Boehringer Ingelheim

Trial Statistical Analysis Plan

BI Trial No.:	1160.218
Title:	Drug persistence/adherence in patients being treated with Pradaxa® (dabigatran etexilate) or vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF)
Investigational Product(s):	Pradaxa® (dabigatran etexilate)
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	13AUG2015
Version:	Final 1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AF	Atrial fibrillation
CHA_2DS_2-VASc-Score	Congestive heart failure, Hypertension, Age (>75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex category
CTCAE	Common Terminology Criteria for Adverse events
CTP	Clinical Trial Protocol
FAS	Full Analysis Set
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke (1 point), bleeding history or predisposition, Labile INR, Elderly (>65 years), Drug and Alcohol
INR	International Normalized Ratio
MedDRA	Medical Dictionary or Regulatory Activities
MG	Matched Group
N	Number
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse events
PS	Propensity Score
PT	Preferred Term
SAE	Serious Adverse event
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TS	Treated Set
TSAP	Trial statistical analysis plan
VKA	Vitamin-K-Antagonists
WHO-DD	World Health Organization Drug dictionary

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 Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Analysis". Therefore, TSAP readers may consult the CTP 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, randomization.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

None.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Proportion of patients, who are still treated with the initial assigned anticoagulant at 12-months visit, derived by Kaplan-Meier estimator for persistence at 12 months, stratified for dabigatran etexilate and VKA. Persistence is defined as the time in months between initiation, i.e. date of first visit, and permanently discontinuation of treatment with Pradaxa® or VKA. Patients who discontinue study prematurely and without documented treatment discontinuation will be censored at date of study termination. Patients completing the study as planned will be censored at the day after last visit, if no earlier treatment discontinuation is documented.

5.2 SECONDARY ENDPOINT(S)

- Proportion of patients with low, medium or high adherence at 6-months visit stratified for dabigatran etexilate and VKA. Categorisation of patients into low, medium or high adherence is done according to Morisky
- Reasons for permanent discontinuation of therapy

5.3 FURTHER ENDPOINT(S)

Not applicable.

5.4 OTHER VARIABLE(S)

Other variables will be baseline characteristics (incl. risk score for stroke and bleeding, this means CHA_2DS_2-VASc and HAS-BLED) and patient's characteristics such as age, gender, height, weight, BMI, education, marital status and health insurance. Additionally information about previous diseases, medical progress and follow-up will also be collected.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Evaluation/ Method	Visit 1 (Baseline)	Visit 2 (after approx. 3 month)	Visit 3 (after approx. 6 month)	Visit 4 (after approx. 9 month)	Visit 5 (after approx. 12 month)
Socio demography	X				
VHF- anamneses	X				
CHA_2DS_2VASc-/ HAS-BLED-Score	X		X		X
Further comorbidities	X		X		X
Date of start of therapy of Dabigatran etexilate/ VKA (incl. dosing)	X				
Concomitant medication (incl. intake frequency)	X		X		X
Treatment with initial oral anticoagulation		X	X	X	X
Morisky-Score			X		
Date of discontinuation (incl. reason)		X	X	X	X
In case of abortion: therapy after disontinuation		X	X	X	X
Adverse events*		X	X	X	X

* AE data will be collected until 30 days after end of therapy

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criteria not met	Inclusion criteria not met as specified in the protocol.	FAS
	A2	Exclusion criteria not met	Exclusion criteria not met as specified in the protocol	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All

Patients who received oral anticoagulants for less than 2 months before study inclusion will be treated as minor protocol deviations. These patients will be further documented and the inclusion criterion regarding the prior treatment with anticoagulants will not be set to 'No'. Subjects who were previously treated with oral anticoagulants for two months or more are excluded from the efficacy analysis.

6.3 PATIENT SETS ANALYSED

Treated Set (TS): All patients with at least one documented prescription of dabigatran etexilate or VKA.

Full Analysis Set (FAS): All patients from the Treated Set with main diagnosis non-valvular atrial fibrillation and who have at least one evaluable efficacy endpoint.

Matched group (MG): Patient cohort resulting from the 1:1 matching based on FAS.

Table 6.3: 1 Patient sets analysed

Class of endpoint	TS	MG
Primary and secondary endpoint		X
Safety endpoints	X	
Demographic/baseline	X	X

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). All available data will be used in the data analysis. Drop-outs will be adequately reflected because of the underlying method (survival analysis). Missing values will be categorized as "Missing" and will not be imputed.

Outliers will not be excluded from analysis.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The treatment with Pradaxa®/ VKA will be documented approximately every 3 months over a period of 12 months (in common control time points after approx. 3, 6, 9 and 12 months).

