Trial Statistical Analysis Plan

BI Trial No.:	1160.249
Title:	Non-interventional study describing patients' perception on anticoagulant treatment and treatment convenience when treated with Pradaxa® or Vitamin K Antagonist for Stroke Prevention in Non-Valvular Atrial Fibrillation
Investigational Product(s):	Dabigatran etexilate (Pradaxa®)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted] [redacted] (oversight) [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	21 NOV 2017
Version:	3.0 (Amendment 2)

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DB	Database
IBA	Institute of Biostatistics and Analyses
ICH	International Conference of Harmonization
INR	International Normalized Ratio
IU	International Unit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable, Not Available
NIS	Non-interventional study
NVAF	Non-valvular atrial fibrillation
PACT-Q	Perception of Anticoagulant Treatment Questionnaire
PT	Preferred Term
PV	Protocol violation
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
SOC	System Organ Class
TFL	Tables, Figures and Listings
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per ICH E9, 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 primary and secondary variables and other data.

This TSAP assumes familiarity with the study protocol, including Protocol Amendments (version of study protocol 1.0 from the 23-JUL-2015) and (e-)CRF (first patient-in 30-11-2015). In particular, the TSAP is based on the planned analysis specification as written in the study protocol Section 9.7 “Data Analysis”. Therefore, TSAP readers may consult the study 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, withdrawal from study and rules for stopping the study.

The analyses and outputs should closely follow the ICH guideline for industry on topic E9 (Statistical Principles for Clinical Trials). The SAP has to be completed as early as possible, the best before enrollment of the first patient and approved the latest prior database (DB) lock and executed after DB lock. This is accompanied also by approval of definitions of the protocol violations and the disposition of patients into analysis sets before compilation of final SAP. Critical dates and times (e.g. of disease progression, treatment administration, deaths, concomitant medications and adverse events) have to be cleaned before DB lock.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Given the nature of this non-interventional study, patients in the two treatment groups of Cohort B may differ with regard to important baseline demographics and disease characteristics. Thus it was originally planned in the protocol that for the comparative analysis, Pradaxa® and VKA patients would be matched with a 1:1 ratio based on propensity scores and the mean PACT-Q2 scores would be compared between the matched Pradaxa® and VKA patients using a paired t-test.

However, it was observed during the course of the study that the number of patients enrolled in the Pradaxa® group was significantly higher than the number of patients enrolled in the VKA group. In order to account for this imbalance and make the best use of available data, it was decided that the final analysis will be based on a variable ratio, parallel, balanced 1:n nearest neighbor propensity score matching without replacement, as described in Rassen (2012). Consequently, the comparison of the PACT-Q2 scores between the two groups will be based on a random intercept model (primary analysis) and the "within-set" treatment effect estimates (sensitivity analysis). See Section 7.4 for more details.

5. OUTCOMES

Brief summary of study design and objectives for definition of outcomes

This is a non-interventional multi-national, multi-centre study based on newly collected data. The study will enroll consented patients with non-valvular atrial fibrillation in Europe with:

- a current VKA therapy and subsequent initiation of Pradaxa® (**Cohort A**) OR
- patients being newly diagnosed with AF and initiated on Pradaxa® or VKA (**Cohort B**).

It is planned that data of approximately 9000 (3000 for Cohort A and 6000 for Cohort B). Details of recruitment and withdrawal of patients and rules for stopping the study are described in study protocol.

Study outcomes are based on two objectives:

- **Objective 1**: 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 2:** characterization of patient population (incl. dosing) in the participating European countries.

5.1 PRIMARY OUTCOMES

For Objective 1:

For **Cohort A** (NVAF patients on VKA who are switched to Pradaxa®)):

- Mean PACT-Q2 scores at second and last assessment compared to baseline assessment.

For **Cohort B** (newly diagnosed NVAF patients initiated to either VKA or Pradaxa®)):

- Mean PACT-Q2 scores at second and last assessment compared between treatment groups.

For Objective 2:

Characterization of patients from both cohorts according to:

- Age
- Gender
- CHA2DS2-VASc score
- HAS-BLED score (modified HAS-BLED for newly initiated patients)
- Kidney function (creatinine clearance)
- Co-morbidities
- Co-medication
- Dosing of Pradaxa®
- Duration of previous VKA treatment (for Cohort A)

5.2 SECONDARY OUTCOMES

For Objective 1:

For **Cohort A** (switched to Pradaxa®):

- Mean PACT-Q2 scores at last assessment compared to second assessment.

For **Cohort B** (newly initiated to VKA or Pradaxa®):

- Description of PACT-Q1 items at baseline

5.4 OTHER VARIABLE(S): DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following procedures will be performed at the baseline visit:

- Sign informed consent form
- Review of inclusion and exclusion criteria
- Collection of demographic data: age, gender (primary outcome variables*)
- Collection of concomitant diseases/comorbidities at baseline (primary outcome variables*)
- Collection of baseline concomitant therapies (primary outcome variables*)
- Weight
- Creatinine Clearance: serum creatinine value (if available) to be entered on eCRF, Creatinine Clearance according to Cockcroft-Gault formula to be automatically calculated (primary outcome variables*)
- CHA_2DS_2-VASc and HAS-BLED score – overall score is calculated in eCRF and will be used for the analysis (primary outcome variables*)
- For Cohort A only: duration of previous treatment with VKA to be documented (primary outcome variable*)
- For Cohort A only: reasons for switch to Pradaxa® to be documented
- Documentation of Pradaxa® dosing (primary outcome variable*)
- Patient will be asked to complete the following patient related questionnaires:
    - PACT-Q2 (Cohort A only)
    - PACT-Q1 (Cohort B only)

- Treatment with Pradaxa® or VKA will be initiated

* *Analysis of baseline primary outcome variables will be described separately in section 7.4 Primary analyses instead of 7.1 Demographic and other baseline characteristics.*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

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

Pradaxa® 110 mg and Pradaxa® 150 mg hard capsules contain Dabigatran etexilate (active ingredient: Dabigatran).

