either potential confounders (associated with both treatment choice and outcome) or potential predictors of outcome will be included as covariates.
  - Age at baseline (< 65, ≥ 65 and < 75, ≥ 75 years)
  - Gender (male, female)
  - Pooled country (South Korea, non-South Korea)

- Creatinine clearance at baseline (<30 and 30 to < 50 combined, 50 to < 80, ≥ 80 mL/min, not available)
- CHA_2DS_2-VASc stroke risk score at baseline (low risk [score of 0], intermediate risk [score of 1], high risk [score of ≥ 2])
- HAS-BLED bleeding risk score at baseline (low risk [score of < 3], high risk [score of ≥ 3])
- Co-morbidities – group 1 (malignancy, no malignancy)
- Co-morbidities – group 2 (ulcerative GI disease or gastritis, no ulcerative GI disease or gastritis)
- Concomitant therapies – group 1 (verapamil, amiodarone, and dronedarone, vs. no p-gp-inhibitors)
- Concomitant therapies – group 2 (any antithrombotic agent, no antithrombotic agent)
- Concomitant therapies – group 3 (NSAIDS, no NSAIDS)
- Type of physician (cardiologist, non-cardiologist)
- Type of hospital or practice (Public and other combined, private)
- Owner of medical practice (Physician or physician group, medical / academic health center, others)

- If a variable is suitable but has a high number of missing values, further discussion will be carried out to decide whether it will be excluded from the propensity score model or still be included in the propensity score model with missing as a separate category.
- Variable selection will be performed with caution to avoid the inclusion of highly correlated variables as well as over-parameterization.
- All covariates from the list above will be set as required covariates in the propensity score model to ensure balance of baseline characteristics of patients. If any additional covariates are deemed necessary to be included in the propensity score model, they need to be defined before database lock.

Pradaxa® and VKA patients will then be matched based on propensity scores using a variable ratio, parallel, balanced 1:n, nearest neighbour matching algorithm with a caliper width of 0.05 and without replacement. The publicly available SAS macro provided by Rassen et al. (5) will be used.

Finally, the percentage of Pradaxa® and VKA patients that are matched with an appropriate maximum ratio (e.g. 2:1) according to the actual patient distribution will be calculated to assess the comparability of the two patient populations, and to estimate the loss of patients from the comparative analysis.

For the final comparative analysis for Cohort B, Pradaxa® and VKA patients will be matched based on propensity scores following the same approach as described above. To assess the performance of the propensity score matching procedure, patient demographics and disease characteristics at baseline will be descriptively summarized again for the matched patients by treatment. For each matched set that includes multiple Pradaxa patients, the mean PACT-Q2 score will be calculated for the Pradaxa patients and used in the final comparative analysis. Finally, the mean PACT-Q2 scores at each of the second and last assessments will be compared between the matched Pradaxa® and VKA patients using paired t-tests.

For both cohorts, the primary analyses will be based on the actual anticoagulation treatment the patients receive (i.e. "as treated" analysis). A patient is considered to have permanently discontinued initial anticoagulation treatment if other relevant anticoagulation treatment is initiated or otherwise dependent on the duration of treatment interruption. Whether a patient discontinued from the Pradaxa® or VKA is recorded on the eCRF. Patients who have permanently discontinued initial anticoagulation treatment at the time of an assessment will be excluded from all analyses where data from that assessment is included.

Patient demographics and disease characteristics at baseline as described in Section 5.1 (main outcomes for objective 2) will be summarized descriptively for all eligible patients in Cohort A and by treatment in Cohort B.

Concomitant disease and concomitant therapies will be summarized for all eligible patients in Cohort A and by treatment in Cohort B.

7.8 EXPOSURE TIME

The exposure will be summarized descriptively for all eligible patients in Cohort A, by treatment in Cohort B, and total.

Exposure time [days] = date of last administration of Pradaxa or VKA – date of Pradaxa or VKA administration + 1 day. In case of death, the treatment stop date will be imputed as the earlier of (date of last administration of Pradaxa or VKA, date of death). Any temporary discontinuation is included in the exposure time.

7.9 SAFETY ANALYSIS

Safety analyses will be performed separately for Cohort A and B and by treatment for Cohort B, and will include all eligible patients. Statistical analysis and reporting of safety parameters will be descriptive in nature; and will be based on BI standards. No hypothesis testing is planned.

7.9.1 Adverse events / adverse drug reactions

Reporting of adverse events (AEs) in this study will focus on serious and non-serious adverse drug reactions (ADRs) to Pradaxa® and VKA, fatal AEs and pregnancies. All analyses of ADRs and fatal AEs will be based on the number of patients with ADRs and fatal AEs and NOT on the number of ADRs and fatal AEs.