Baseline visit will include historical data/ registration and visit 1- initial examination.

Visit 2, 3, 4 and 5 will be labelled as retained from the eCRF. Final examination will include data collected at end of study examination.

7. PLANNED ANALYSIS

All analyses in this study are descriptive; results are to be interpreted in an explorative manner.

For categorical variables summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables N, mean, SD, minimum, median, maximum and number of missing values will be presented. To achieve a valid comparability of compliance (persistence and adherence) patients prescribed to dabigatran etexilate or VKA will be matched 1:1 based on the Exposure Propensity Score (PS) and caliper matching with caliper of width equal to 0.2xStandard deviation of PS.

The Propensity Score will be calculated based on a logistic regression model taking the choice of treatment as dependent variable and baseline characteristics as independent variables into account. All baseline variables with an a priori association to persistence and adherence will be included into the regression analysis.

These variables correspond to the potential cofounder variables for a comparative analysis.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. All baseline analyses will be done for the cohort resulting from the 1:1 matching and for the Treated Set, respectively. The analysis sets will be stratified by treatment group to investigate demography, severity of atrial fibrillation and further baseline characteristics (incl. risk scores for stroke and bleeding measured by CHA_2DS_2-VASc and HAS-BLED).

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report and all analyses will be done for the cohort resulting from the 1:1 matching and for the Treated Set, respectively.

7.3 TREATMENT COMPLIANCE

Not applicable.

7.4 PRIMARY ENDPOINT(S)

The analysis of the primary endpoint will be based on the patient cohort resulting from the 1:1 matching. Time until termination of treatment will be presented for both treatment groups (Dabigatran exetilate vs. VKA) by Kaplan-Meier estimates and displayed graphically, respectively. Especially for time points 3, 6, 9 and 12 months Kaplan-Meier estimates for persistence will be calculated.

The comparison of persistence between the treatments with dabigatran etexilate versus VKA will be conducted by means of the stratified Log-rank test, which takes dependencies resulting from the matching of the treatment groups into account. Patients who discontinue

study prematurely and without documented treatment discontinuation will be censored at study termination. Patients completing the study as planned will be censored at the day after last visit, if no earlier treatment discontinuation is documented. Association between patient characteristics (incl. method of treatment) and persistence will be determined by means of cox regression (univariate and multivariate model). First, univariate regression for each of the independent variables will be performed. Afterwards, all covariates will be entered into a stepwise multivariate regression. The entry level will be p=0.5 and the stay level p=0.1. Baseline characteristics will be presented stratified by patients who discontinued the study prematurely versus no discontinuation.

A multivariate Cox Regression model (including factors for the calculation of the propensity score and the choice of treatment) will be used as sensitivity analysis. All patients, who are within the "common support" of the empiric PS density function (instead of the matched pairs), will be included in this analysis. The "common support" will be determined after patients with a propensity score above the 97.5% percentile and below the 2.5% percentile have been excluded for each treatment group, respectively. This will be done to avoid high influence of patients with extreme PS.

The following covariates will be used -depending on the sample size- for the Propensity Score Matching and the sensitivity analysis

- CHA_2DS_2-VASc Score (<2, ≥2)
- HAS BLED-Score (<3, ≥3)
- Age at registration (<65, 65-<75, ≥75)
- Previous stroke (Yes, No)
- Treatment (VKA, Pradaxa®) (sensitivity analysis only)

and the following covariates will be used –depending on the sample size- for the Cox regression

- CHA_2DS_2-VASc Score (<2, ≥2)
- HAS BLED-Score (<3, ≥3)
- Age at registration (<65, 65-<75, ≥75)
- Previous stroke (Yes, No)
- Medical specialty of attending physician (Internist, Cardiologist, General practitioner, Other)
- Treatment (VKA, Pradaxa®).

Additionally, the following subgroups will be presented for persistence (overall and for each treatment group):

- CHA_2DS_2-VASc-Score (<2, ≥2)
- Age (<65, 65- <75, ≥75)
- Previous stroke (Yes, No)
- Medical specialty of attending physician (Internist, Cardiologist, General practitioner, Other)
- Daily dose of Pradaxa® at initial visit (2x110mg daily, 2x150mg daily) [Patients treated with Pradaxa® only]
- HAS-BLED-Score (<3, ≥3).

7.5 SECONDARY ENDPOINT(S)

Absolute number and percentage of patients, who discontinue the initial treatment during study, will be summarized collectively and according to reasons for discontinuation for the dabigatran etexilate and VKA cohort, respectively.