Patients will receive daily dose of Pradaxa® according to the Summary of Product characteristics and physician´s discretion.

The choice of vitamin K antagonist and the appropriate dosing is in the discretion of the physician. Dosing of VKA has to be monitored and individually adapted by regular measurements of INR values (International Normalized Ratio).

6.2 IMPORTANT PROTOCOL VIOLATIONS

The list of important PVs will be created and agreed before database lock and execution of statistical analysis. If the proportion of patients with any important PVs reaches a given threshold (e.g. 30%), a sensitivity analysis will be performed based on the per-protocol set. For each important PV that occurs during the study, the need for exclusion of patients from the analysis will be assessed. Any such steps that are taken in the analysis will be described in the study report.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Specification or requirements	Excluded from *
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met		MAS
	A1.1	Written informed consent not given prior to participation	Date of written informed consent missing or given after baseline visit	SS, MAS
	A1.2	Patients aged < 18		MAS
	A1.4A	For Cohort A no diagnosis of non-valvular atrial fibrillation	Patient is not diagnosed with non-valvular atrial fibrillation prior enrolment in Cohort A.	MAS
	A1.4B	For Cohort B patient is not newly diagnosed with non-valvular atrial fibrillation or patient used one year prior to enrolment any OAC treatment for stroke prevention	Patient is not newly or at all diagnosed with non-valvular atrial fibrillation prior enrolment in Cohort B or patient had previous treatment for stroke prevention (use of any OAC within one year prior to enrolment).	MAS
	A1.5	For Cohort A patient does not have 3 months of continuous VKA	At least 3 months of continuous VKA treatment for stroke prevention prior to baseline assessment not confirmed.	MAS

Category / Code		Description	Specification or requirements	Excluded from *
		treatment for stroke prevention prior to baseline assessment		
	A1.6A	For Cohort A patient did not switch to Pradaxa®	Patient did not switch to Pradaxa at all.	MAS
	A1.6B	For Cohort B stroke prevention treatment not initiated with Pradaxa® or VKA	Patient did not initiate Pradaxa® or VKA prior enrolment at all or according to Summary of Product Characteristics and physician`s discretion in Cohort B	MAS
	A2	Exclusion criteria not met	Exclusion criteria not met as specified in the protocol	MAS
	A2.1	Contraindication to the use of Pradaxa® or VKA at baseline	In accordance with description in the Summary of Product Characteristics (SmPC)	MAS
	A2.2	Patients receiving Pradaxa® or VKA for any other condition than stroke prevention in non-valvular atrial fibrillation		MAS
	A2.3	Current participation in any clinical trial of a drug or device		MAS
	A2.4	Current participation in a Registry, e.g. the Gloria registry program, on the use of oral anticoagulation in AF		MAS

* Safety set (SS) or Main analysis set (MAS).

6.3 PATIENT SETS ANALYSED

All analyses will be based on all eligible patients [i.e. all patients without an important protocol violation (see Table 6.2: 1)].
The flow of patients will be based primarily on analysis sets and if appropriate any other conditions which lead to exclusion of patients from the main analysis set of patients should be also included.

The following analyses sets are described in the study protocol (section 9.7.2 Planned analyses, page 26):

Main analysis set (MAS)

The main analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria, thus without an important protocol violation (see Table 6.2: 1)) from all participating countries.

Propensity score matched set (PSMS)

For Cohort B the propensity score matched set will be used for comparative analysis.

The PSMS will include all patients that will be matched with a 1:n ratio (VKA: Pradaxa) based on propensity scores calculated using logistic regression model. Details of methodology of propensity score matching are described in section 7.4.

Safety set (SS)

Safety analyses will be performed separately for Cohort A and B, and will include all enrolled patients with an actual follow-up.

6.5 POOLING OF CENTRES

Centre will not be used as a factor in any analysis model; therefore this topic is not applicable. If the sample size allows, subgroup analysis by countries will be performed (for details please see section 6.4 Subgroups).

6.6 HANDLING OF MISSING DATA AND OUTLIERS, VALIDATION OF PROGRAMMING

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 if any technique will be used then will be described more in details in statistical report.

The percentage of and reason for loss to follow-up will be summarized overall in Cohort A, by treatment in Cohort B, and by other relevant factors. In addition, if the proportion of patients with loss to follow-up is substantial enough (e.g. ≥ 10%) to warrant further investigation, baseline characteristics will be described for patients who were lost to follow-up in comparison to patients who have completed follow-up.

Handling/classification of concomitant medication and adverse events

Patients will be analyzed according to the anticoagulation treatment received at the time of the event. If no concurrent anticoagulation treatment is administered, then events occurring within a washout period of 3 days (for Pradaxa®) or 6 days (for VKA) after discontinuation of anticoagulation treatment will be assigned to the last treatment given.

Concomitant medication will be assigned by the same manner.

Incomplete dates are not possible to record in the e-CRF. Only missing values can be entered.