For analysis multiple AE occurrence data in the eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (lowest level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (4, 6).

Occurrences of AEs will be analysed relative to the number of patients treated as well as observed person-years (i.e. time at risk). Analysis of AEs will be based on the concept of treatment emergent AEs. Patients will be analysed according to the anticoagulation treatment received at the onset of the AE. If no concurrent anticoagulation treatment is administered, then AEs occurring within a washout period of 3 days (for Pradaxa®) or 6 days (for VKA) after discontinuation of anticoagulation treatment will be assigned to the last treatment given. This washout period will also be included as time at risk for derivation of total person-years. AEs that deteriorate under treatment will also be considered as “treatment emergent”. Events occurring prior to first intake of anticoagulation treatment prescribed at baseline, during periods without any anticoagulation treatment (excluding washout periods), or after the end of the 6 month follow-up (excluding washout periods) will not be considered treatment emergent AEs and will not be included in the summary tables.

According to ICH E3 (7), AEs classified as ‘other significant’ needs to be reported and will include those non-serious AEs with
(i) ‘action taken = discontinued’ or ‘action taken = reduced’, or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

An overall summary of ADRs and fatal AEs will be presented. The frequency of patients with ADRs or fatal AEs will be summarised by treatment, primary system organ class and preferred term (mention MedDRA levels to be displayed in the tables). Separate tables will be provided to summarize ADRs or fatal AEs leading to discontinuation of anticoagulation treatment, serious ADRs or fatal AEs, ADRs leading to deaths and fatal AEs, and ADRs or

fatal AEs leading to dose change (including dose reduced, increased, and discontinued and re-introduced). Patient with pregnancies will be listed.

The primary system organ classes will be sorted in alphabetic order; preferred terms will be sorted by frequency (within system organ class).

7.9.2 Laboratory data

Creatinine clearance is calculated in the eCRF according to Cockcroft-Gault formula at each visit and will be summarized descriptively. No additional laboratory data is collected systematically.

7.9.3 Vital signs

Weight is collected for creatinine clearance calculation purpose and is required at Visit 1 only though it is also collected at Visits 2 and/or Visit 3 if a new creatinine clearance is available at those visits. Weight at Visit 1 will be summarized as baseline characteristics. No other vital signs data is collected systematically.

7.9.4 ECG

Not applicable.

7.9.5 Others

Not applicable.

7.10 INTERIM ANALYSES

No interim analysis is planned for Cohort A.

For Cohort B, it is planned that a preliminary assessment that assesses the comparability of patients in the Pradaxa® and VKA groups based on propensity scores will be performed when approximately half of the target sample size is reached.

For each cohort, the final analyses as specified in Section 7.6 will be performed once the data collection is completed, the data sets are cleaned, and the database is locked for that cohort. The final analysis for both cohorts may be performed together, if their complete data becomes available at the same time. One final report will be prepared at the completion of both cohorts.

Additional reports (e.g. for country-specific analyses) may be prepared if deemed appropriate.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	ISPE Guidelines of Good Pharmacoepidemiology Practice, Pharmacoepidemiology and Drug Safety 2008; 17: 200–208
3	PACT-Q© Perception of Anticoagulant Treatment Questionnaire Information booklet, 4th Edition, March 2014, MAPI Research Trust.
4	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", version 5; IDEA for CON.
5	Jeremy A. Rassen, Abhi A. Shelat, Jessica Myers, Robert J. Glynn, Kenneth J. Rothman, One-to-many propensity score matching in cohort studies, Pharmacoepidemiology and Drug Safety, 2012, 21(S2): 69-80.
6	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
7	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**25-JUL-16**		None	This is the initial SEAP with necessary information for trial conduct. This initial SEAP is based on the protocol finalized on 25Jan2016.
Final	**11-APR-17**		None	This is the final SEAP without any modification. Changes to the planned analysis are summarized in Section 4 and detailed in the corresponding sections of the SEAP.
Revised	**02-JAN-18**		Sections 6.1, 6.2, , 6.7, 7.6, 7.9	Update the requirement for IPV category A1.2 to consider the case where date of written informed consent was after date of first dose taken or PACT-Q at V1 date. Update the wording about interim analysis in Section 3 and Section 7.6 because a preliminary assessment will be done instead of a formal interim analysis. Visit window for Visit 3 has been updated to 125 to 365 days. Safety analyses will include all eligible patients. Update the country factor considered in the logistic model to pooled country. Added the criteria to exclude certain PACT-Q scores from the summary