Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

c17636581-01

BI Trial No.:	1160.271
Title:	Bioequivalence of tablet formulation of dabigatran etexilate compared to commercial capsule formulation following oral administration in healthy male subjects (an open-label, randomised, single-dose, replicate design in a two-treatment, four-period, two-sequence crossover study)
Investigational Product(s):	Pradaxa® (Prazaxa® in Japan), Dabigatran etexilate, BIBR 1048 MS
Responsible trial statistician(s):	[redacted] [redacted] Address: [redacted] Phone: [redacted]
Date of statistical analysis plan:	12/JUL/2017 SIGNED
Version:	Final

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
CTP	Clinical Trial Protocol
ICH	International Conference On Harmonisation
MedDRA	Medical Dictionary For Regulatory Activities
PK	Pharmacokinetics
PV	Protocol Violation
RPM	Report Planning Meeting
SD	Standard Deviation
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9 (1), 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 Methods and Determination of Sample Size”. 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 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There are no changes in the planned analysis of the study.

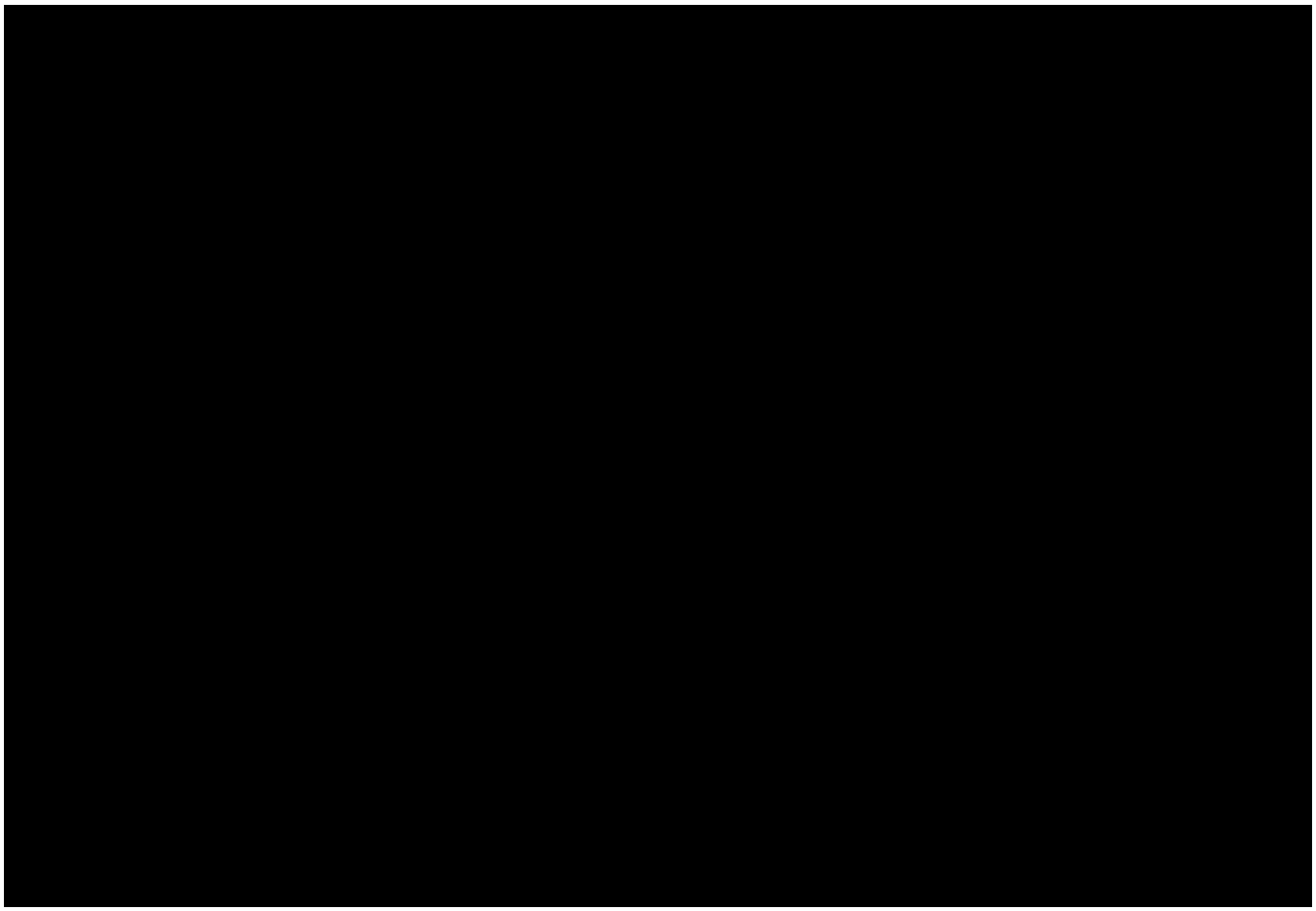
5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

No efficacy endpoints will be evaluated in this trial. Primary endpoints are defined in CTP (see Section 5.5.1.1).