Following rules will be applied for missing dates:

- Start date of concomitant medication: No replacement, the medication is considered to have started before the study
- Start date of adverse event: The earlier of the end date of the AE and the date of study drug administration (the first study drug administration if it is not possible to distinguish which study drug administration preceded the AEs)
- End date of concomitant medication: No replacement, the medication is considered to last till end of study.
- End date of adverse event: No replacement, the AE is considered to last till end of study.

If the treatment discontinuation does not occur during the course of the study, "the date of the last treatment administration during the study" is defined as the last available visit date (normally the date of the Visit 3, unless the data on Visit 3 are missing).

Methods for handling of incomplete dates/ times

Dates and times will not be replaced if missing. Missing date information will be excluded from possible computation.

Validation of data

Data quality, e.g. presence of outliers for the most important variables or percentage of missing data will be discussed during a data review meeting before the database lock.

Validation of statistical programming

The second statistician or data analyst will check the final results. The check will include following:

- The double programming of the primary and secondary efficacy analyses and of frequency tables of adverse events
- Check of disposition of patients in analysis sets

- Review of other outputs
- Check of errors and unexpected warnings in logs of all programs used for analysis and data preparation
- Review of handling of missing data and outliers

In statistical programs (scripts) any corrections or updating of study data has to be documented in statistical report if the modification in clinical DB or source data was not done till the DB lock. Namely, this refers to the cases when patients or the data are added/ changed using a script rather than updating the DB. This kind of hard coding is usually proposed to correct deficiencies in the DB (missing values, wrong values, and wrong measurement units).

The hard coding may not be done in any programs used for the creation of analysis data sets, tables, listings, or analyses that are intended for external reporting after DB lock (i.e. clinical study reports /all phases/, publications, abstracts, etc.).

Since no changes are made to the study data without appropriate documentation from the investigator sites and appropriate audit trails within the clinical trial DB, this process ensures integrity of clinical data.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline

The baseline visit is defined as the physical visit where the patient is enrolled in the study.

Study duration and time windows

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 defined above should be seen as a guidance for the treating physician. Visit schedule deviations are expected as the visits are being scheduled according to local clinical routine. For the analysis purpose, the initiation visit 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 first or second intake; rational for the higher limit is to make sure that there is no overlap with the continuation period visit). The continuation period visit data that were collected between 125 and 365 days after initiation will be included in the analysis. For the baseline visit, the following approach regarding the PACT-Q data will be applied:

- For Cohort A, patients who had the baseline PACT-Q2 after the first dose are considered acceptable. These patients would not be excluded from Cohort A analysis.

- For Cohort B, PACT-Q1 is collected at baseline, which is considered a secondary outcome for the study and only summarized descriptively. If a patient had the baseline PACT-Q1 after the first dose, this patient's PACT-Q1 data would be excluded from the PACT-Q1 descriptive summary. However, since this doesn't affect the PACT-Q2 data, this patient would still be included in the PACT-Q2 analyses in Cohort B.

Baseline values

No special assumptions have to be specified for baseline values. Baseline values are all values collected at baseline. Baseline values will not be replaced or imputed.

Labels and tags used in sap and/or outputs

For individual study visits following abbreviated terms will be used in the study report:

- Visit 1 (Baseline) = "V1"
- Visit 2 (30-45 days after initiation on Pradaxa® or VKA) = "V2"
- Visit 3 (150-210 days after initiation on Pradaxa® or VKA) = "V3"

For designation of cohorts following labels will be used:

- Cohort A (switchers): "CohA"
- Cohort B (newly initiated): "CohB"

7. PLANNED ANALYSIS

This section describes the data analysis in details. The statistical methods are planned in accordance with the study protocol (section 9.7 Data analysis) and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

General principles

The 'SOP111 Statistical analysis of clinical data' of IBA describes generally the procedure for carrying out statistical analysis of clinical data and has to be followed during inspection of data and analyses as well as instruction in this SAP.

Statistical package SAS (version 9.3 or higher) or eventually SPSS (version 20 or higher) will be used for analysis and for generation of tables, figures and listings (TFL).

Descriptive statistics

Standard descriptive statistics are used in the analysis; all results are described by number of samples in the base for given computation; valid N is also reported in case of missing values in continuous variables. Median, min-max and interquartile range are used for continuous variables. Mean supplemented by standard deviation are adopted for continuous variables when normality of data is shown; geometric mean and its 95% confidence interval are adopted for log-normally distributed data.

Categorical data are described using absolute and relative prevalence (frequencies) of categories; missing values can be included in the computation of categories percentages when necessary. Estimates will be presented with 95% confidence intervals.

Results will be presented overall and if appropriate by treatment/study groups and subgroups.

Figures used to illustrate selected summary tables will always refer to the number of patients included in the analysis set.

Rounding

The number of decimals used to display summary tables will be derived from raw data according the following rules: Mean (Geom. mean) +1; SD +2, Median +1, Min/Max +0, interquartile range +1, 95% confidence intervals +1.

Percentage in frequency tables will be displayed to one decimal place.

All p-values will be rounded to three decimal places.

Handling of data in case of patients' discontinuation

A patient is considered to have permanently discontinued initial anticoagulation treatment if another relevant anticoagulation treatment is initiated.

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. If any case is revealed, exclusion will be commented in the study report.

Interim analyses

No interim analysis is planned for Cohort A.