The analysis of secondary endpoints will be based on the patient cohort resulting from the 1:1 matching.

The Morisky questionnaire consists of 8 question and will be answered at the 6- months visit. Each question can be scored with 0 or 1. For questions 1-7, 'no' will be scored with 0 and 'yes' with 1. For question 8, 'None/rarely' will be scored with 0 and all other answers with 1. The Morisky score is given by the sum of the values of each question, which implies a score between 0 and 8.

The categorisation of patients into low adherence (score >2), medium adherence (score=1,2) and high adherence (score=0) is done according to Morisky. The score will only be calculated for patients who answered all eight questions. In case that the proportion of the patients who did not answers all questions is too high (i.e. >20%) a sensitivity analysis will be conducted in which the score will be calculated if up to 2 questions per patient are missing. Patients who changed their initial treatment or withdrew from the study before the 6-months visit, will be displayed seperatly from those for which the Morisky score could not be calculated for other reasons. Patients with missing data will be analyzed regarding to their baseline characteristics in comparision to the patients with an evaluable Morisky score; patients with missing values at the 6-months visit will be stratified into (i) the groups of study drop-outs, (ii) treatment drop-outs and (iii) patients with missing values because of other reason. The last mentioned analyses will only be done for strata of at least 200 patient (overall and for each treatment group).

Number and percentage of patients within the different adherence classes will be displayed for dabigatran etexilate and VKA patients, respectively. Furthermore the following subgroups will be presented for adherence (overall and for each treatment group):

- CHA_2DS_2-VASc-Score (<2, ≥2)
- Age (<65, 65- <75, ≥75)
- Previous stroke Yes, No)
- Medical specialty of attending physician (Internist, Cardiologist, General practitioner, Other)
- Daily dose of Pradaxa® at initial visit (2x110mg daily, 2x150mg daily) [Patients treated with Pradaxa® only]
- HAS-BLED-Score (<3, ≥3).

7.6 FURTHER ENDPOINT(S)

This section is not applicable as no further endpoint has been specified in the protocol.

7.7 EXTENT OF EXPOSURE

For duration of treatment see section 7.4. In addition, the duration of treatment with Viramune® will be given for the Treated Set with the number of patients and percentage in the following categories of duration:

<4 weeks, 4 - <10 weeks, 10-<30 weeks, 30-<50 weeks, 50-<70 weeks, ≥70 weeks.

In addition, the total treatment time of all patients will be provided in years.

Further on, the dosage of Pradaxa® at initial visit, which could be 2x110mg daily or 2x150mg daily, will be displayed (Section 7.1) as well as changes in dosage for the Treated Set.

7.8 SAFETY ANALYSIS

The analysis of adverse events will be descriptive and conducted according to Boehringer Ingelheim standards. The main focus will be on treatment emergent events. All AE that occurred between start of treatment and six days after permanently discontinuation of therapy or end of study will be considered as treatment emergent and will be displayed in frequency tables for dabigatran etexilate and VKA treated patients, respectively. Non-treatment-emergent events will be assigned to "screening" or "post-treatment" and only be displayed in listings. All analyses will be based on the safety population.

Frequency, severity and causality of treatment-emergent AEs will be tabulated according to MedDRA-SOC and PT. Treatment-emergent SAEs will be tabulated as well as adverse events leading to treatment discontinuation.

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs, except the analyses of action taken and the analysis of reason for serious TEAE.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events 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 for patients with serious adverse events. An additional table will be done for all non-serious adverse events with a frequency of more than 5%.

The system organ classes will be sorted alphabetically, preferred terms will be sorted by frequency (within system organ class).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (PT, NCI grade, 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 classification into TEAE or Non-TEAE, the first documented start of event will be used.

8. REFERENCES

See Protocol (23 references) and the underlying Boehringer Ingelheim document "Template Trial Statistical Analysis Plan- template" (Ref-Doc: 001-MCG-160_RD-06 (6.0) / Saved on 12 May 2014).

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Draft v1.0	**23-FEB-2015**		None	This is the first Draft-Version of TSAP without any modification
Draft v1.1	**18-MAR-2015**		None	This is the second Draft-Version of TSAP with slight modifications
Draft v1.2	**17-JUN-2015**		6.3, 7.7	This is the third Draft-Version of TSAP with slight modifications
Draft v1.3	**27-JUL-2015**		3, 6.3, 7, 7.8	This is the fourth Draft-Version of TSAP with slight modifications
Final v1.0	**13-AUG-2015**		None	This is the final Version of TSAP