5.2 SECONDARY ENDPOINT(S)

Secondary endpoints are defined in CTP (see Section 5.5.1.2).



5.4 OTHER VARIABLE(S)

Safety of the investigational drugs will be assessed based on:
- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

Demographic data:
- Gender (male)
- Ethnicity (Not Hispanic/Latino)

- Race (Asian)
- Age [years]=integer[(date of informed consent – date of birth)/365.25]
- Height [cm]
- Weight [kg]
- Body mass index (BMI) [kg/m2] = weight [kg] at screening / (height [m] at screening)^2
- Smoking status (Never smoked, Ex-smoker, Currently smokes)
- Alcohol status (Does not drink any alcohol; Drinks alcohol, but to an extent that would not interfere with participation in trial; Drinks alcohol to an extent that could interfere with participation in trial)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

6.1.1 TREATMENT REGIMENS / STUDY INTERVALS

There will be 10 phases in this trial:
screening, the first reference treatment (Ref 1), the second reference treatment (Ref 2) , the first tablet treatment (Test 1) , the second tablet treatment (Test 2), Washout 1 - 3, Post-treatment and post-study.
The treatment regimens/intervals in which a subject can lie during the course of the trial are defined as Table 6.1.1: 1.

Table 6.1.1: 1 Treatment regimens/Intervals.

Label	**Sort order**	**Start date** (CRF)	**Start time** (CRF/derived)
Screening	00	Date of informed consent	0:00
Ref 1	01	Date of the first Ref administration	Time of the first Ref administration
Ref 2	02	Date of the second Ref administration	Time of the second Ref administration
Test 1	03	Date of the first Test administration	Time of the first Test administration
Test 2	04	Date of the second Test administration	Time of the second Test administration
Washout 1	05	Date of last administration of Period 1	Time of last administration in Period 1 + 1 minute
Washout 2	06	Date of last administration of Period 2	Time of last administration in Period 2 + 1 minute
Washout 3	07	Date of last administration of Period 3	Time of last administration in Period 3 + 1 minute
Post-treatment	09	Date of last administration	Time of last administration + 1 minute
Post-study	99	Date of EOT + 1	0:00

KEY: Ref (Reference treatment): DE commercial capsule formulation; Test (Tablet Formulation): investigational formulation

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e., treated subjects and subjects with serious AE (SAE) which the investigator considered related to the screening procedure). Consistency check listings (for identification of violations of time windows) and a list of
protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the report planning meeting (RPM). At this meeting, it will be decided whether a discrepant data value can

be used in analyses or whether it must be corrected in the clinical database.
Each protocol deviation must be assessed to determine whether it is an important protocol violation (PV). For definition of important PVs, and for the process of identification of these, refer to the Boehringer Ingelheim reference document 'Protocol Violation Handling Definitions' (7).
If any important PVs are identified, they are to be summarised into categories and will be captured in the RPM minutes via accompanying Excel spreadsheet (8) [001-MCS-50-413_RD-02]. The following table contains the categories which are considered to be important PVs in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM.
If substantial numbers of PVs are reported at the RPM, a decision about summarising the PVs in a tabular format will be made. Otherwise, only a PV listing will be provided.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements/Comment	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criteria violated	Automatically detectable	None
	A2	Exclusion criteria violated	Automatically detectable	PKS
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date is missing or informed consent is not given. Automatically detectable	All
	B2	Informed consent too late	Informed consent date was after screening visit Automatically detectable	None
C		**Trial medication and randomisation**		
	C1	Non-compliance with trial medication	No trial drug administration. Automatically detectable	TS and PKS
	C2	Incorrect trial medication taken	e.g. trial medication was swapped, Manually detectable	None
	C3	Improper intake of trial medication	Manually detectable	PKS
	C4	Improper washout between treatments	Washout period has to be more than 3 days. Automatically detectable	PKS
D		**Concomitant medication**		
	D1	Administration of any drugs and/or intake of any foods which might influence the results of PK.	For example; Administration of any drugs before or during the trial Violation of restricted lifestyle Manually detectable.	PKS
E		**Missing data**		
	E1	Certain violations of procedures used to measure primary or secondary data	Violations of procedures which may lead to invalid measurements with respect to primary or secondary PK endpoints. Manually detectable	PKS
F		**Incorrect timing**		
	F1	Certain violations of time schedule used to measure primary or	PK sample taken too early/too late Manually detectable	PKS

Category / Code		Description	Requirements/Comment	Excluded from
		secondary data		

6.3 SUBJECT SETS ANALYSED

- Randomised set (RS):
  This subject set includes all randomised subjects, whether treated or not.