For Cohort B, it is planned that an interim analysis that assesses the comparability of patients in the Pradaxa® and VKA groups based on propensity scores will be performed when approximately half of the target sample size is reached (see details below in section 7.4).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic, physical characteristics and medical history data will be tabulated, using the standard sets of summary statistics as defined in Section 7. Most of these baseline characteristics will be analyzed as further outcome for Objective 2 (for concrete variables please see *Section 5.4. Other variables: Demographic and baseline characteristics,* details of analyses are specified in *Section 7.4 Primary analyses*).

Computation of age

Age in years will be calculated using birth date and date of baseline visit or the first available visit date of follow-up (if baseline visit date is not available). Formula for calculation (same as in the DB) is as follows:

$$\text{IF birthday (in the same year as baseline visit)} \leq \text{date of baseline}$$

$$\text{THEN age [years]} = \text{baseline year} - \text{birth year;}$$

$$\text{ELSE age [years]} = \text{baseline year} - \text{birth year} - 1;$$

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and comorbidities will be summarized using categories pre-specified in the eCRF (group of concomitant diseases/comorbidities and a specific concomitant disease/comorbidity). In all other relevant aspects, it will be analysed in a similar manner as adverse drug reactions, described in following Section 7.7 Safety analyses. Concomitant diseases and comorbidities ongoing at Visit 1 will be presented separately from those which started after the end of Visit 1.

Concomitant medications will be also summarized using categories pre-specified in the eCRF (medication category and medication type). Medications ongoing at Visit 1 will be presented separately from those which started after the end of Visit 1.

Concomitant therapies will be listed. Therapies ongoing at Visit 1 will be listed separately from those which started after the end of Visit 1. Since concomitant therapies were recorded as a free text field, it was noted during the course of the study that information reported does not contain only terms strictly related to concomitant therapies, but might include administration of drugs, repeated interventions etc. Since the information of the number of concomitant therapies will be used for the Cohort B data analysis (for the propensity score matching), it was deemed appropriate that a medical review expert revises the data and identifies which terms should be considered as a concomitant therapy and which terms were entered in the corresponding field by an error. The process is described in a document “Revision of Text Fields”. The outcome of the revision will be included in the statistical analysis datasets. Only the terms indicated as

a concomitant therapy during the revision will be used for the propensity score matching. However, all terms entered in the database will be listed, together with their translations and indicators whether they were considered in the statistical analysis (variable "revision").

7.3 TREATMENT ADHERENCE

Not applicable. Treatment adherence cannot be assessed in this study.

7.4 PRIMARY ANALYSES: MAIN ANALYSES

For both cohorts, the primary analyses will be based on the actual anticoagulation treatment that patients receive (i.e. "as treated" analysis) otherwise the main analysis set will be used for analysis or propensity score analysis set in case of Cohort B and PACT-Q2 analysis.

Comparisons of PACT-Q (Objective 1)

PACT-Q©:

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

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

- The PACT-Q1 is composed of a single dimension (7 items), covering the expectations of patients regarding their anticoagulant treatment, and is to be administered before treatment initiation.

- The PACT-Q2 is composed of three dimensions covering: convenience (11 items), burden of disease and treatment (2 items), and anticoagulant treatment satisfaction (7 items). The PACT-Q2 is to be administered to patients once treatment is ongoing.

Scoring of questionnaires is described for example in following publication:

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

Cohort A

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

Cohort B

For Cohort B, mean PACT-Q2 scores will be compared between Pradaxa® and VKA patients at the second and last assessments. Given the nature of this non-interventional study, patient in the two treatment groups may differ with regard to important baseline demographics and

disease characteristics. When approximately half of the target sample size is reached, propensity scores that estimate the probabilities that patients would be initiated on Pradaxa® will be calculated using a logistic regression model as specified below:

- Dependent variable in the propensity score model is treatment choice.
- Appropriate baseline variables that are either potential confounders (associated with both treatment choice and outcome) or potential predictors of outcome from the proposed list below will be included as covariates. Final list will be provided in separate document (Appendix 1):

  Gender
  Age at baseline
  Country
  Weight at baseline
  Healthcare system characteristics (reimbursement status, specialty of treating physician)
  PACT-Q1 score at baseline
  HAS-BLED score
  CHA2DS2-VASc score
  Creatinine clearance
  Concomitant medications (e.g. the number of medications) at baseline
  Comorbidities/concomitant diseases

- If a variable is suitable but have a high number of missing values, it will not be used in the propensity score model.

Variable selection will be performed with caution to avoid the inclusion of highly correlated variables as well as over-parameterization. The final list of variables will be determined and agreed by all involved parties (statistical and medical (or market access) team members) before execution of interim analysis and then revised and updated, if needed (new version have to be agreed), before execution of final analysis.

Interim analysis

The percentage of Pradaxa® and VKA patients that are matched with a 1:1 ratio and without replacement based on propensity scores will be calculated to assess the comparability of the two patient populations, and to estimate the loss of patients from the comparative analysis.

In this study Pradaxa® and VKA patients will be matched based on propensity scores using an allowable absolute difference between the exact propensity scores, or a "radius" around the score (caliper width). This matching will be done using the nearest neighbor matching algorithm in SAS that can match a "control group" to a "patient group" at a 1:1 ratio, without replacement [Coca-Perraillon, 2007]. The caliper width will be set to 0.2 of the standard deviation of the logit of propensity scores, as this setting, according to literature [Austin, 2011], allows the optimal match.

If a sufficient percentage of matching (e.g. 90%) is achieved, the loss is considered minimal. If the percentage is considered not to be sufficient, the target sample size might be raised to increase the power of the comparative analysis. Recalculation of sample size will be done by the same way as the first sample size estimation but loss to matching will be set in accordance

with results of propensity scores analysis (e.g. if loss to matching is 20% the same percentage will be set to new sample size estimation to achieve target power of analysis).

Final analysis

With respect to Cohort B, it was observed during the course of the study that the number of patients enrolled in the Pradaxa® group was considerably higher than the number of patients enrolled in the VKA group. In order to account for this imbalance and make the best use of available data, the final analysis will be based on a variable ratio, parallel, balanced 1:n nearest neighbor propensity score matching without replacement, as described by Rassen et al (2012). It will be implemented using the "Pharmacoepidemiology Toolbox" referenced in the Rassen et al paper (2012) and available at http://www.hdpharmacoepi.org.

To assess the performance of the matching, the following approach based on suggestions by Rassen et al (2012) will be implemented. Patient demographics and disease characteristics at baseline will be summarized in a table which will present descriptive statistics for all matched patients from the VKA group along with descriptive statistics for the Pradaxa® group in the following two ways:

1) calculated based on a dataset including each matched set's single best match

2) where each patient's contribution is weighted by matched set size

The analysis of the treatment effect itself must account for the matched nature of the sample (see Austin, 2008). Due to the variable size of the matched sets, the primary analysis of PACT-Q2 scores will be based a random intercept model, where the matched group is considered as a random effect, the treatment as a fixed effect and the score as the response variable. The following SAS code will be used:

```
proc mixed data=Data method=reml;
     class Treatment MatchID;
     model Score=Treatment;
     random intercept /subject=MatchID;
run;
```

where

"Treatment" stands for the Treatment variable (VKA/Pradaxa)
"Score" stand for the variable with the PACT-Q2 scores
"MatchID" stand for the variable with the identification of the matched group

As the sensitivity analysis, the method used in Rassen et al (2012) will be implemented. The "within-set" treatment effect estimates will be obtained by calculating the difference within each matched set between the VKA patient's score and the mean score of the matched Pradaxa® patients; the overall treatment effect will be then estimated as the mean of those differences and its statistical significance will be evaluated by a t-test.

Patients' characteristics (Objective 2)

Patient demographics and disease characteristics at baseline as described in section 5.1 Primary outcome variables for Objective 2 will be summarized descriptively for all eligible patients in Cohort A and by treatment in Cohort B. This analysis will be repeated by additional relevant factors as country, or if appropriate by other variables as age categories (to be defined according to distribution of variable) or gender.

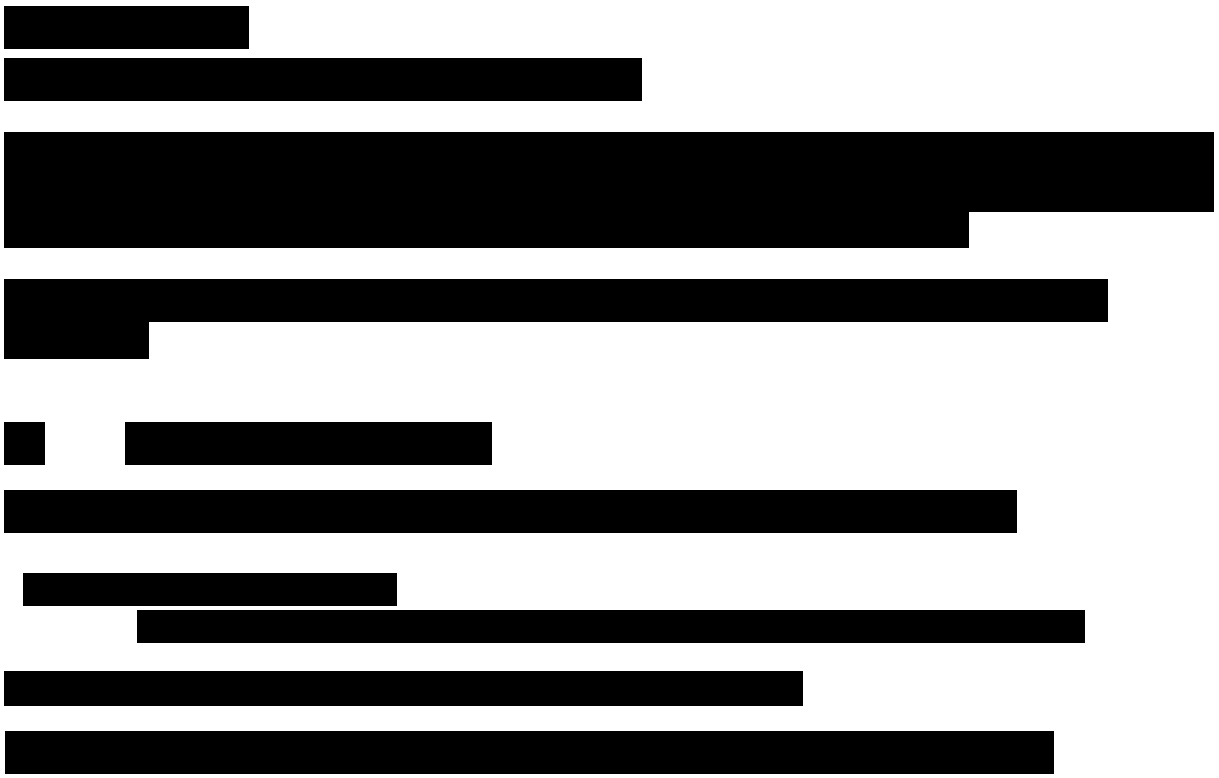
7.5 SECONDARY OUTCOMES AND FURTHER ANALYSES

Secondary outcomes

Secondary outcomes are described in section 5.2.