- Treated set (TS):
  This subject set includes all subjects from the RS who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

- Pharmacokinetic set (PKS):
  This subject set includes all subjects from the TS who provide at least one observation for at least one primary endpoint that was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he contributes only one primary endpoint value for one period to the statistical assessment.

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to populations will be made at latest at the RPM.

The following table summarizes which subject sets will be used for the different analyses.

Table 6.3: 1 Subject sets analysed

Class of endpoint	RS	TS	PKS
Disposition, exposure	X		
Important PVs	X		
Primary endpoints			X
Secondary and further endpoints			X
Safety endpoints		X	
Demographic/baseline endpoints		X	X

6.5 POOLING OF CENTRES

Pooling centres is not planed in the study, since the study is conducted in one site.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of screened subjects, who discontinued from the trial due to screening failures prior to administration of any trial medication, will not be included in the CTR except for those with SAE which the investigator considered related to the screening procedures. The safety data of treated subjects who were withdrawn from the trial prematurely will be reported as far as available. All withdrawals will be documented and the reason for withdrawal recorded.

Handling of missing data is described in section 7.4 of the CTP. Additionally, handling missing data is described as follows:
Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (3).
Missing data and outliers of PK data are handled according to (2).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline values of laboratory data and value of vital sign for safety analysis will be defined as the last values before drug administration of period 1.

In this trial, calculated visits will not be planned.

7. PLANNED ANALYSIS

In general, a set of descriptive statistics to be displayed for continuous variables in the clinical trial report will be as follows:

Non-pharmacokinetic variables:

For End-Of-Text tables, the set of summary statistics is: N, mean, standard deviation (SD), min, median, and max.

Tabulation of frequencies for categorical or categorised data will include all possible categories and display number of observations (subjects) with the percentage relative to the respective treatment sequence / regimen. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

Pharmacokinetic variables:

The analysis of standard PK parameters will be performed according to (2).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only listing is planned for this section of the report.

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

The analysis will be performed as defined in the CTP, Sections 7.1, 7.2 and 7.3.1.

7.5 SECONDARY ENDPOINT(S)

The analysis will be performed as defined in the CTP, Sections 7.1, 7.2 and 7.3.2.

[redacted]

7.7 EXTENT OF EXPOSURE

Only listing is planned for this section of the report.

7.8 SAFETY ANALYSIS

The analysis will be performed as defined in the CTP. All safety analyses will be performed on the treated set.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- 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)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer (3,4).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between the first drug intake till 3 days after last drug intake will be assigned to the treatments period. During the treatment period, all adverse events occurring after a drug intake till 3 days after the drug intake will be assigned to ‘on-treatment’ and those occurring after on-treatment period till the next drug intake will be assigned to ‘off-treatment’. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after last drug intake + 3 days will be assigned to ‘post-treatment’ (for listings only).

According to ICH E3 (5), AEs classified as ‘other significant’ needs to be reported and will include those non-serious and non-significant adverse events with
(i) ‘action taken = discontinuation’ 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 adverse events will be presented.

The frequency of subjects with adverse events will be summarised by treatment, primary system organ class and preferred term (mention MedDRA levels to be displayed in the tables).

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature by treatment sequence and will be based on BI standards (6).
Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis.
The last value on-treatment is defined as the last non-missing value observed during 'on-treatment period' (See section 7.8.1).

7.8.3 Vital signs

Only descriptive statistics by treatment sequence and planned visit are planned for this section of the report.
Clinically relevant findings in vital signs data will be reported as AEs and will be analysed as part of AE analysis.

7.8.4 ECG

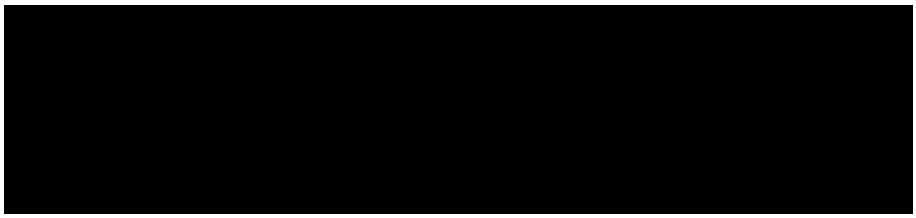
ECG data will not be listed but clinically relevant abnormal findings will be reported as adverse events.

7.8.5 Others

No other parameter will be analysed.

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.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", version 5; IDEA for CON.
5.	*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
6.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
7.	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version; IDEA for CON.
8.	*001-MCS-50-413_RD-02*: "Important Manual Protocol Violations Spreadsheet", current version; IDEA for CON.



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**16-JUN-2017**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct.
Final	**12-JUL-2017**		Section 5, 6 and 7	Details for analysis are specified. For iPV Table 6.1.1: 1, “none or PKS” and “All” was replaced with “PKS” and “TS and PKS” for clarification. iPV categories have not been changed.