For Cohort A, mean PACT-Q2 scores at the last and second assessments will be compared using the same statistical procedure as described for the primary outcome.

For Cohort B, PACT-Q1 scores at baseline will be summarized descriptively for all patients overall and by treatment.



7.7 SAFETY ANALYSIS

Adverse events/Adverse drug reactions

Adverse drug reactions will be coded using last versions of MedDRA dictionary.

Detailed definitions and classification of ADRs is specified in Study Protocol.

Safety analyses will be performed separately for Cohort A and B, and will include all enrolled patients with an actual follow-up. Statistical analysis and reporting of ADRs will be descriptive in nature, will be based on BI standards, and will focus on adverse drug reactions (ADRs) to Pradaxa® and VKA. No hypothesis testing is planned.

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

The following parameters will be included in the safety analyses:

- Adverse drug reactions (ADRs)
- Adverse drug reactions leading to discontinuation of anticoagulation treatment
- Serious adverse drug reactions (SADRs)
- Adverse events leading to deaths

A reconciliation of serious adverse drug reactions (i.e. a comparison of the number of SADRs in the clinical database and the number of SADRs reported to sponsor) will be performed before DB lock. Assignment of treatment to ADRs and coding should be done and approved by the sponsor before DB lock, as well.

The number (%) of patients reporting each treatment emergent ADR (TEADR) will be summarized by primary System Organ Class (SOC) and Preferred Term (PT) where patients with more than one TEADR within a particular SOC and PT are counted only once for that SOC and PT. Percentages are based on the number of patients actually receiving a given treatment (based on the safety set) within each treatment group. Furthermore, ADRs will be summarized by its severity.

Laboratory data

Summary tables presenting descriptive statistics will be presented for creatinine clearance at each time-point of assessments.

Creatinine clearance is calculated in the e-CRF directly according to Cockcroft-Gault formula:

$$\text{Creatinine clearance (mL/min)} =$$

For creatinine in micromol/L:

$$\frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23 \times (0.85 \text{ if female})}{\text{Creatinine (micromol/L)}}$$

8. REFERENCES

1	*ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96*
2	*ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95*
3	*SAS 9.3; © 2008 by SAS Institute Inc., Cary, NC, USA; OnLine Doc.*
4	*Peter C. Austin, Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies, Pharmaceut. Statist. 2011, 10 150–161*
5	*Marcelo Coca-Perraillon, Local and Global Optimal Propensity Score Matching, SAS Global Forum 2007, Paper 185-2007*
6	*Jeremy A. Rassen, Abhi A. Shelat, Jessica Myers, Robert J. Glynn, Kenneth J. Rothman and Sebastian Schneeweiss, One-to-many propensity score matching in cohort studies, Pharmacoepidemiol Drug Saf. 2012, 21 69–80*
7	*Peter C. Austin, A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003, Statist. Med. 2008; 27 2037–2049*

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**09-MAY-16**	[redacted]	None	This is the final TSAP without any modification
2.0 (Amendment 1)	**28-JUN-17**	[redacted]	4, 7.4 6.2 [redacted] 6.6 6.7 7.2 8 [redacted] Appendix 1 Appendix 2	1:1 propensity score matching changed to variable ratio 1:n matching Minor modifications in a definition of important protocol violations - consistency with data collected in the eCRF Validation of data - data quality will be discussed during a data review meeting rather than detailed in the report Visit windows for the analysis specified in more detail Specification of the data analysis of -comorbidities and concomitant medications reflecting the categories collected in the eCRF -concomitant therapies reflecting that they were collected as free-text fields Relevant references added More detailed specifications of some variables to be included in the propensity score analysis. Modified based on a new BI template for NIS studies
3.0 (Amendment 2)	**21-NOV-17**	[redacted]	6.6 Appendix 2	"The date of the last treatment administration during the study" defined. Minor changes in the list of outputs.

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APPENDIX 1

List of variables to be included in the propensity score analysis

This document contains the list of variables to be agreed by all parties involved in the selection process of propensity score variables. List have to be agreed from statistical and also medical (or market access) view.

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. When approximately half of the target sample size is reached, propensity scores that estimate the probabilities that patients would be initiated on Pradaxa® will be calculated using a logistic regression model 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:
  - ✓ **Gender** (Male/Female)
  - ✓ **Age at baseline** (< 65, ≥ 65 and < 75, ≥ 75 years)
  - ✓ Healthcare system characteristics:
    - **Reimbursement status** (Reimbursed, Partially reimbursed, Private pay, Other)
    - **Specialty of treating physician** (Cardiologist, Internist, Neurologist, General practitioner, Other)
  - ✓ **HAS-BLED score** (low risk [score of < 3], high risk [score of ≥ 3])
  - ✓ **CHA2DS2-VASc score** (low or intermediate risk [score < 2], high risk [score of ≥ 2])
  - ✓ **Creatinine clearance** (30 to < 50, 50 to < 80, ≥ 80 mL/min)
  - ✓ **Concomitant medications** (number of medications, 0, 1-3, 4 and more) at baseline
    - Note: Concomitant medications for which "Ongoing at time of Visit 1" is marked as "No" (i.e. stopped earlier), will NOT be considered. This is also applicable for the more specific groups mentioned below.
  - ✓ **Concomitant therapies** (number of therapies, 0, 1 and more) at baseline
    - Note: Concomitant therapies for which "Ongoing at time of Visit 1" is marked as "No" (i.e. stopped earlier), will NOT be considered.
  - ✓ **Co-morbidities – group 1** (malignancy, no malignancy)
    - Note: Co-morbidities for which "Ongoing at time of Visit 1" is marked as "Yes" or "No" (i.e. stopped earlier), will be considered.
  - ✓ **Co-morbidities – group 2** (GERD or gastroduodenal ulcer disease, no GERD or gastroduodenal ulcer disease)
    - Note: Co-morbidities for which "Ongoing at time of Visit 1" is marked as "Yes" or "No" (i.e. stopped earlier), will be considered.
  - ✓ **Concomitant medications – group 1** (no antiarrhytmic drug, antiarrhytmic drug: Class I agents: Na+ channel block (e.g. Quinidine, Lidocaine), Class II agents: Beta-blockers , Class III agents:K+ channel blocker (e.g. Amiodarone, Sotalol, Ibutilide, Dofetilide) , Class III agents:K+ channel blocker (e.g. Dronedarone, Ketoconazole, Cyclosporine, Itraconazole), Class IV agents: Calcium channel blockers (top-down: Verapamil, Diltiazem) , Class V agents, Others))
  - ✓ **Concomitant medications – group 2** (antiplatelet drug, no antiplatelet drug)
  - ✓ **Concomitant medications – group 3** (NSAIDS, no NSAIDS)

- If a variable is suitable but has a high number of missing values, it will not be used in the propensity score model.
- 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 execution of final analysis.

APPENDIX 2

List of tables, figures and listings

The table below presents preliminary list of tables, figures and listings which will be included in study report. The numbering and structure is proposed according the BI 001-MCS-90-118_RD-08_2.0_Non-interventional Study Report template.

Section 10.1 of CSR: Participants

Output	Numbering	Title	Analysis Set*
		Disposition of patients	
Table	10.1.1	Disposition of patients and analysis sets	Enrolled patients
Figure	10.1.2	Flow of patients in analysis sets	Enrolled patients
Table	10.1.3	Total number of patients enrolled by centre and by anticoagulation treatment	Enrolled patients
Table	10.1.4	Reasons for permanent discontinuation of the study	MAS
		Protocol violations	
Table	10.1.5	Reasons for exclusion from analysis sets and protocol violations	Enrolled patients
Table	10.1.6	Inclusion and exclusion criteria, informed consent recording	Enrolled patients

* MAS = Main analysis set

Section 10.2 of CSR: Descriptive data

Output	Numbering	Title	Analysis Set*
		Demographic data (Including primary outcomes of Objective 2)	
Table	10.2.1	Primary outcomes of Objective 2: Demographic and baseline characteristics (age, gender, weight)	MAS
Table	10.2.2	Healthcare system characteristics	MAS
Table	10.2.3	Primary outcomes of Objective 2: Comorbidities and concomitant diseases at baseline	MAS
Table	10.2.4	Primary outcomes of Objective 2: Concomitant medication at baseline	MAS
Table	10.25	Primary outcomes of Objective 2: CHA2DS2-VASc and HAS-BLED score	MAS
Table	10.2.6	Primary outcomes of Objective 2: Duration of previous treatment with VKA (Cohort A only)	MAS
Table	10.2.7	Primary outcomes of Objective 2: Previous VKA treatments (Cohort A only)	MAS
Table	10.2.8.x**	Primary outcomes of Objective 2: Comparison of baseline characteristics in patients discontinued the treatment and completed patients	MAS
Table	10.2.9.1	Comparability of the treatment groups in Cohort B before and after propensity score matching; based on a dataset including each matched set's single best match (Cohort B only)	MAS/PSMS

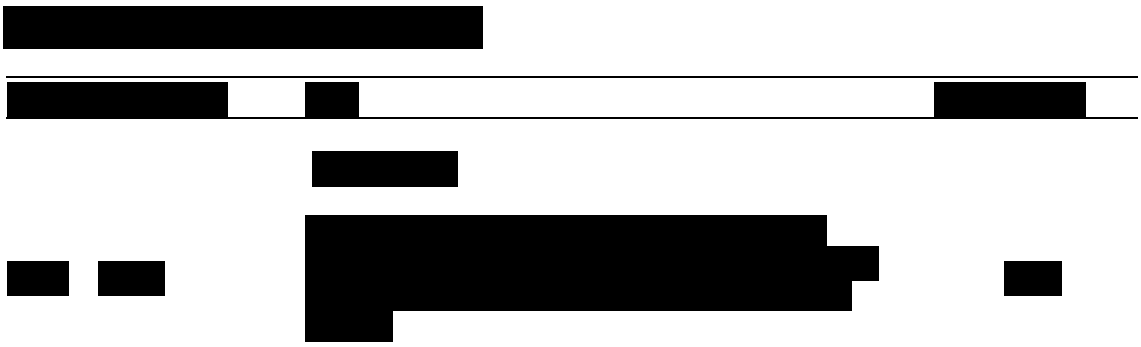
Output	Numbering	Title	Analysis Set*
Table	10.2.9.2	Comparability of the treatment groups in Cohort B before and after propensity score matching; weighted patient's contribution (Cohort B only)	MAS/PSMS

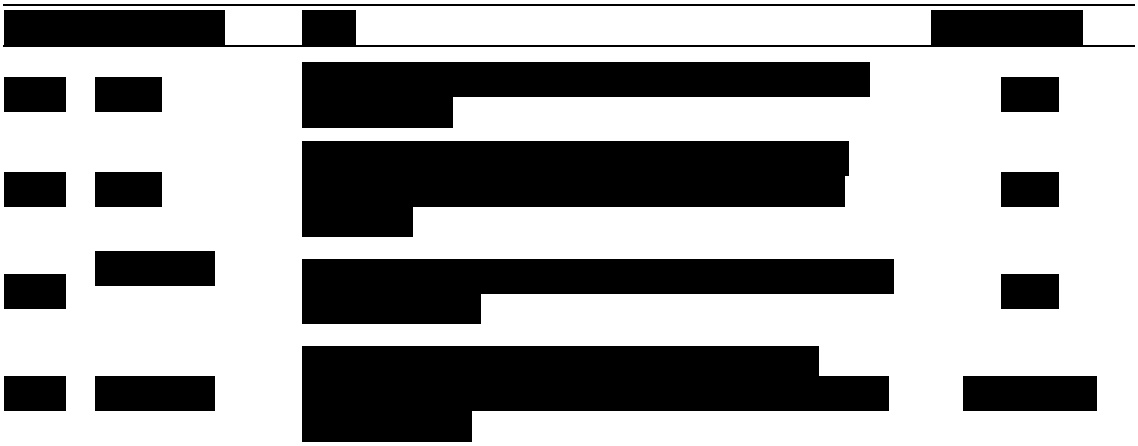
* MAS = Main analysis set, PSMS = Propensity score matched set, SS = Safety set
** the "x" depends on number of meaningful tables.

Section 10.4 of CSR: Main results

Output	Numbering	Title	Analysis Set*
		Efficacy data	
Table	10.41	Primary outcome for Objective 1 - Cohort A: Mean PACT-Q2 scores at second and last assessment compared to baseline assessment	MAS
Table	10.4.2	Primary outcome for Objective 1 - Cohort B: Mean PACT-Q2 scores at second and last assessment between treatment groups	PSMS
Table	10.4.3	Secondary outcome for Objective 1 - Cohort A: Mean PACT-Q2 score at last assessment compared to second assessment (Cohort A)	MAS
Table	10.4.4	Secondary outcome for Objective 1 - Cohort B: Description of PACT-Q1 items at baseline	MAS
Table	10.4.5	Primary outcome for Objective 2: Kidney function (creatinine clearance) at baseline, during initiation and continuation period (both cohorts)	MAS
Table	10.4.6	Primary outcomes of Objective 2: Dosing of Pradaxa® during the study	MAS
		Safety data	
Table	10.4.7	Exposure to study drugs	SS
Table	10.4.8	VKA treatments (Cohort B only)	SS

* MAS = Main analysis set, PSMS = Propensity score matched set





Safety data

Table	10.5.12	Weight at baseline, during initiation and continuation period (both cohorts)	SS
Table	10.5.13	Changes in comorbidities/concomitant diseases during initiation and continuation period	MAS
Table	10.5.14	Changes in concomitant medications during initiation and continuation period	MAS

* MAS = Main analysis set, PSMS = Propensity score matched set
** the "x" depends on number of meaningful tables.

Section 10.6 of CSR: Adverse events

Output	Numbering	Title	Analysis Set*
Table	10.6.1	Summary of all adverse drug reactions and observed person-years (i.e. time at risk)	SS
Table	10.6.2	Treatment-emergent adverse drug reactions by preferred term within primary system organ class	SS
Table	10.6.3	Treatment-emergent serious adverse drug reactions by preferred term within primary system organ class	SS
Table	10.6.4	Treatment-emergent adverse drug reactions leading to discontinuation of anticoagulation treatment by preferred term within primary system organ class	SS
Table	10.6.5	Treatment-emergent adverse drug reactions leading to death by preferred term within primary system organ class	SS
Table	10.6.6	Treatment-emergent adverse drug reactions by intensity and by preferred term within primary system organ class	SS

* MAS = Main analysis set, SS = Safety set

Section Appendix of CSR: Patient data listings

Output	Numbering	Title	Analysis Set*
Listing	A.1	Concomitant therapies at baseline	MAS
Listing	A.2	Comorbidities and concomitant diseases at baseline; category "Other"	MAS
Listing	A.3	Concomitant medication at baseline; category "Other"	MAS
Listing	A.4	Reasons for switch to Pradaxa® (Cohort A only)	MAS
Listing	A.5	Previous VKA treatments; category "Other" (Cohort A only)	MAS
Listing	A.6	Reasons for Pradaxa® dose change during the study	SS
Listing	A.7	VKA treatments; category "Other" (Cohort B only)	SS
Listing	A.8	Specifications of changed VKA (Cohort B only)	SS
Listing	A.9.1	Adverse drug reactions	SS
Listing	A.9.2	Adverse drug reactions - original terms and coding	SS
Listing	A.10	Changes in concomitant therapies during initiation and continuation period	SS
Listing	A.11	Changes in comorbidities/concomitant diseases during initiation and continuation period; category "Other"	SS
Listing	A.12	Changes in concomitant medications during initiation and continuation period; category "Other"	SS

* MAS = Main analysis set, SS = Safety set